Practical Guide to
Canine and Feline Neurology

3rd Edition

Curtis W. Dewey • Ronaldo C. da Costa

with website

WILEY Blackwell

PRACTICAL GUIDE TO CANINE AND FELINE NEUROLOGY

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Third Edition

Edited by

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Dedication

Alexander de Lahunta, DVM, PhD, DACVIM (Neurology), DACVP.

As neurologists, Ronaldo and I shudder to think where we would be professionally without the myriad and substantial contributions that Alexander ("Sandy") de Lahunta has made to our specialty. He has–in a career spanning nearly half a century–laid the framework for our understanding of neuroanatomy and neuropathology. It is a testament to this man's legendary and iconic status in veterinary medicine overall that any veterinarian who opens this book will immediately feel respect and gratitude for "Dr. D" and know that he deserves all the accolades we can bestow upon him. And if you would like to read about the accolades that Dr. D has earned, you should go online; they are far too numerous to fit on a textbook dedication page. Dr. D's contributions to our understanding of embryology, anatomy, neurology, and neuropathology are voluminous and ongoing. His passion has been and remains fulfilling the role of teacher. As one of his former students, I can personally attest to his unequalled skill in this arena. I can also attest to the fact that Dr. D has kept in touch with many of his students after they graduated and moved forward with further educational endeavors and careers. Years after I left Cornell as a student, I would hear of Dr. D telling his current students about something I had published in a journal. It meant a lot to know that someone I revered so highly was proud of my accomplishments. Ronaldo and I are proud of Alexander de Lahunta, as all veterinarians should be, and feel incredibly fortunate that he influenced our career paths. We dedicate this edition to someone who has positively and permanently changed the face of veterinary neurology and veterinary medicine in general—Dr. Alexander de Lahunta.

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About the Editors

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Ronaldo Casimiro da Costa, DMV, MSc, PhD, Dipl. ACVIM (Neurology), Associate Professor and Service Head, Neurology and Neurosurgery, The Ohio State University College of Veterinary Medicine. Prior to joining the Ohio State University in 2008, Dr. Ronaldo C. da Costa was a faculty member at the Federal University of Paraná in Brazil (1997–2008), the same school where he obtained his DMV degree. Following that, he got his Masters in Surgery in Brazil, and completed his residency and PhD at the Ontario Veterinary College, University of Guelph. He has authored and coauthored dozens of peer-reviewed journal articles and several book chapters in authoritative textbooks. He was also the Guest Editor of a Veterinary Clinics of North America Small Animal Practice focused on spinal diseases. Dr. da Costa actively serves the profession as a member of the ACVIM, AVMA, and other associations, a reviewer of several national and international veterinary journals, and as the founding President of the Brazilian Veterinary Neurology Association. He has an active clinical and research program on spinal diseases, primarily cervical spondylomyelopathy, and has received over 30 awards for academic, research, and teaching excellence. Dr. da Costa has lectured extensively nationally and internationally, and is passionate about teaching. He has received eight teaching awards including the Pfizer Norden Excellence in Teaching Award (highest college teaching award) and the Excellence in Graduate Teaching Award at Ohio State. He was a finalist for the National Pfizer Norden Award Excellence in Teaching Award.

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Preface

In the preface to the second edition of *A Practical Guide to Canine and Feline Neurology*, I mention the increasingly difficult task of keeping up with the rapidly expanding knowledge base in the field of small animal neurology and neurosurgery. As the time approached to consider working on the third edition, I became increasingly anxious about this endeavor. I am proud of this book and truly believe it has helped many veterinary students, general small animal practitioners, interns, residents and specialists; however, and perhaps because of the book's success, the thought of writing a third edition struck me as less the labor of love that the previous edition had been and more a herculean task, with all the feelings of trepidation that engendered. I realized that this transformation from positive to negative was rooted in my concern that this textbook's next iteration—in order to stay true to my vision of maintaining a comprehensive, up-to-date, visually attractive, and clinically useful reference source—was beyond my capability to create as a sole editor. I came to the conclusion that this book had outgrown me as a sole editor, and that I needed help. I chose Ronaldo da Costa for this monumental task and—fortunately for me and anyone who reads this book—he agreed to be co-editor.

Ronaldo's insight and passion for this project reinvigorated my outlook and drive to create the best edition of this textbook yet. His resourcefulness and attention to detail are also very evident in the pages. This time around, both Ronaldo and I pooled comments we had heard about the second edition, in order to make the third edition better than the second. This edition is obviously in color (mostly), which is great, but looks aren't everything (it's true, despite what the media portrays). There are quite a few new features of this edition that I am sure will be very helpful.

You will notice some new contributing authors (in addition to Ronaldo, of course), some new chapters, and some new images. A few of the exciting (I think) additions include a differential diagnosis chapter (by Ronaldo and me), a chapter devoted solely to magnetic resonance imaging (Ronaldo and Silkie Hecht), and a chapter dealing with movement disorders (Simon Platt). These additions, along with approximately 400 new figures and dozens of videos, will hopefully greatly enhance the reader's experience.

As with the first and second editions, we requested assistance with images from a number of colleagues and, as before, these individuals came through for us. You will notice that there are quite a few new images provided by Diane Shelton, Jen Bouma, and Scott Fellows. We also have a number of fantastic new illustrations by Tim Vojt, Medical Illustrator, and beautiful new pictures by Jerry Harvey, Medical Photographer, both from the Ohio State University. A number of our colleagues have expressed interest in assisting with the next edition. The fact that these individuals volunteered their involvement for the fourth edition is quite a compliment. And we will likely be contacting you about your impending involvement very soon.

Ronaldo and I hope you like this edition and that you find it "user friendly" in teaching, clinical practice, or both. And if you have been referring to this book as "Dewey," please refer to it now and in the future as "Dewey/da Costa." I think that this has a nice alliterative ring to it.

Acknowledgments

Something like this that you have in your hands could not happen without the help of countless individuals, people that cared for us way before we were something in life! We would like to thank our entire families, starting with Curtis' parents (Pam and Maurie), wife (Janette), and kids (Jordan, Isaiah, Ethan, Carver, Sole, and Jolie), and Ronaldo's parents (Sirlei and Ivo), wife (Luciana) and kids (Felipe, and Rafaela). Without their love, support, and patience (!) over the years, this would not have come to fruition.

On the professional side we both had several mentors who guided us in our professional growth as veterinary neurologists. I (Curtis) have had the privilege of having been trained and inspired by legends of the veterinary profession at Cornell University, the University of Georgia, and the University of California-Davis. I (Ronaldo) would like to thank the faculty members at the Federal University of Paraná, Federal University of Santa Maria, and the Ontario Veterinary College, University of Guelph, especially Dr. Joane Parent for everything!

We are indebted to all contributors—Linda Barter, Mary Tefend Campbell, David Dorman, Julie Ducoté, Daniel Fletcher, Thomas Fletcher, Silke Hecht, Janice Huntingford, Karen Kline, Paula Martin-Vaquero, Simon Platt, Jacques Penderis, Bruno Pypendop, Sean Sanders, Lauren Talarico, and Bill Thomas—who generously offered their time and expertise to make this book a comprehensive and up-to-date resource. We are also very thankful for the images and advice offered by Diane Shelton for the neuropathy and myopathy chapters.

Obviously without the inspiration and support of our friends, colleagues, technicians, and residents at the Cornell University and the Ohio State University (too many to be named!) this book would not have been completed. Two people in particular were key to making this third edition what it is: Paula Sharp at Cornell and Tim Vojt at Ohio State. We cannot thank them enough for their time and expertise. Additionally, the videos you see could not be possible without the assistance of Heather Myers and Amanda Disher. We are also very grateful to our patients and their guardians who allowed us to care for and learn from them. Ultimately, this book only exists because of them.

Thanks also to the staff at Wiley-Blackwell, especially Nancy and Catriona, for bearing with us through this process.

Finally, I (Ronaldo) want to personally thank Curtis for inviting me to join him on this journey. It is truly an honor to work with him on a book that I used extensively as resident and neurologist, and have recommended to countless students and veterinarians. By working on this book over the past few years, it became clear that no one edits a textbook for financial reasons! Those that have the vision to do this, do so sacrificing their personal and professional time to benefit their profession and their patients. Curtis had the vision to do this 12 years ago and I applaud him for that. This third edition is an evolution of his dedication and commitment to the veterinary profession. I cannot thank him enough for giving me the opportunity to assist him in such a noble task.

About the Companion Website

This book is accompanied by a companion website:

www.wiley.com/go/dewey/neurology

The website includes:

- Videos
- Link to the University of Minnesota's Canine Brain Atlas

The password for the companion website is the last word in the caption for Figure 2.22.

CHAPTER 1

Signalment and History: The First Considerations

Curtis W. Dewey & Ronaldo C. da Costa

Introduction

When presented with a patient that is suspected of having a neurologic disorder, the signalment (i.e. breed, age, and sex) and history are often helpful in guiding the clinician toward the most likely diagnosis. It is important to recognize, however, that this information is *adjunctive* to the neurologic examination. Properly weighting the importance of signalment and history will help avoid "tunnel vision" when devising diagnostic plans and implementing treatment strategies.

Signalment[1–3, 5]

The information in Table 1.1 and Table 1.2 provides a summary of suspected and confirmed breed predilections for various neurologic disorders. Knowledge of breed predilections can be very helpful when considering differential diagnoses, especially for uncommon presentations (e.g. neuropathies in juvenile patients). The clinician should be aware of the limitations of breed predilection tables, however. Newly discovered breed predilections or undiscovered breed predilections will not necessarily be represented in a table. In other words, breed predilection tables tend to increase in size with successive textbook editions. Also, breeds other than those reportedly predisposed to a particular disorder may occasionally be affected by that disorder. Finally, certain rare disorders may have only one or a few members of a certain breed reported in the literature. Since some of these disorders are inherited (e.g. lysosomal storage diseases), it may be assumed that the breed is at risk, despite low numbers of actually confirmed cases.

Certain disease categories tend to be more likely with specific age groups. In general, neoplasia (e.g. brain tumor) is more common in older patients. Congenital disorders (e.g. hydrocephalus) are more commonly encountered in juvenile patients. As with other aspects of patient signalment, there are no "absolutes" in regard to age for the various neurologic disorders encountered in clinical practice. Some congenital disorders tend to cause clinical dysfunction in adult patients (e.g. Chiari-like malformation (CLM)) and some neoplasms are typically encountered in young patients (e.g. nephroblastoma of the spinal cord).

There are very few neurologic disorders with sex predilections. One example would be muscular dystrophy in Golden Retrievers, an X-linked heritable disease.

History[4]

Obtaining a concise and accurate medical history as it pertains to a specific neurologic complaint is often crucial to guiding the diagnostic plan. It is important to allow the pet owner to elaborate on pertinent historical details; it is equally important to dissuade the pet owner from delving into historical details that have little or nothing to do with the chief clinical complaint. For example, an intricate account of events concerning a cranial cruciate ligament repair from 10 yrs ago is unlikely to be of value in a patient that presents for head-pressing and generalized seizure activity. Alternatively, pet owners often omit pertinent historical details. A pet owner may not necessarily think, for instance, that a change in the sound of their myasthenic dog's bark (dysphonia) is in any way related to the pelvic limb weakness that prompted them to seek medical advice. Although definitely related to the chief complaint, dysphonia may be regarded by the owner as an unrelated and clinically unimportant observation. In such instances, it is up to the clinician to ask specific questions that may help to elucidate the nature of the patient's neurologic disorder.

It is very important to get a specific history that does not involve *interpretation* of signs by the owner but rather descriptive facts related to the owner's *observation* of signs only. This is a common mistake in clinical neurology. For example, a client may observe a dog getting disoriented, falling into lateral recumbency, and paddling for a few seconds. This event could either be an acute vestibular episode or a seizure. Owners will likely interpret this event as a seizure. If the clinician accepts the owner's interpretation of the event as a seizure, he/she could follow an

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Table 1.1 Breed-associated neurologic abnormalities of dogs.

Afghan Hound	Acquired (idiopathic) laryngeal paralysis
	Hereditary myelopathy (leukodystrophy)
	Narcolepsy/cataplexy
	Retinal degeneration
Airedale Terrier	Cerebellar abiotrophy
	Cerebellar hypoplasia
	Congenital myasthenia gravis
	Degenerative lumbosacral stenosis
Akita	Acquired myasthenia gravis
	Congenital deafness
	Congenital vestibular disease (bilateral)
	Glycogenolysis (type III)
Alaskan Husky	Gangliosidosis (GM1)
	Mitochondrial encephalopathy (Leigh's disease, subacute necrotizing encephalopathy)
Alaskan Malamute	Hereditary polyneuropathy
	Myelodysplasia
	Muscular dystrophy
	Osteochondromatosis of the vertebrae
American Bulldog	Ceroid lipofuscinosis
American Eskimo dog	Congenital deafness
Australian Blue Heeler	Congenital deafness
Australian Cattle dog	Ceroid lipofuscinosis
	Congenital deafness
	Dermatomyositis
	Mitochondrial encephalomyelopathy
	Myotonia congenita
	Polioencephalomyelopathy
Australian Kelpie	Cerebellar abiotrophy
Australian Shepherd	Ceroid lipofuscinosis (CLN 6)
	Congenital deafness
Basset Hound	Cervical spondylomyelopathy (bony stenosis)
	Degenerative disc disease (type I)
	Globoid cell leukodystrophy (Krabbe's disease)
	Glycoproteinosis (Lafora's disease)
Bavarian Mountain dog	Cerebellar abiotrophy
Beagle	Agenesis vermis cerebellum
	Congenital deafness
	Congenital vestibular disease
	Cerebellar abiotrophy
	Globoid cell leukodystrophy (Krabbe's disease)
	Glycoproteinosis (Lafora's disease)
	Idiopathic epilepsy
	Intervertebral disc disease (type I)
	Methionine deficiency-related spinal myelinopathy
	Narcolepsy
	Necrotizing vasculitis (steroid meningitis, Beagle pain syndrome)
Beagle mix	Gangliosidosis (GM1)
Belgian Sheepdog	Congenital nystagmus
	Muscular dystrophy
Belgian Shepherd (Groenendael)	Muscular dystrophy
Belgian Shepherd (Malinois)	Degenerative myelopathy
	Degenerative lumbosacral stenosis
	Leukodystrophy/spongy degeneration (encephalomyelopathy; Belgian Shepherd (Malinois)/Shepherd mixed-breed dogs)
Belgian Shepherd (Tervuren)	Idiopathic epilepsy
	Muscular dystrophy
Bern Running dog	Cerebellar degeneration
Bernese Mountain dog	Aggression
	Cerebellar abiotrophy
	Degenerative myelopathy
	Epilepsy
	Hepatocerebellar degeneration
	Histiocytic sarcoma
	Hypomyelination/dysmyelination (dysmyelinogenesis)
	Meningitis/meningomyelitis (necrotizing vasculitis)
Bichon Frise	Atlantoaxial instability
	Caudal occipital malformation syndrome
	Congenital deafness
	Idiopathic tremor syndrome (steroid responsive)
Blue Tick Hound	Globoid cell leukodystrophy
Boerboel	Cervical spondylomyelopathy
Border Collie	Cerebellar abiotrophy
	Ceroid lipofuscinosis
	Congenital deafness
	Fibrocartilaginous embolic myelopathy
	Idiopathic epilepsy
	Sensory neuropathy
Border Terrier	Spongiform leukoencephalopathy
Borzoi	Cervical spondylomyelopathy
	Congenital deafness
Boston Terrier	Brain tumor (gliomas)
	Cerebellar abiotrophy
	Congenital deafness
	Congenital hydrocephalus
	Congenital vertebral malformation (hemivertebrae)
	Intracranial arachnoid cyst
	Muscular dystrophy
	Myelodysplasia
	Vermian hypoplasia
Bouvier des Flandres	Distal sensorimotor polyneuropathy
	Hereditary laryngeal paralysis
	Muscular dystrophy
	Pharyngeal/esophageal myopathy
Boxer dog	Autoimmune polymyositis (+/– paraneoplastic)
	Congenital deafness
	Corticosteroid-responsive (aseptic) meningitis
	Degenerative myelopathy
	Disseminated idiopathic skeletal hyperostosis (DISH)
	Head-bobbing (suspected dyskinesia)
	Neuroaxonal dystrophy
	Neuronal vacuolation
	Pilonidal (dermoid) sinus
	Primary brain tumor (glioma, meningioma)
	Progressive axonopathy
	Sensory neuropathy
	Spondylosis deformans
Briquet Griffon Vendéen	Spinal muscular atrophy (motor neuron disease)

Table 1.1 (*Continued*)

Brittany Spaniel	Cerebellar abiotrophy (late onset)
	Muscular dystrophy
	Sensory ganglioradiculitis
	Spinal muscular atrophy
	Spinocerebellar degeneration
Brussels Griffon	Chiari-like malformation (CLM)
Bull Mastiff	Cerebellar abiotrophy
	Cervical spondylomyelopathy
	Extradural synovial cyst
	Leukodystrophy/spongiform degeneration
Bull Terrier	Cerebellar abiotrophy
	Congenital deafness
	Hereditary laryngeal paralysis
	Hyperkinesis
	Tail chasing
Cairn Terrier	Globoid cell leukodystrophy
	Hydrocephalus
	Portosystemic shunt (hepatic encephalopathy)
	Spinal muscular atrophy (motor neuron disease)
Cardigan Welsh Corgi	Congenital deafness
	Sensory ganglioradiculitis
Catahoula Leopard dog	Congenital deafness
Cavalier King Charles Spaniel	Chiari-like malformation (CLM)
	Cerebellar infarct
	Congenital deafness
	Dorsolateral vertebral canal stenosis and compression at C2–C3
	Episodic muscle hypertonicity ("falling cavaliers"—probable dyskinesia)
	Femoral thromboembolism
	Fly chasing behavior
	Idiopathic epilepsy
	Primary secretory otitis media
Chihuahua	Atlantoaxial instability
	Ceroid lipofuscinosis
	Congenital deafness
	Congenital hydrocephalus
	Muscular dystrophy
	Necrotizing meningoencephalitis
	Neuroaxonal dystrophy
Chinese Crested	Cerebellar abiotrophy
Chow Chow	Cerebellar hypoplasia
	Congenital deafness
	Hypomyelination/dysmyelination (dysmyelinogenesis)
	Myotonia congenita
Clumber Spaniel	Cerebellar abiotrophy
	Mitochondrial myopathy
Cocker Spaniel	Cerebellar abiotrophy
	Ceroid lipofuscinosis
	Congenital deafness
	Congenital vestibular disease (English)
	Cryptococcosis (American)
	Hydrocephalus
	Idiopathic facial nerve paralysis
	Intervertebral disc disease (type I)
	Juvenile epilepsy
	Leukodystrophy/spongiform degeneration

Table 1.1 (*Continued*)

	Multisystem neuronal degeneration (red-haired)
	Muscular dystrophy
	Myopathy (lipid storage, mitochondrial, phosphofructokinase deficiency)
	Myotonia congenita
Collie (rough-coated)	Cerebellar abiotrophy
	Dermatomyositis
	Optic nerve hypoplasia
	Sensory trigeminal neuropathy
Collie (scotch)	Congenital deafness
	Dermatomyositis
	Distal polyneuropathy
Collie (smooth-coated)	Congenital deafness
	Dermatomyositis
	Neuroaxonal dystrophy
	Spinal muscular atrophy
Coton de Tuléar	Cerebellar abiotrophy (two forms)
Dachshund	Cerebellar abiotrophy
	Ceroid lipofuscinosis
	Congenital deafness (dappled)
	Glycoproteinosis
	Idiopathic epilepsy
	Intervertebral disc disease (type I)
	Mucopolysaccharidosis (type III; wire-haired)
	Myasthenia gravis (congenital, acquired)
	Narcolepsy/cataplexy
	Neuronal glycoproteinosis (Lafora's disease)
	Sensory neuropathy (long-haired)
Dalmatian	Ceroid lipofuscinosis
	Cervical spondylomyelopathy
	Congenital deafness
	Episodic muscle hypertonicity ("cramp")
	Hypomyelination/dysmyelination (dysmyelinogenesis)
	Laryngeal paralysis/polyneuropathy complex
	Leukodystrophy/spongy degeneration
Doberman Pinscher	Cervical spondylomyelopathy
	Congenital deafness
	Congenital vestibular disease (uni or bilateral)
	Dancing Doberman disease
	Idiopathic head tremor
	Idiopathic self-mutilation (sensory neuropathy)
	Immune mediated myositis
	Narcolepsy/Cataplexy
Dogo Argentino	Congenital deafness
	Laryngeal paralysis/polyneuropathy complex
Dogue de Bordeaux	Cranial thoracic stenosis
English Bulldog	Cerebellar abiotrophy
	Congenital deafness
	Congenital vertebral malformation (Hemivertebra)
	Hydrocephalus
	Idiopathic head tremor
	Sacrococcygeal malformation
	Spina bifida

(*continued*)

Table 1.1 (*Continued*)

English Foxhound	Methionine deficiency-related spinal myelinopathy (Hound ataxia)
English Pointer	Cerebellar abiotrophy
	Sensory neuropathy (automutilation)
	Spinal muscular atrophy
English Setter	Ceroid lipofuscinosis
	Congenital deafness
Fila Brasileiro	Intervertebral disc disease (type II)
Fox Terrier	Congenital deafness
	Myasthenia gravis (congenital)
	Spinocerebellar degeneration
French Bulldog	Arachnoid diverticulum
	Congenital deafness
	Congenital vertebral malformation (Hemivertebrae)
	Idiopathic head tremor
Gammel Dansk Honsehund	Congenital myasthenic syndrome (presynaptic)
German Shepherd dog	Acquired myasthenia gravis
	Autoimmune polymyositis
	Cervical spondylomyelopathy
	Congenital deafness
	Congenital megaesophagus
	Congenital vestibular disease
	Cranial thoracic disc disease (protrusion)
	Degenerative lumbosacral stenosis
	Degenerative myelopathy
	Fibrotic myopathy
	Giant axonal neuropathy
	Hereditary laryngeal paralysis (white coat)
	Idiopathic epilepsy
	Intervertebral disc disease (type II)
	Masticatory myositis
	Mitochondrial myopathy
	Mucopolysaccharidosis
	Nephroblastoma
	Neuroaxonal dystrophy
	Spinal muscular atrophy (motor neuron disease)
German Shorthaired Pointer	Coccygeal muscle injury
	Gangliosidosis (GM2)
	Hemivertebra
	Pyogranulomatous meningoencephalomyelitis
	Sensory neuropathy
Golden Retriever	Acquired myasthenia gravis
	Eosinophilic meningoencephalitis
	Extraocular myositis
	Horner's syndrome
	Hypomyelinating polyneuropathy
	Idiopathic epilepsy
	Multiple cartilaginous exostoses
	Multisystem axonopathy and neuronopathy
	Muscular dystrophy
	Myasthenia gravis
	Primary brain tumor (meningioma)
	Sensory neuropathy
Gordon Setter	Cerebellar abiotrophy
Great Dane	Cervical spondylomyelopathy
	Inherited (noninflammatory/central core) myopathy
	Congenital deafness
	Congenital myotonia
	Disseminated idiopathic skeletal hyperostosis (DISH)
	Distal symmetric polyneuropathy
	Extradural synovial cyst
	Fibrocartilaginous embolic myelopathy (FCE)
	Myasthenia gravis
	Nemaline myopathy
	Primary orthostatic tremor
	Spinal muscular atrophy (Great Dane crosses)
Great Pyrenees (Pyrenean Mountain dog)	Congenital deafness
	Laryngeal paralysis/polyneuropathy complex
	Optic nerve hypoplasia
Greyhound	Cervical disc disease
	Congenital deafness
	Congenital megaesophagus
	Corticosteroid (aseptic) responsive meningitis
	Degenerative lumbosacral stenosis
	Exertional myopathy
	Fibrocartilaginous embolic myelopathy
	Thalamic infarct
Harrier	Cerebellar abiotrophy (Finnish)
	Methionine deficiency-related spinal myelinopathy
Hound	Methionine deficiency-related spinal myelinopathy
	Polyradiculoneuritis
Hovawart	Degenerative myelopathy
Ibizan Hound	Axonopathy (central and peripheral)
	Congenital deafness
Irish Setter	Acquired (idiopathic) laryngeal paralysis
	Cerebellar abiotrophy
	Ceroid lipofuscinosis
	Congenital megaesophagus
	Hereditary quadriplegia and amblyopia
	Idiopathic epilepsy
	Laryngeal paralysis (acquired idiopathic)
	Lissencephaly
Irish Terrier	Muscular dystrophy
Irish Wolfhound	Cervical spondylomyelopathy
	Fibrocartilaginous embolic myelopathy (juvenile)
	Spinal epidural empyema
Italian Greyhound	Cervical intervertebral disc disease
	Congenital deafness
Italian Spinone	Cerebellar abiotrophy
Jack Russell Terrier	Congenital deafness
	Congenital myasthenia gravis
	Hereditary ataxia
	Intracranial arachnoid cyst
	Mitochondrial encephalopathy
	Myokymia/neuromyotonia
	Myotonia congenita
	Neuroaxonal dystrophy
	Sensory neuropathy
Japanese Chin	Atlantoaxial instability
Japanese Spaniel	Gangliosidosis (GM2)
Japanese Spitz	Muscular dystrophy
Keeshond	Idiopathic epilepsy

Table 1.1 (*Continued*)

Kerry Blue Terrier	Cerebellar abiotrophy
	Degenerative myelopathy
	Multisystem degeneration
Kuvasz	Congenital deafness
Labrador Retriever	Acquired (idiopathic) laryngeal paralysis
	Cerebellar abiotrophy
	Congenital deafness
	Exercise intolerance-collapse syndrome
	Idiopathic epilepsy
	Labrador Retriever (central) axonopathy
	Labrador Retriever myopathy
	Leukodystrophy/spongy degeneration (encephalomyelopathy)
	Lumbosacral stenosis
	Myasthenia gravis (acquired)
	Myotonia congenital
	Narcolepsy/cataplexy
	Organic aciduria
	Reflex myoclonus
Lagotto Romagnolo dog	Cerebellar abiotrophy
	Idiopathic epilepsy
Leonberger dog	Laryngeal paralysis/polyneuropathy complex
	Leukoencephalomyelopathy
Lhasa Apso	Congenital hydrocephalus
	Lissencephaly
Lurcher Hound	Hypomyelination/dysmyelination (dysmyelinogenesis)
Malinois Shepherd cross	Spongiform degeneration (gray matter)
Maltese	Chiari-like malformation (CLM)
	Congenital deafness
	Congenital hydrocephalus
	Idiopathic (steroid responsive) tremor syndrome
	Necrotizing meningoencephalitis
	Organic aciduria
Mastiff	Cerebellar abiotrophy
	Cervical spondylomyelopathy
	Extradural synovial cyst
Miniature Pinscher	Atlantoaxial subluxation
	Congenital deafness
	Idiopathic tremor syndrome
	Mucopolysaccharidosis (type 2)
Miniature Poodle	Congenital deafness
Newfoundland	Myasthenia gravis
	Polymyositis
Norwegian Hound (Dunker)	Congenital deafness
Norwich Terrier	Episodic muscle hypertonicity
Nova Scotia Duck Tolling Retriever	Congenital deafness
	Idiopathic epilepsy
	Steroid responsive meningitis arteritis
Old English Sheepdog	Cerebellar abiotrophy
	Congenital deafness
	Mitochondrial myopathy
	Muscular dystrophy
Papillon	Congenital deafness
	Neuroaxonal dystrophy
Pekingese	Atlantoaxial instability
	Congenital hydrocephalus
	Intervertebral disc disease (type I)
	Optic nerve hypoplasia
Pembroke Welsh Corgi	Degenerative myelopathy
	Dermatomyositis
	Intervertebral disc disease (type I)
	Sensory ganglioradiculoneuritis
Pit Bull Terrier	Congenital deafness
Plott Hound	Mucopolysaccharidosis (type 1)
Pointer	Congenital deafness
	Spinal muscular atrophy
Pomeranian	Atlantoaxial instability
	Chiari-like malformation (CLM)
	Congenital hydrocephalus
	Globoid cell leukodystrophy
	Intracranial arachnoid cyst
Poodle (Miniature)	Atlantoaxial instability
	Chiari-like malformation (CLM)
	Cerebellar abiotrophy
	Degenerative myelopathy
	Glycoproteinosis
	Intervertebral disc disease (type I)
	Leukodystrophy/spongy degeneration (brain)
	Narcolepsy/cataplexy
	Optic nerve hypoplasia
	Sphingomyelinosis
	Spinal cord leukodystrophy
Poodle (Standard)	Idiopathic epilepsy
	Organic aciduria (neonatal encephalopathy)
	Polymicrogyria (neuronal migration disorder)
Poodle (Toy)	Atlantoaxial instability
	Congenital hydrocephalus
Portuguese Water dog	Gangliosidosis (GM1)
Pug dog	Arachnoid diverticulum
	Chiari-like malformation (CLM)
	Congenital vertebral malformation (hemivertebra)
	Degenerative myelopathy
	Intracranial arachnoid cyst
	Necrotizing meningoencephalitis
Puli	Congenital deafness
Queensland Blue Heeler	Ceroid lipofuscinosis
Rat Terrier	Muscular dystrophy
Rhodesian Ridgeback	Cerebellar abiotrophy
	Congenital deafness
	Degenerative myelopathy
	Dermoid (pilonidal) sinus
	Myotonia congenital
Rottweiler	Cervical spondylomyelopathy
	Congenital deafness
	Distal sensorimotor polyneuropathy
	Laryngeal paralysis-polyneuropathy complex
	Leukoencephalomyelopathy
	Myopathy (distal)
	Neuroaxonal dystrophy
	Neuronal vacuolation
	Spinal arachnoid cyst
	Spinal muscular atrophy (motor neuron disease)

(*continued*)

Table 1.1 (*Continued*)

Russian Wolfhound	Optic nerve hypoplasia
Saint Bernard	Acquired (idiopathic) laryngeal paralysis
	Congenital deafness
	Episodic dyscontrol (rage syndrome)
	Idiopathic epilepsy
	Narcolepsy/cataplexy
Saluki	Ceroid lipofuscinosis
	Leukodystrophy
	Spinal muscular atrophy (motor neuron disease)
	Spongiform degeneration (gray matter)
Samoyed	Cerebellar abiotrophy
	Cerebellar hypoplasia/lissencephaly
	Congenital myasthenia gravis
	Hypomyelination/dysmyelination (dysmyelinogenesis)
	Leukodystrophy/spongiform degeneration
	Muscular dystrophy
	Myotonia congenital (Samoyed cross-breed)
Schnauzer (Giant)	Congenital deafness
	Narcolepsy/cataplexy
Schnauzer (Miniature)	Congenital megaesophagus
	Fibrocartilaginous embolic myelopathy
	Hyperlipidemia (seizures)
	Idiopathic adipsia
	Idiopathic epilepsy
	Intervertebral disc disease (Type I)
	Muscular dystrophy
	Myotonia congenita
Scottish Deerhound	Primary orthostatic tremor
	Vertebral articular process (facet) hypertrophy
Scottish Terrier	Cerebellar abiotrophy
	Congenital deafness
	Episodic muscle hypertonicity (Scotty cramp)
	Leukodystrophy/spongy degeneration (fibrinoid leukodystrophy/Alexander's disease)
	Sensory ganglioradiculitis
Sealyham Terrier	Congenital deafness
Shar Pei	Congenital megaesophagus
Shetland Sheepdog	Congenital deafness
	Dermatomyositis
	Hyperlipidemia (seizures)
	Mitochondrial encephalopathy (Kearnes–Sayre syndrome)
	Spongiform encephalopathy
Shih Tzu	Atlantoaxial instability
	Intervertebral disc disease
	Intracranial arachnoid cyst
Shiloh Shepherd dog	Vertebral articular process (facet) hypertrophy
Shropshire Terrier	Congenital deafness
Siberian Husky	Congenital deafness
	Degenerative myelopathy
	Hereditary laryngeal paralysis
	Sensory ganglioradiculoneuritis
Silky Terrier	Leukodystrophy/spongy degeneration

Table 1.1 (*Continued*)

Smooth-coated Fox Terrier	Congenital myasthenia gravis
	Hereditary ataxia
Soft-coated Wheaten Terrier	Congenital deafness
	Degenerative myelopathy
	Dyskinesia (movement disorder)
Springer Spaniel	Congenital deafness
	Congenital myasthenia gravis
	Episodic dyscontrol (rage syndrome)
	Hypomyelination/dysmyelination (dysmyelinogenesis)
	Fucosidosis
Staffordshire Terrier	Chiari-like malformation (CLM)
	Cerebellar abiotrophy
	Myotonia congenita
	Organic aciduria (L-2-hydroxyglutaric aciduria)
Sussex Spaniel	Congenital deafness
	Mitochondrial myopathy
Swedish Lapland dog	Glycogenosis type II
	Spinal muscular atrophy (motor neuron disease)
Sydney Silky Terrier	Glucocerebrosidosis
Terrier Mix	Multiple cartilaginous exostoses
Tibetan Mastiff	Hypertrophic neuropathy
Tibetan Spaniel	Congenital deafness
Tibetan Terrier	Ceroid lipofuscinosis
	Congenital deafness
Toy Poodle	Congenital deafness
Walker Hound	Congenital deafness
	Mononeuropathy
Weimaraner	Cerebellar hypoplasia
	Hypomyelination/dysmyelination (dysmyelinogenesis)
	Spinal dysraphism
West Highland White Terrier	Congenital deafness
	Corticosteroid responsive (idiopathic) tremor syndrome
	Globoid cell leukodystrophy
	Organic aciduria (L-2-hydroxyglutaric aciduria)
Whippet	Congenital deafness
	Sensory neuropathy
Wire-haired Fox Terrier	Cerebellar abiotrophy
	Congenital deafness
	Congenital megaesophagus
	Lissencephaly
Yorkshire Terrier	Atlantoaxial instability
	Chiari-like malformation (CLM)
	Congenital deafness
	Congenital hydrocephalus
	Intervertebral disc disease (type I)
	Microvascular hepatic dysplasia
	Mitochondrial encephalopathy
	Myokymia/neuromyotonia
	Necrotizing leukoencephalitis
	Portosystemic shunt (hepatic encephalopathy)
Yugoslavian Sheepdog	Ceroid lipofuscinosis

Table 1.2 Breed-associated neurologic abnormalities of cats.

Abyssinian	Acquired myasthenia gravis
Balinese	Sphingomyelinosis (Niemann–Pick disease, type A)
Birman	Distal polyneuropathy
	Leukodystrophy/spongy degeneration
Burmese	Congenital vestibular disease
	Hypokalemic myopathy
	Meningoencephalocele
Cornish Rex	Congenital deafness (white coat)
Devon Rex	Congenital deafness (white coat)
	Muscular dystrophy
Domestic Short-haired cat	Acquired (idiopathic) laryngeal paralysis
	Ceroid lipofuscinosis
	Globoid cell leukodystrophy (Krabbe's disease)
	Gangliosidosis (GM1)
	Gangliosidosis (GM2)
	Hyperoxaluria
	Mannosidosis
	Metachromatic leukodystrophy
	Mucolipidosis II (I-cell disease)
	Mucopolysaccharidosis (type I) (Hurler's syndrome)
	Mucopolysaccharidosis (type VI) (Maroteaux–Lamy syndrome)
	Muscular dystrophy
	Neuroaxonal dystrophy
	Sphingomyelinosis (Niemann–Pick disease, type C)
	Spinal muscular atrophy
Domestic Tri-colored cat	Neuroaxonal dystrophy
Egyptian Mau	Leukodystrophy/spongy degeneration
Exotic Short Hair	Congenital deafness (white coat)
Himalayan	Esophageal hypomotility
	Fibrotic myopathy
	Pendular nystagmus (congenital)
Korat	Gangliosidosis (GM1)
	Laryngeal paralysis
	Lissencephaly
Manx	Congenital deafness (white -coat Manx)
	Sacrocaudal (sacrococcygeal) dysgenesis
Norwegian Forest cat	Glycogenosis (type IV)
Persian	Cerebellar abiotrophy (late onset)
	Congenital deafness (white coat)
	Mannosidosis-alpha
Rex	Myopathy
Scottish Fold	Congenital deafness (white coat)
Siamese	Cerebellar abiotrophy
	Ceroid lipofuscinosis
	Congenital vestibular disease
	Gangliosidosis (GM1)
	Hypomyelination/dysmyelination (dysmyelinogenesis)
	Mucopolysaccharidosis
	Muscular dystrophy
	Myasthenia gravis
	Pendular nystagmus (congenital)
	Sphingomyelinosis
Somali	Acquired myasthenia gravis
Sphynx	Muscular dystrophy
Turkish Angora	Congenital deafness (white coat)

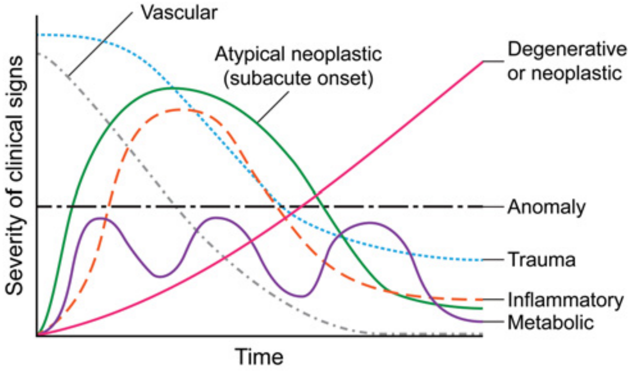

Figure 1.1 Sign–time graph of neurologic diseases. This applies to the majority of cases but there are exceptions in essentially all categories. (The Ohio State University. Reproduced with permission.)

erroneous diagnostic approach. It is important to ask the client to simply state the signs he/she observed, without interpretative connotations, leaving the interpretation of all signs to the clinician.

For any episodic event or signs seen only intermittently, it is very helpful to have a video recording of the event. In this day, video recording is easily available, and in cases where the history is unclear and the neurologic signs inconclusive, it is important to review videos showing the events/episodes to decide on the diagnostic approach.

The neurologic history should allow the clinician to obtain information regarding the possible etiologies. In general, there are expected time course patterns characteristic of certain categories of neurologic disease. Ischemic/vascular and traumatic disorders tend to have peracute onsets (within minutes to a few hours) and often progress minimally or not at all after the initial 24 hrs of onset of clinical signs. Inflammatory/infectious disorders tend to have acute onsets (hours to days) with fairly rapid progression if not aggressively treated. Neoplastic and degenerative disorders often display insidious onset of clinical dysfunction (days to several months) with slower progression of clinical signs (Fig. 1.1). Some degenerative disorders (e.g. type II disc disease) may progress slowly over several years. Many anomalous disorders are characterized by static disease courses, that is the clinical abnormality is recognized at a young age and the disease is nonprogressive. Finally, there are some neurologic disorders that are typically episodic in nature, such as idiopathic epilepsy. As with signalment information, the nature of disease onset and progression is often helpful in ranking differential diagnoses in terms of likelihood for a specific patient, but should be considered as a rough guideline only. There are numerous and notable exceptions to the expectations outlined above. For example, spinal lymphoma in cats is characterized by acute onset of clinical signs.

The history can also provide therapeutic and prognostic information. For example, a large-breed dog with progressive proprioceptive ataxia and paraparesis that received treatment with corticosteroids and showed no improvement would have degenerative myelopathy as a higher diagnostic consideration, as opposed to one that responded favorably to steroid treatment. Similarly, the duration of clinical signs could provide prognostic consideration. The prognosis for a deep pain negative (absent nociception) paraplegic dog for 2 wks is significantly worse than a dog that has similar signs for 12 hrs.

Listed below are examples of questions that are provided to students at the Ohio State University to guide them in the history taking of patients with neurologic signs.

General questions applicable for most conditions

- When did you first observe the signs?
- Did they appear quickly or slowly (acute or chronic)?
- Are the signs progressing?
- How is the behavior/personality at home? Did you notice any change?
- Have you noticed any mentation changes at home (e.g. quiet, dull, somnolent)?
- Is he/she or was he/she on any medication (try to learn dose and frequency)?
- Have you had any tests (blood work, radiographs, etc.) done for this problem?
- Have you noticed any other sign?
- Does he/she have, or has he/she had, any other medical problems?
- Has he/she had any vomiting, diarrhea, coughing, sneezing?
- How is he/she eating or drinking? What does he/she eat?
- Is he/she updated on vaccines?
- Is he/she indoors/outdoors? Did you travel with him/her?

Questions pertinent to spinal problems (gait problems)

- What is the problem (present complaint)?
- When did you first observe the signs?
- Which limb(s) is (are) affected?
- Did the signs appear quickly or slowly (acute or chronic)?
- Are the signs progressing?
- Do you think he/she is in pain? If so, where?
- If yes, why do you think he/she is in pain?
- Any possibility of trauma? How?
- Has he/she had any similar episodes?
- Are you giving him/her any medicine for this problem?
- Have you noticed any response to treatment(s)?
- Have you had any tests (blood work, radiographs, etc.) done for this problem?

Questions pertinent to seizures and episodic events

When phrasing the questions, be careful to not repeat and reinforce the idea of a specific event like a seizure. Refer to any episodic event as "episodes" or "events."

- Can you please describe the *event* that you observed in details (describe the entire event, i.e. signs before, during, and after the event)?
- How was the muscle tone during the event (e.g. flaccid/floppy or rigid/stiff)?
- Did you notice anything happening on his/her face (e.g. drooling, facial/eyelid twitching)?
- Was the head involved in the episode (e.g. tremors, tilting)?
- Did you observe any evidence of lateralizing signs (one eye/limb more affected)?
- Have you seen any drooling, urination, or defecation associated with the event?
- Was he/she responsive and aware during the event?
- When was the event first noted?
- What is the frequency of these events?
- How long do these events last?
- Are they increasing in frequency or duration?
- How is your dog after the event (evidence of postictal signs)?
- Are the events associated with anything (stress, sleeping, feeding, etc.)?
- How is their behavior/personality at home? Did you notice any change?
- Have you noticed any mentation changes at home (e.g. quiet, dull, somnolent)?
- Is he/she on any anticonvulsant, or any other, medication (try to learn specific drug, dose, and frequency)?
- If on anticonvulsants, ask for results of serum levels.
- Have you noticed any other signs?
- Is he/she indoors/outdoors? Any possible toxin or drug exposure?
- Did you travel with him/her?
- Any family history of the same event?

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CHAPTER 2

Performing the Neurologic Examination

Curtis W. Dewey, Ronaldo C. da Costa, & William B. Thomas

Introduction

A thorough neurologic examination can be performed in 10 to 15 min. The main components are evaluation of mental status and behavior, gait and postural reactions, cranial nerves, spinal reflexes, palpation, and pain perception. General observation of mental status, posture, attitude, and gait is performed while taking the history. Once the history is clarified, the remainder of the examination is completed. Based on the presenting complaint, it may be necessary to modify portions of the examination. For example, a tetraplegic patient after being hit by a car is not subjected to postural reactions for fear of exacerbating a possible unstable cervical injury. Start with procedures least likely to upset the patient. Disagreeable or painful procedures, such as palpating painful areas, are left until the end of the examination. If the clinician upsets the patient early on, it may be difficult to complete the examination. Also, once pain is elicited, the patient will often anticipate further painful stimuli, making it difficult to determine if other procedures are truly painful. The purposes of the various procedures are explained to the client as the examination proceeds. This lessens the client's distress when he or she observes unfamiliar procedures performed on a pet. Some abnormalities will be blatantly obvious, whereas others will be subtle. A subtle abnormality is still an abnormality. There is a tendency for subtle abnormalities to be chalked up to anything but a neurologic lesion; trust your neurologic findings.

Tools for performing the neurologic examination

A pleximeter (rubber hammer) is used to test myotatic reflexes. Other instruments, such as scissors, are not recommended because these do not provide a consistent stimulus and appear less professional to the client. A hemostat is often useful when testing for nociception (deep pain perception) or eliciting a cutaneous trunci reflex. A strong light source is necessary to elicit pupillary light reflexes in excited dogs and cats. A cotton-tipped applicator or a piece of cotton to cover a hemostat is useful to evaluate the nasal sensation. Finally, a moistened cotton-tipped applicator stick is recommended for performing the corneal reflex. A light touch with your fingertip is acceptable, but if a client is watching you, it may appear that you are poking the pet in the eye.

Performing the neurologic examination[1–12]

A. Mental status and behavior (Video 1)
   1. Before handling the patient, let the patient have the run of the examination room, if ambulatory, and observe the patient's reaction to the surroundings.
   2. Mental status should be evaluated in terms of both level and content of consciousness.
      a. Level of consciousness
         1. Alert—the patient responds appropriately to environmental stimuli.
         2. Depressed/obtunded—the animal is drowsy but arousable. Depressed/obtunded dogs and cats are typically inattentive and display little spontaneous activity.
         3. Stuporous—the patient is in a sleep state, but arousable with a strong stimulus.
         4. Comatose—the patient is unconscious and cannot be aroused even with painful stimuli.
      b. Content of consciousness
         1. Refers to the quality of consciousness
         2. Dementia/delirium—the patient has an alert level of consciousness, but exhibits abnormal behavior and responds inappropriately to stimuli.
      c. Mental status is a function of the ascending reticular activating system (ARAS) that extends over the entire length of the brain stem to activate the cortex. Brainstem disease can cause changes in mental status.
   3. Abnormal behavior is identified by comparing the patient's behavior to expected behavior for animals of a similar breed and age. The client is often able to bring

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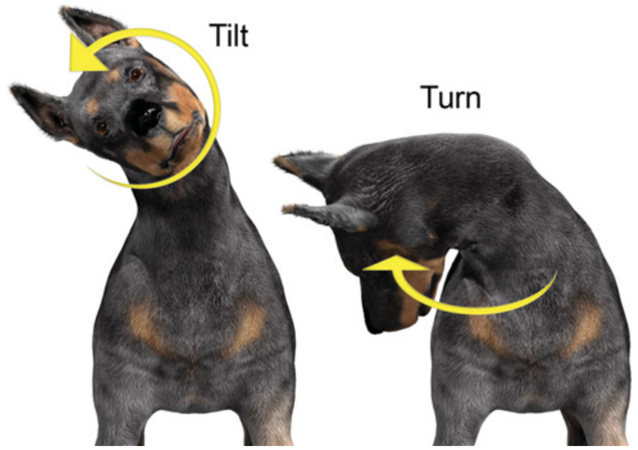


Figure 2.1 A head tilt posture should be differentiated from head turn. Head tilt indicates vestibular disease, whereas head turn suggests a forebrain (thalamocortical) lesion. (The Ohio State University. Reproduced with permission.)

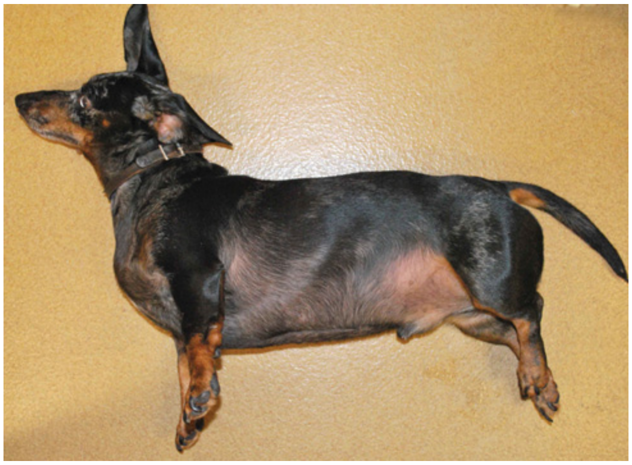


Figure 2.2 Schiff–Sherrington posture in a Dachshund with thoracolumbar intervertebral extrusion.

subtle changes in behavior to the veterinarian's attention. Behavioral changes may be an indication of forebrain (cortical) disease.

B. Attitude/posture

1. Attitude refers to the position of the eyes and head in relation to the body. Abnormal head position is often manifested as a head tilt or a head turn (Fig. 2.1). In a patient with a head tilt, one ear is held lower than the other. It is also important to make sure that the eye in the affect side is also lower than the other, because sometimes ear diseases can cause a dropped ear without an associated head tilt. Unilateral vestibular dysfunction will often cause a head tilt. When an animal develops a head turn, the head is held level, but the nose is turned right or left. Animals with forebrain lesions may tend to turn their heads and circle in one direction. (Videos 7 and 8).
2. Posture is the position of the body with respect to gravity. Abnormal postures, such as a wide-based stance, are common in dogs and cats with neurologic disease. Several classic abnormal postures indicative of neurologic dysfunction have been described.
   a. Decerebrate rigidity—due to a brain-stem lesion and characterized by extension of all limbs and sometimes opisthotonus (dorsiflexion of the head and neck). A decreased level of consciousness (often stupor or coma) usually accompanies this posture.
   b. Decerebellate rigidity—due to an acute cerebellar lesion and characterized by opisthotonus, thoracic limb extension, and flexion of the hips. Consciousness is not impaired due to lack of brain-stem involvement.
   c. Schiff–Sherrington posture—frequently encountered in veterinary practice and caused by a lesion in the thoracic or lumbar spinal cord segments. Extension of the thoracic limbs (best appreciated in lateral recumbency) with paralysis of the pelvic limbs characterizes Schiff–Sherrington posture (Fig. 2.2).
   d. Kyphosis, lordosis and scoliosis—abnormal spinal postures frequently observed. A kyphotic posture is commonly seen with painful conditions of the thoracolumbar vertebral column. Scoliosis may be seen with congenital malformation and in cases of caudal occipital malformation (Chiari-like syndrome and syringomyelia). Lordosis is infrequently seen and reflects weakness of the epaxial musculature.
   e. Abnormal limb postures—plantigrade or palmigrade postures are used to describe an abnormal posture of the pelvic or thoracic limb, respectively (Fig. 2.3). These postures are frequently seen in cases of neuromuscular diseases, primarily polyneuropathies, but can also be seen in patients with musculoskeletal diseases.

C. Gait (Video 2)

1. Lameness
   a. Limb pain can cause a limp when the patient tries to bear weight on a painful limb and then quickly plants the contralateral limb to relieve the pain. As a result, the stride of the painful limb is often shortened. When a single limb is severely painful, it is often carried. This is in contrast to a paretic limb, which is often dragged. Lameness is usually caused by orthopedic disease, but some neurologic lesions—such as attenuation or inflammation of a nerve root or spinal nerve by intervertebral disc extrusion or nerve sheath tumor—can cause lameness. This form of lameness is often referred to as a "root signature."
   b. Patients with bilateral limb pain, such as hip disease or ruptured cruciate ligaments, may not walk at all or

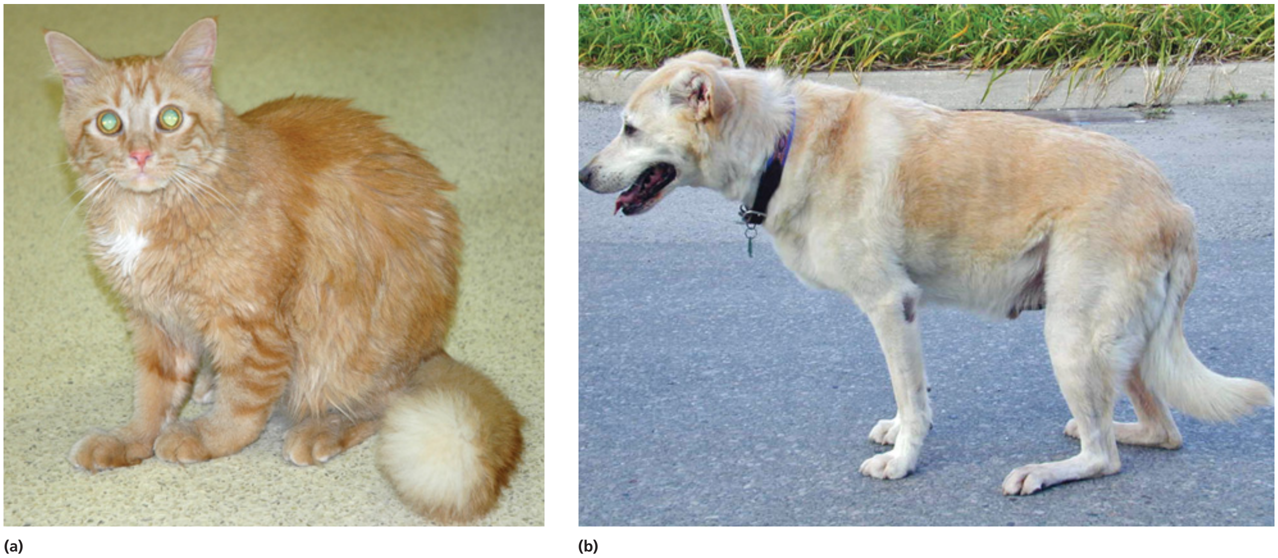


Figure 2.3 (A) Palmigrade posture in a cat. (B) Plantigrade posture in a dog.

have short-strided, stilted gaits. This can mimic weakness due to neurologic disease.

- c. Lower motor neuron (LMN) weakness can cause a short-strided gait in the affected limb(s).

2. Ataxia—inability to perform normal, coordinated motor activity that is not caused by weakness, musculoskeletal problems, or abnormal movements, such as tremor. There are three types:
    - a. Sensory or proprioceptive ataxia (Videos 11, 26 and 27)
        1. Loss of the sense of limb and body position due to interruption of ascending proprioceptive pathways (primarily unconscious proprioception).
        2. Characterized by clumsiness and incoordination, resulting in a wide-based stance and a swaying gait. This type of ataxia is often seen in association with paresis. The stride of the affected limb(s) is often longer than normal and the toes may drag or scuff the ground.
        3. Caused by a lesion affecting primarily the white matter of the spinal cord (unconscious proprioceptive pathways).
    - b. Cerebellar ataxia (Videos 9 and 21)
        1. Inability to regulate the rate and range of movement (unconscious proprioception).
        2. Characterized by dysmetria, especially hypermetria—an overreaching, high-stepping gait.
        3. Caused by cerebellar disease or selective dysfunction of spinocerebellar tracts (less likely).
    - c. Vestibular ataxia (Videos 8, 19 and 20)
        1. Unilateral vestibular lesions cause leaning and falling to one side. Other signs of vestibular disease, such as head tilt and abnormal nystagmus, may be evident.
        2. With bilateral vestibular dysfunction, the patient maintains a crouched position, is reluctant to move, and exhibits side-to-side head movements, without an obvious head tilt (since both vestibular receptors and nuclei are affected).
3. Paresis/paralysis
   Paresis is a partial loss of voluntary movement. This is manifested as a decreased rate or range of motion, increased fatigability, decreased muscle tone, or limited ability to perform certain motor acts. Paralysis (plegia) is a complete loss of voluntary movement. Paresis or paralysis indicates a lesion of either the upper motor neuron (UMN) system or the lower motor neuron (LMN) system. It is not possible to discriminate between UMN weakness and LMN weakness based solely on the severity of the weakness.
4. Abnormal movements
    - a. Tremor—a rhythmical, oscillatory movement localized to one region of the body or generalized to involve the entire body. A terminal tremor, or intention tremor, occurs as the body part nears a target during goal-oriented movement. This is most evident as a head tremor when the patient attempts to sniff an object, eat, or drink. A postural tremor occurs as the limb or head is maintained against gravity.
    - b. Myotonia—delayed relaxation of muscle following voluntary contraction. Myotonia is manifested as muscle stiffness that is relieved by exercise. Attacks of myotonia may culminate in recumbency with rigid extension of the limbs. Some patients with myotonia will display “dimpling” of sustained indentation of affected muscle when percussed.
    - c. Myoclonus—a brief, shock-like muscle contraction producing a quick, jerking movement of a body part.

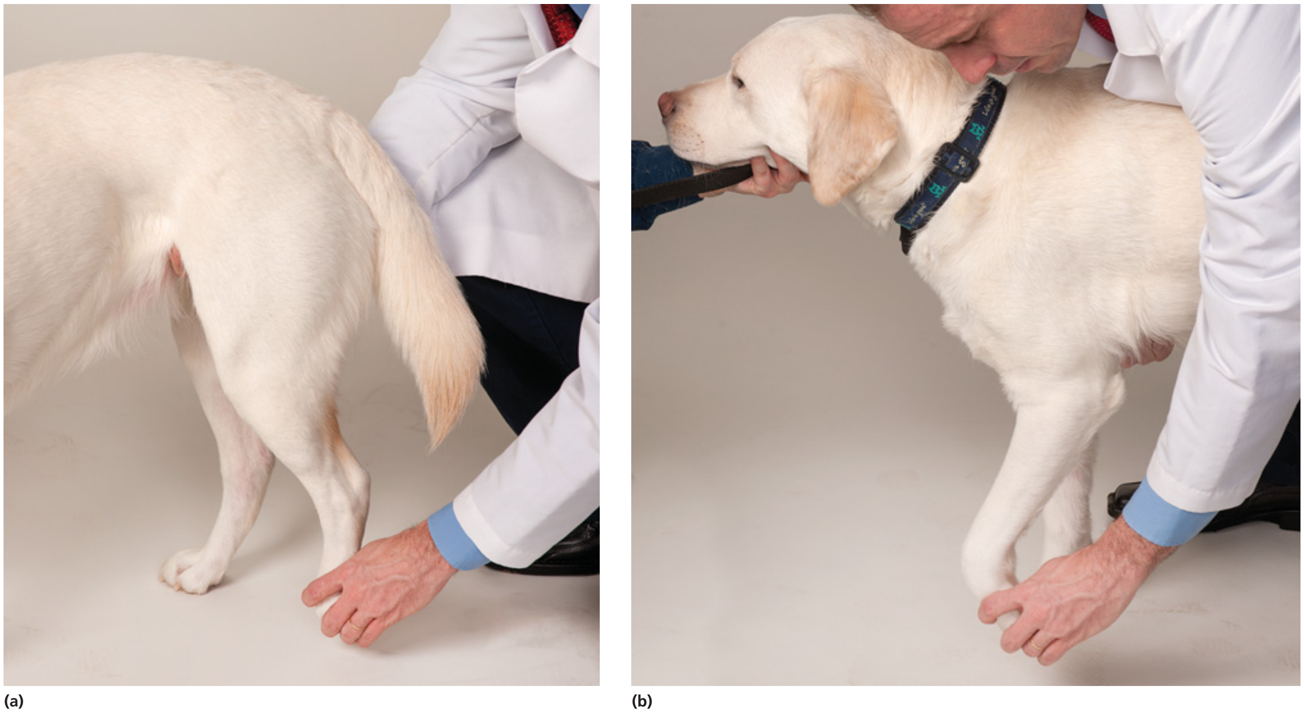
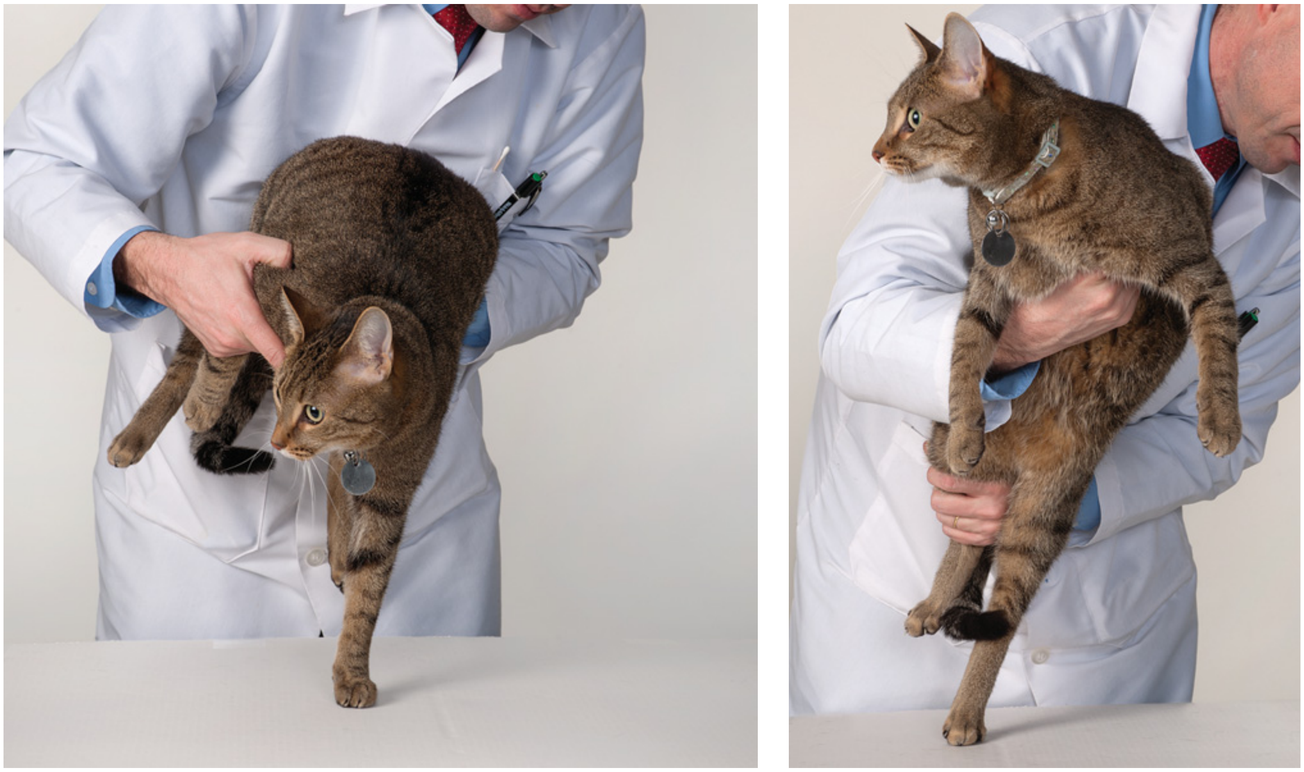

(a) (b)

Figure 2.4 Proprioceptive positioning is evaluated with the patient supported in a standing position in the pelvic (A) and thoracic limbs (B). Proper support of the patient is essential. The dorsal surface of the paw is placed on the floor without pushing it down. The patient should immediately replace the paw to a normal position.

D. Postural reactions (Video 3)

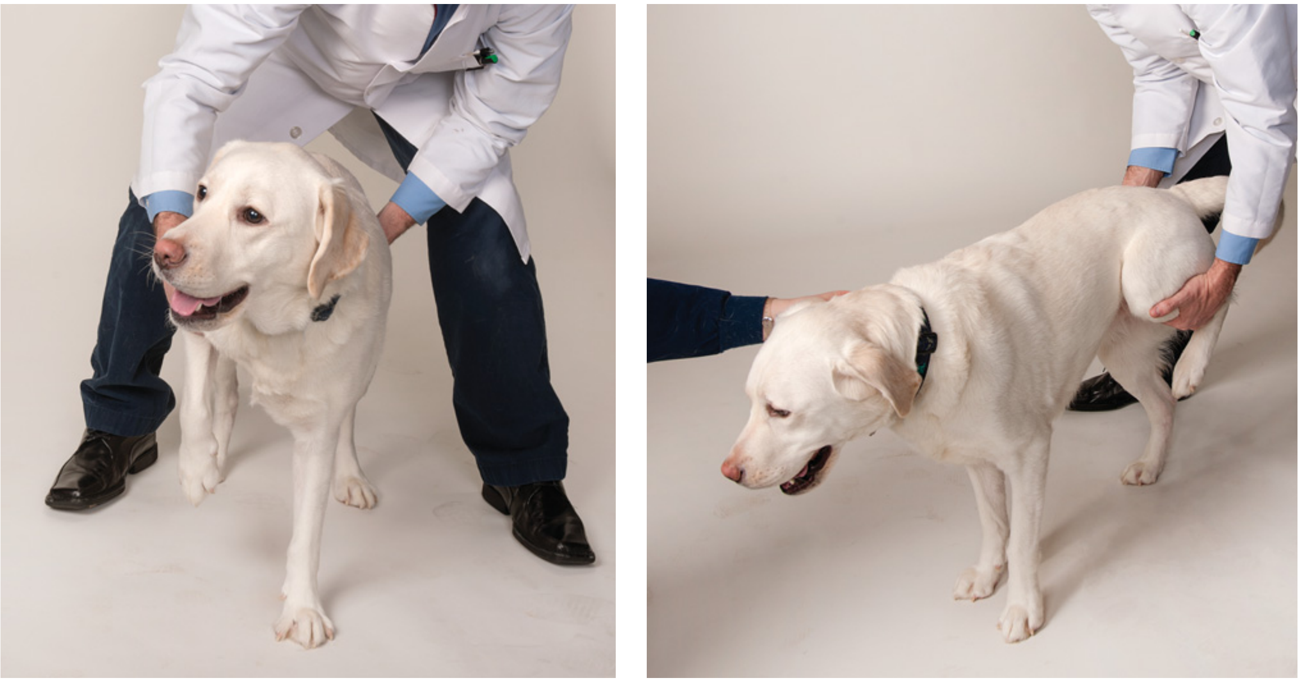
Postural reactions test the same neurologic pathways involved in gait, namely the proprioceptive and motor systems. Their main value is detecting subtle deficits or inconspicuous asymmetry that may not be obvious during the observation of gait. Postural reactions are also useful in discriminating between orthopedic and neurologic disorders. Frequently it is only necessary to perform two postural reaction tests: proprioceptive positioning and hopping.

1. Proprioceptive positioning
    a. Support the animal to avoid body tilt and turn one paw over so that the dorsal surface is in contact with the ground. The patient should immediately return the foot to a normal position (Fig. 2.4).
    b. When properly supported, most patients with orthopedic disease will have normal proprioceptive positioning. On the other hand, proprioceptive pathways are often compromised early in the course of neurologic diseases, so defects in proprioceptive positioning may be detected before there are obvious signs of weakness.
2. Hopping
    a. Hold the patient so that the patient's weight is supported by one limb and move the animal laterally. The amount of support and the technique are different in small dogs or cats (Fig. 2.5 A and B), compared to large dogs (Fig. 2.6 A and B). Normal animals will hop on the limb while keeping the foot under their body for support.
    b. Each limb is tested individually and responses on the left and right are compared. This is a sensitive test for subtle weakness or asymmetry.
3. Placing response
    a. The nonvisual (tactile) test is performed first. Cover the patient's eyes, pick the animal up, and move it toward the edge of a table. When the paw touches the table, the animal should immediately place the limb forward to rest the paw on the table surface (Fig. 2.7).
    b. Visual placing is tested similarly, except the patient's eyes are not covered. The normal response is to place the paws on the surface as the table is approached, before the paws make contact with the table. This test may detect visual deficiencies.
4. Hemiwalking, wheelbarrowing, and extensor postural thrust
    a. These tests can be performed if other postural reactions are equivocal.
    b. For hemiwalking, hold up the limbs on one side of the body and move the patient laterally (similarly to the technique demonstrated in Fig. 2.6). The normal reaction is as described for the hopping response.



(a) (b)

Figure 2.5 The hopping response in small dogs and cats is tested by lifting and supporting the patient such that most of its weight is borne on one limb. The patient is moved laterally to test the thoracic limb (A) and pelvic limb (B). Note how the support and position of the hands differ.



(a) (b)

Figure 2.6 The hopping response in large dogs can be tested by just lifting the contralateral limb and moving the patient laterally to test the thoracic limb (A) and pelvic limb (B). It is unnecessary to try to hop medially or cranially.

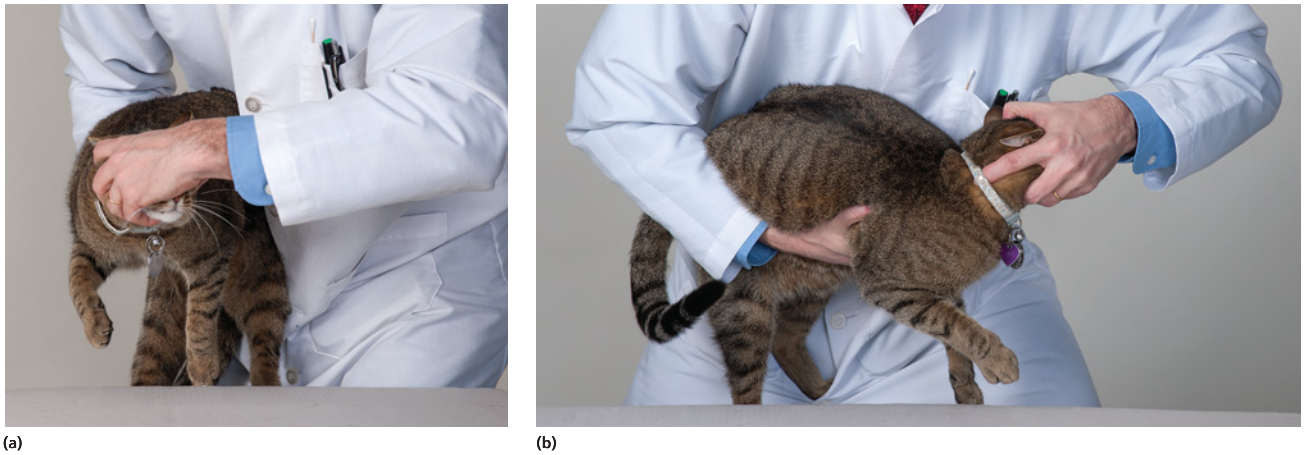


Figure 2.7 Tactile placing is tested by covering the patient's eyes and moving the patient toward the edge of a table. The test can be brought toward the table frontally (A), or laterally (B). Normal dogs and cats will place their paw on the table as soon as they contact the edge of the table.

   c. Wheelbarrowing in the thoracic limbs is done by supporting the patient under the abdomen so that the pelvic limbs do not touch the ground and moving the patient forward (Fig. 2.8). Normal animals will walk with symmetrical, alternate movements of the thoracic limbs.
   d. Extensor postural thrust is tested by lifting the patient by the thorax and lowering the pelvic limbs to reach the floor. Normal patients will move the pelvic limbs caudally as soon as they touch the floor (Fig. 2.9).

E. Cranial nerves (CN) (Fig. 2.10, Table 2.1) (Video 4)
   1. CN I (olfactory nerve) is not routinely tested. After ascertaining patency of the nostrils, cover the patient's eyes and present a morsel of food beneath the nose, observing for normal sniffing behavior. Irritating substances, such as ammonia or isopropyl alcohol, should not be used, because they stimulate trigeminal nerve endings in the nasal passages and produce false results.

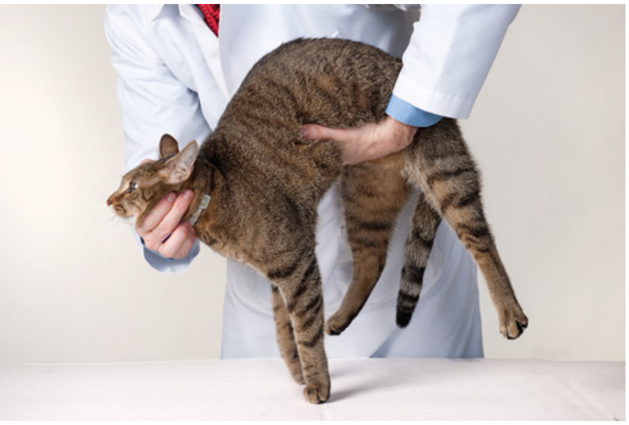


Figure 2.8 Wheelbarrowing is tested by supporting the patient under the abdomen so that the pelvic limbs do not touch the ground and moving the patient forward.

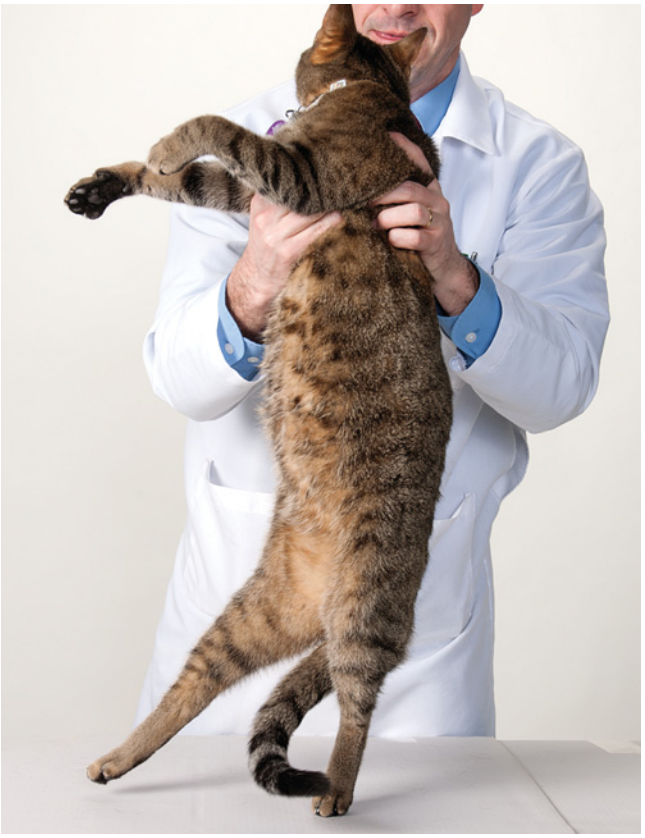


Figure 2.9 Extensor postural thrust is tested by supporting the patient under the thorax and lowering it until it touches the ground.

   2. CN II (optic nerve)
      a. Note pupillary size and any anisocoria before actually testing the pupillary light reflex (Fig. 2.11). There should be a direct and consensual pupillary light reflex in each eye (Fig. 2.12).

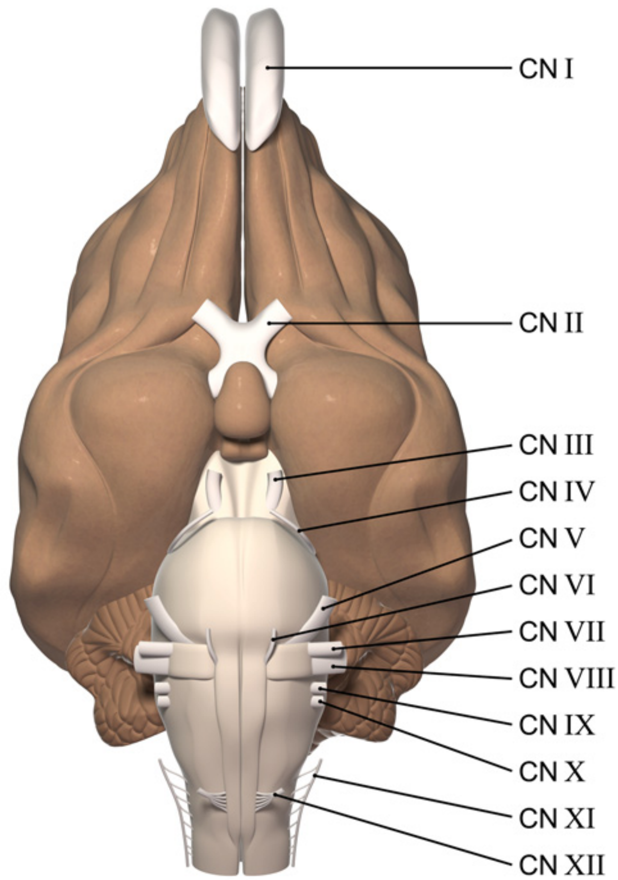


Figure 2.10 Ventral aspect of the canine brain, showing the relative anatomic positions of the cranial nerves. (The Ohio State University. Reproduced with permission.)

Table 2.1 Cranial nerves and their function

Cranial nerve	Function/Innervation
CN I	Olfaction
CN II	Vision
CN III	Somatic motor to most of the extraocular muscles (dorsal, medial, ventral rectus; ventral oblique; levator palpebrae superioris) Parasympathetic innervation to pupil (pupillary light response)
CN IV	Somatic motor to dorsal oblique muscle of the eye
CN V	Somatic motor to muscles of mastication Somatic motor to tensor tympani muscle Sensory to most of face
CN VI	Somatic motor to lateral rectus and retractor bulbi muscles (extraocular)
CN VII	Somatic motor to muscles of facial expression Somatic motor to stapedius muscle Parasympathetic innervation to salivary glands (mandibular, sublingual)[a] and lacrimal, palatine, and nasal glands[b] Sensory to inner pinna Sensory (mechanoreception, thermal) and taste to rostral 2/3 of tongue (chorda tympani nerve)[c]
CN VIII	Vestibular function and hearing
CN IX–XI	Parasympathetic innervation of viscera (CN X) Parasympathetic innervation to salivary glands (parotid and zygomatic, CN IX)[d] Sensory and taste to caudal 1/3 of tongue (CN IX) Sensory innervation of pharynx (CN IX and X) Somatic motor for laryngeal and pharyngeal function (nucleus ambiguus)
CN XII	Somatic motor to extrinsic and intrinsic tongue muscles

[a] Postganglionic axon in CN V, mandibular branch (after mandibular and sublingual ganglia).

[b] Postganglionic axon in CN V, maxillary branch (after pterygopalatine ganglion).

[c] Chorda tympani nerve joins lingual branch of mandibular branch of CN V near middle ear.

[d] Postganglionic axon in CN V, mandibular branch (after otic ganglion).

b. Menace response. Move your hand toward the patient's eyes in a threatening manner, observing for a blink response (Fig. 2.13A). Make sure you test the ability to blink before menacing the patient. The menacing hand should stop about half to one foot away from the patient's face. This would avoid generating air currents that would stimulate the ophthalmic branch of the trigeminal nerve and cause false positive results. By covering the contralateral eye, you can test the nasal (medial) and temporal (lateral) visual fields of each eye. The efferent part of this reaction is controlled by the facial nucleus and nerve (CN VII). The menace response may be deficient in puppies and kittens (less than 12 wks) due to cerebellar immaturity.

c. The menace response evaluates the ipsilateral optic and facial cranial nerves, as well as the ipsilateral cerebellum (ipsilateral) and the contralateral forebrain (thalamocortex) (Fig. 2.13B).

d. Visual following. Drop cotton balls or move a toy or ball in front of the patient and observe if the patient's eyes and head follow the object.

3. CN III (oculomotor nerve), IV (trochlear nerve), and VI (abducent nerve) are considered together because they control eye movements. CN III also mediates pupillary constriction (parasympathetic function), which is evaluated by the pupillary light reflex.
   a. Strabismus may be obvious or can be detected by shining a light on the cornea. When the eyes are aligned, the light reflection is on the same area in each eye.
   b. Observe spontaneous eye movements when the patient looks about. Move the patient's head from side to side and up and down to induce horizontal and vertical nystagmus.
   c. Oculocephalic reflex, vestibulo-ocular reflex or physiologic nystagmus is elicited by moving the patient's head side to side and up and down. Normal physiologic nystagmus has a fast phase in the direction of the head movement (Fig. 2.14A). This test evaluates

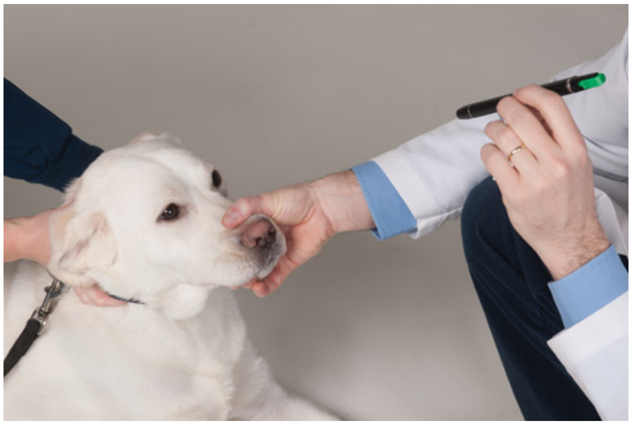


Figure 2.11 The size and pupillary symmetry are tested by holding a good light source one to two feet away from the patient's face so that the light shines equally on both eyes.

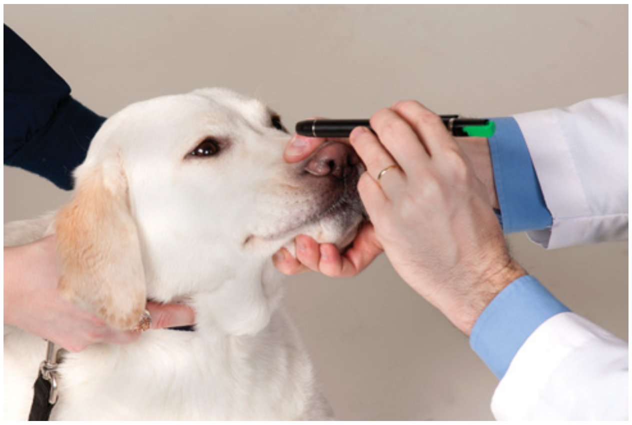


Figure 2.12 The pupillary light reflex is elicited by shining a bright light in each eye. Normally, there is a brisk constriction of the ipsilateral (direct pupillary light reflex) and contralateral pupil (indirect or consensual pupillary light reflex). There is no need to cover the contralateral eye when testing the direct pupillary light reflex.

cranial nerves VIII (sensory) and III, IV, VI (motor) (Fig. 2.14B). In small dogs or cats, primarily those with significant cervical pain, the test can be performed moving the entire patient sideways (Fig. 2.15).

   d. To induce the corneal reflex, touch the cornea with a cotton-tipped applicator moistened with saline. Corneal sensation depends on the ophthalmic branch of the trigeminal nerve. The normal response is a retraction of the globe, mediated by the abducent nerve (CN VI).

4. CN V (trigeminal nerve)
   a. Motor portion—the temporalis and masseter muscles are visualized and palpated to detect any swelling, atrophy, or asymmetry (Fig. 2.16). If there is bilateral weakness, the patient may not be able to close the mouth.
   b. Sensory portion
      1. Ophthalmic branch—this branch of CN V can be evaluated via the corneal reflex (discussed above) and by specifically touching the medial canthus of the eyelid region during the palpebral reflex (Fig 2.17A). The efferent part of this reflex is dependent on normal function of the facial nucleus and nerve (CN VII).

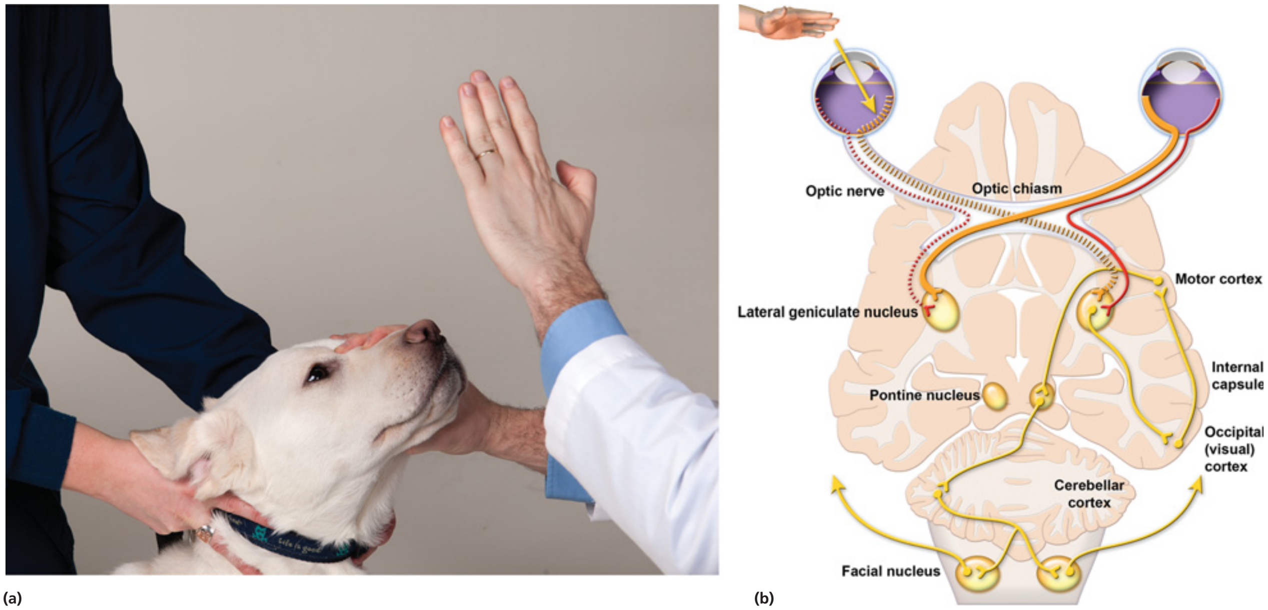


Figure 2.13 (A) The menace response is elicited by making a threatening gesture at the eye, which should induce a blink. Be careful to not get too close to the eye. (B) Pathways and structures involved in the menace response—optic (II) and facial (VII) nerves, as well as the cerebellum and thalamocortical (forebrain) regions. (The Ohio State University. Reproduced with permission.)

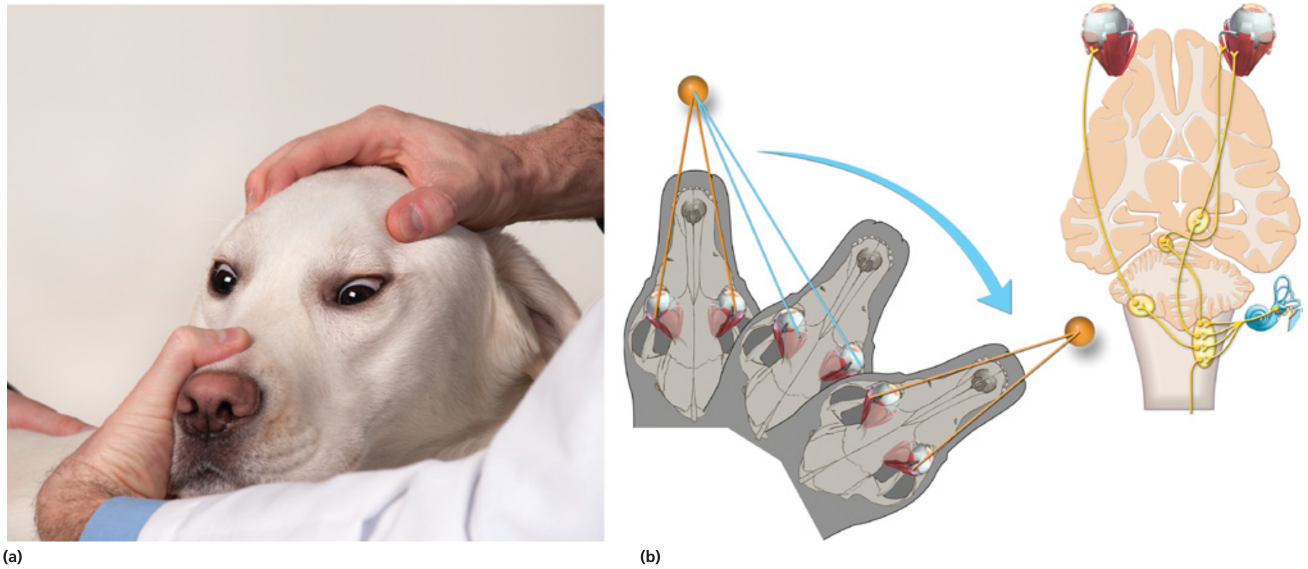


Figure 2.14 (A) The oculocephalic or vestibulo-ocular reflex is elicited by moving the patient's head side to side or up and down and observing the eye movements. Normal response is to see a nystagmus with the fast phase toward the direction of movement. (B) This test evaluates cranial nerves VIII (sensory) and III, IV, and VI (motor). (The Ohio State University. Reproduced with permission.)

2. Maxillary branch—the maxillary branch can be tested touching the lateral canthus during the palpebral reflex (Fig. 2.17B). Pinch the upper lip lateral to the canine tooth. A normal response is a wrinkling of the face and a blink, which also depends on motor supply by the facial nerve. Some animals also turn or withdraw their head, indicating a conscious response mediated at the level of the forebrain.
3. Mandibular branch—pinch the lower lip lateral to the canine tooth. The patient should show a behavioral response. Touching the base of the ear as done with the palpebral reflex can also induce a blinking response (although not as reliable as the medial and lateral canthus).
4. Nasal sensation—evaluation of nasal sensation can evaluate the ophthalmic branch if the stimulus is directed toward the nasal septum, or the maxillary branch if the stimulus is directed toward the external parts of the nare. To be able to detect subtle deficits, it may be better to use a cotton-tipped instrument to evaluate the response (Fig. 2.18A).

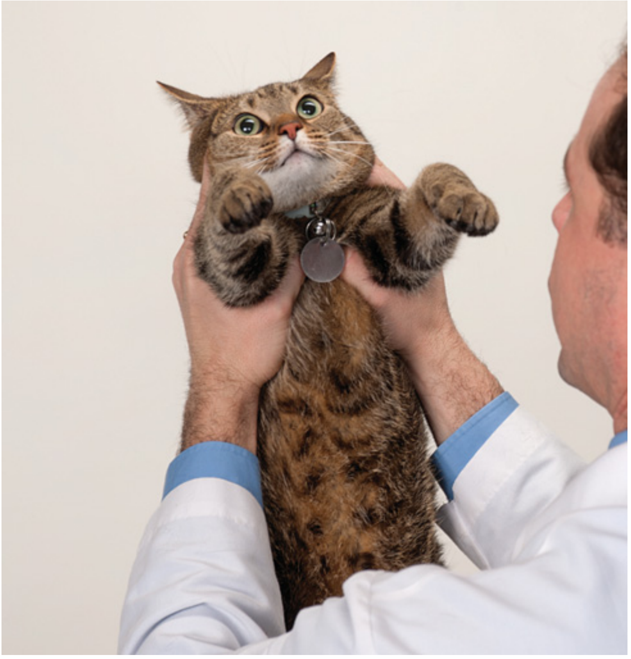


Figure 2.15 In small dogs or cats, primarily those with significant cervical pain, the oculocephalic reflex can be tested moving the entire patient side to side and observing the eye movements.

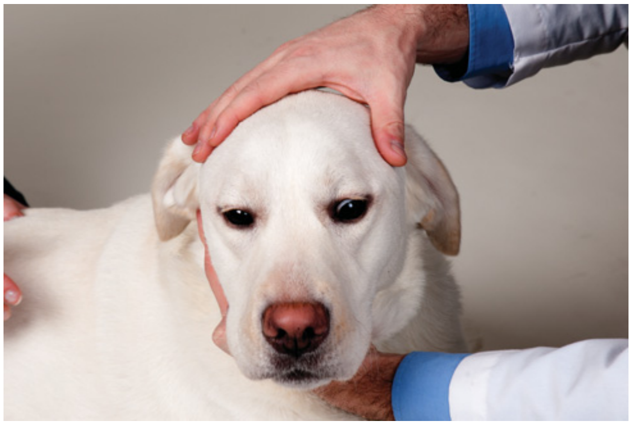


Figure 2.16 The motor function of the trigeminal nerve is evaluated by palpating the masticatory muscles (temporalis and masseter). Compare the muscles on both sides of the face in relation to the zygomatic arch.

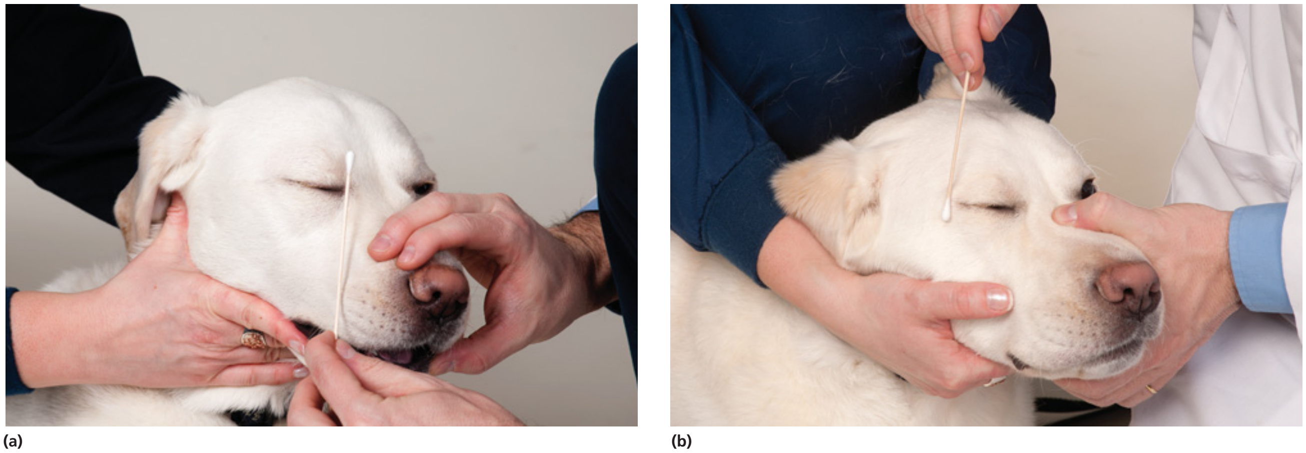


Figure 2.17 The palpebral reflex is elicited by touching the skin medial to the eye (ophthalmic branch, of the trigeminal nerve, panel (A) and lateral to the eye (maxillary branch of the trigeminal nerve, panel (B). Normally, this will induce a blink mediated by the facial nerve. It is recommended to always test both the lateral and medial canthi of the eye to evaluate both branches of the trigeminal nerve.

This test is performed with the intent of evaluating the conscious cortical response (in the contralateral side of the nostril being stimulated) with withdrawal of the head (Fig. 2.18B). The degree of response is variable among animals, so it is important to perform this test, alternating testing sides to compare the response of the right and left sides.

5. CN VII (facial nerve)
   a. Observe the patient's face carefully (preferably a few feet away) and compare the position of the upper and lower lips, eyes, ears, and nostrils (Fig. 2.19). Watch for asymmetrical deficits, such as a droopy upper lip, a widened palpebral fissure, spontaneous blinking, or a drooping ear (Fig. 2.20).
   b. The ability to blink is tested by eliciting the palpebral reflex (Fig. 2.17A and B). Facial paresis or paralysis causes a decreased palpebral reflex (Fig. 2.21).
   c. The facial nerve also mediates lacrimation (parasympathetic function), which is evaluated with Schirmer test strips.
6. CN VIII (vestibulocochlear)
   a. Cochlear portion
      1. Alert patients should orient their head and ears toward a loud or unexpected noise, such as a squeaky toy, whistle, or pager/beeper.
      2. The client may notice signs of subtle hearing loss. For example, the animal may sleep soundly or not respond readily to being called.

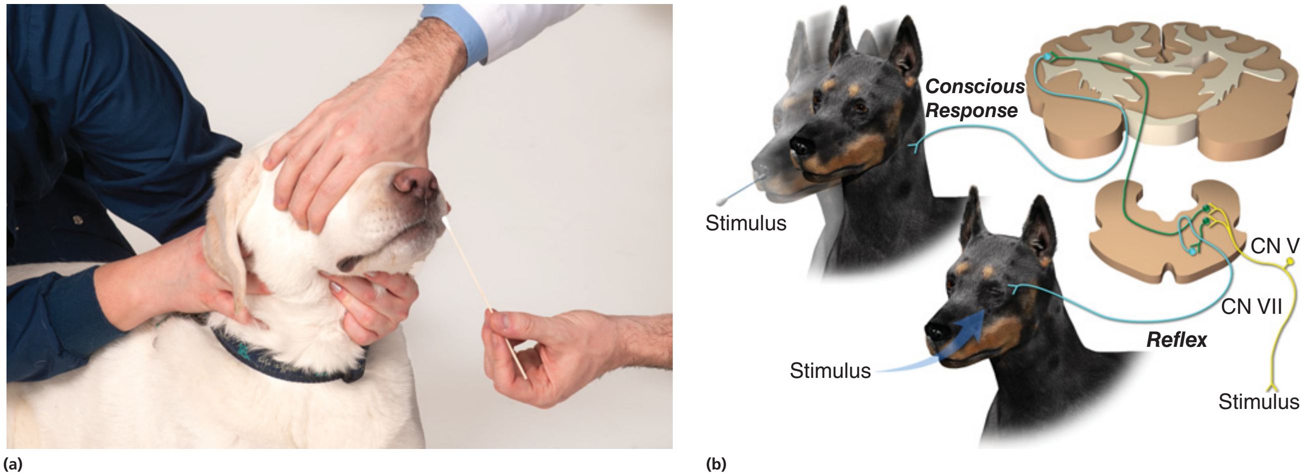


Figure 2.18 (A) The sensory portion of the trigeminal nerve (CN V) is tested by stimulating the nasal mucosa with an instrument such as forceps or a cotton-tipped applicator. Start with the lightest possible stimulus and progressively increase it, alternating sides, until getting a response. The eyes should be covered to avoid the patient seeing and anticipating the touch. The normal response is to pull their head away. Decreased sensation or exaggerated responses are abnormal. (B) Diagram illustrating that, with nasal stimulation, the pathways for the palpebral reflex and cortical response are triggered.

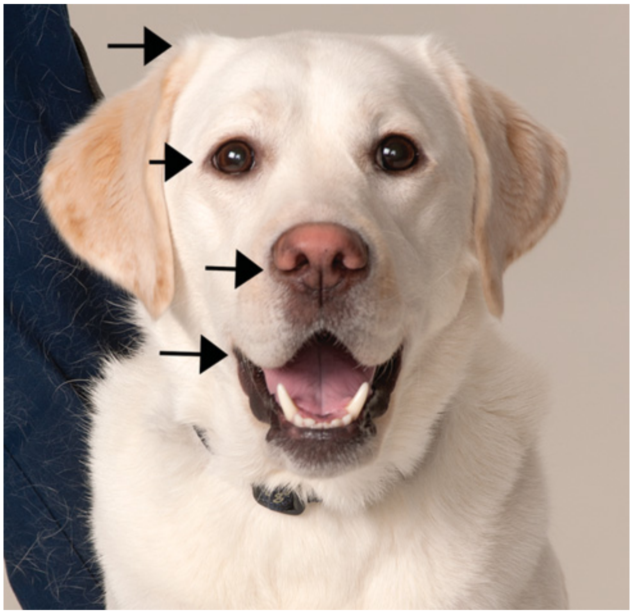


Figure 2.19 Evaluation of the motor function of the facial nerve involves assessment of muscles of facial expression. Pay attention to the position of the upper lip, eyes, ears, and nostrils (arrows), comparing both left and right sides.

b. Vestibular portion
   1. Signs of vestibular dysfunction include head tilt, abnormal nystagmus, and an ataxic, broad-based stance (Fig. 2.22).
   2. Physiologic nystagmus is elicited by rotating the patient's head. Normal physiologic nystagmus has a fast phase in the direction of the head rotation (Fig. 2.14 and Fig. 2.15).
   3. Putting the head in different positions is done to elicit positional nystagmus or positional strabismus (both are abnormal) (Fig. 2.23).

7. CN IX (glossopharyngeal nerve) and CN X (vagus nerve)
   a. Ask the client about any dysphagia, regurgitation, voice change, or inspiratory stridor.
   b. Touch the left or right side of the caudal pharyngeal wall with an applicator stick or finger and watch for elevation of the palate and contraction of the pharyngeal muscles, called the gag reflex (Fig. 2.24).

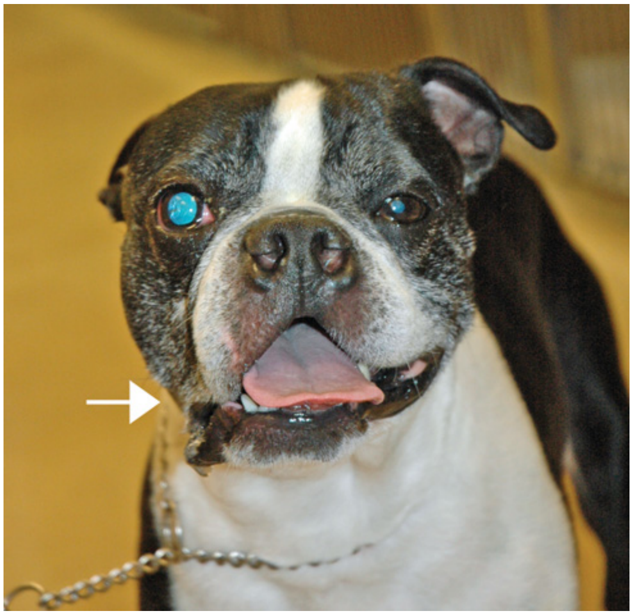


Figure 2.20 Facial nerve paralysis in the right side demonstrated by the facial asymmetry with a droopy upper lip (arrow) and a widened palpebral fissure. Observe saliva accumulation in the right lip commissure.

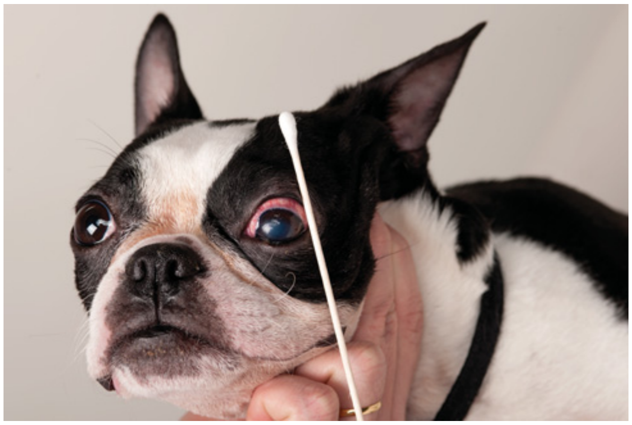


Figure 2.21 Facial nerve paralysis demonstrated by the lack of palpebral reflex.

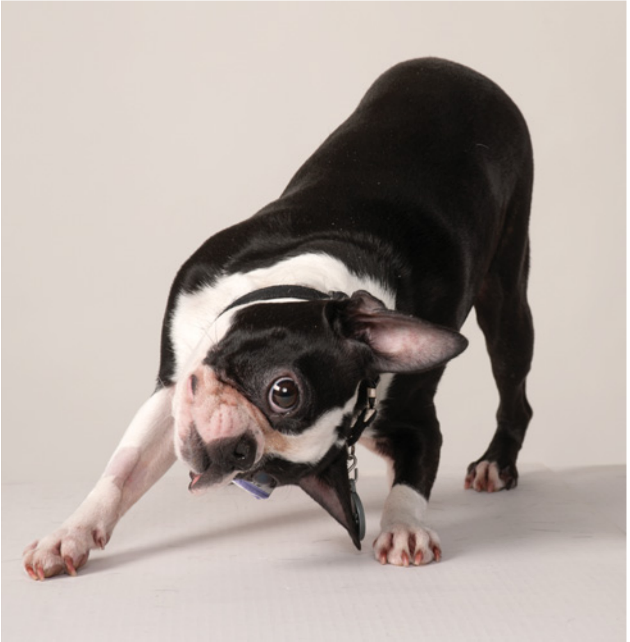


Figure 2.22 Head tilt is the most consistent sign of vestibular dysfunction. The dog in the picture had granulomatous meningoencephalitis affecting the left rostral medulla, causing central vestibular disease and facial paralysis.

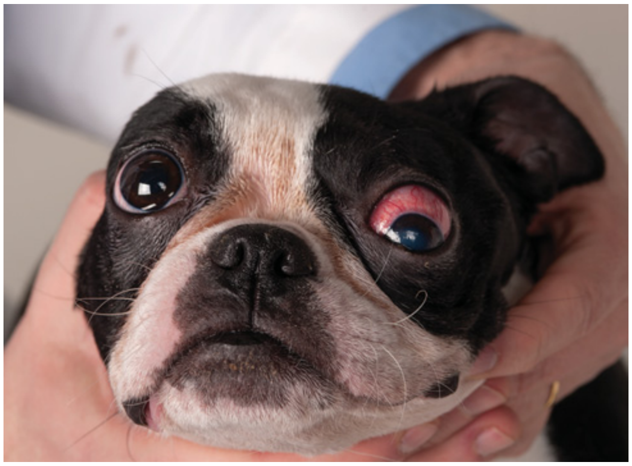


Figure 2.23 Patients with vestibular disease may have abnormal eye positions such as ventral strabismus in the affected side (same dog as shown in Fig. 2.22).

An asymmetrical response is more significant than a bilateral loss of the gag reflex, because this reflex is difficult to elicit in some normal animals. If the patient's demeanor precludes stimulating the pharyngeal mucosa, a similar reflex can sometimes be elicited by externally palpating the pharyngeal region dorsal to the larynx.

8. CN XI (spinal accessory branch) supplies motor innervation to the trapezius muscle. A lesion in this nerve results in atrophy of the trapezius muscle. However, this is difficult to detect in most patients, and lesions restricted to this nerve are rarely recognized. The internal branch of CN XI is structurally and functionally part of CN X.
9. CN XII (hypoglossal nerve)
   - a. Inspect the tongue for atrophy, asymmetry, or deviation (Fig. 2.25).
   - b. Animals usually lick their nose immediately after the gag reflex is tested. Patients with unilateral loss of innervation may be able to lick only one side of the nose, with the tongue usually deviating toward the side of the lesion when actively protruded.
   - c. Watching the patient drink water also helps assess tongue function.

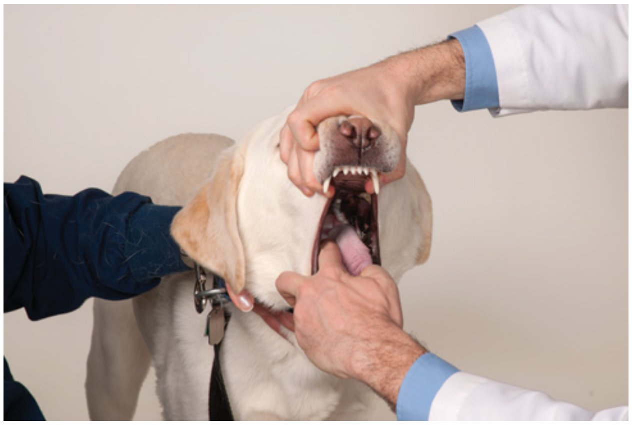


Figure 2.24 The gag reflex is tested by touching the pharynx. A swallowing reflex with contraction of the pharyngeal muscles should occur immediately after the touch.

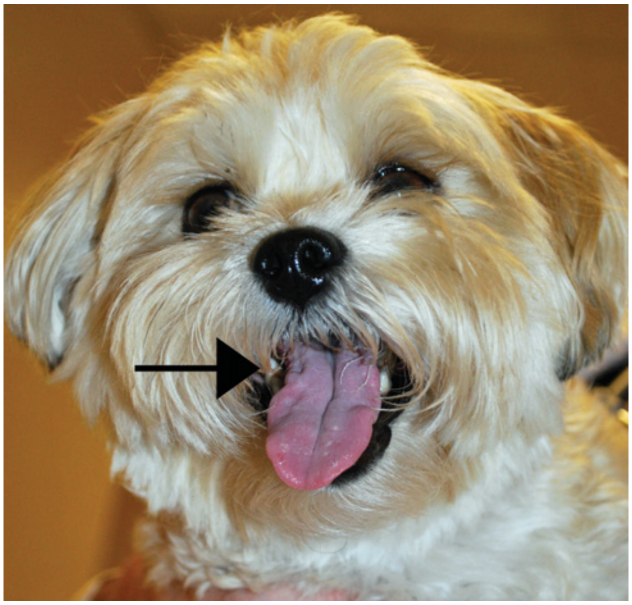


Figure 2.25 Hypoglossal nerve function is evaluated by observing the tongue position and symmetry. This dog had a lesion in the caudal medulla that led to a focal area of atrophy at the base of the tongue and its deviation to the right (arrow).

F. Spinal reflexes (Video 5)

1. Spinal reflexes assess the integrity of the sensory and motor components of the reflex arc and the influence of descending UMN motor pathways.
2. Reflexes are graded as follows:
   - a. Absent
   - b. Weak (present but reduced)
   - c. Normal
   - d. Exaggerated
   - e. Clonus (repetitive flexion and extension of the joint in response to a single stimulus).

   These grades are translated into numbers used to fill the neurologic examination form (see the end of the chapter). A normal reflex is graded as "2," whereas a decreased reflex is assigned "1," an absent reflex "0," an increased "3," and a clonic reflex "4".
3. Causes of weak or absent reflexes are:
   - a. A lesion affecting any part of the reflex arc, including the peripheral nerve, nerve roots, spinal segments, neuromuscular junction, and muscle. Other signs of weakness are usually apparent.
   - b. Severe rigidity or muscle contraction that limits joint movement, such as fibrosis of a joint or muscle. Absent muscle stretch reflexes can also be seen in normal

animals that are excited or unable to relax. In these patients, other signs of LMN weakness are absent.

   c. Spinal shock, which can occur immediately after severe spinal cord injury. This is characterized by paralysis and absent reflexes caudal to the level of injury. In dogs and cats, spinal shock is generally considered to be short-lived, with reflexes returning within about 30 min. after trauma. However, there is evidence that pelvic limb withdrawal reflexes may be decreased due to spinal shock following a UMN spinal cord lesion for periods of 12–48 hr. In the authors' experience, this phenomenon occurs most frequently with ischemic/vascular diseases (e.g. FCE in dogs).

4. Causes of exaggerated reflexes or clonus are:
   a. A lesion in the UMN pathways cranial to the spinal segment involved in the reflex. Other signs of UMN disease, such as paresis or paralysis, are also evident.
   b. Patients who are excited or anxious. In this case, other signs of a UMN lesion are absent. Never diagnose a UMN lesion in a patient with exaggerated reflexes but normal gait and postural reactions.
   c. A lesion of the L6–S1 spinal segments or sciatic nerve can cause an exaggerated patellar reflex (pseudohyperreflexia). This is due to decreased tone in the muscles that flex the stifle and normally dampen stifle extension when the patellar reflex is elicited. Such lesions also cause other abnormalities, such as a decreased flexor reflex.
5. Order of spinal reflex testing—it is important to only perform tests that can be perceived as uncomfortable to the patient last, as it is important to have their cooperation to properly perform testing of spinal reflexes. It is recommended to start with an assessment of muscle tone, proceed with myotatic reflexes next, and leave the flexor (withdrawal) reflexes last. It is recommended to begin testing the pelvic limbs before testing the thoracic limbs. The perineal reflex and cutaneous trunci reflex are the last reflexes tested.
6. In order to be complete, all possible spinal reflexes are described in this section. However, some of the reflexes described below are difficult to elicit, or are not reliable, and thus their presence or absence has limited clinical utility. The following spinal reflexes are consistently observed in most dogs and cats and should always be tested: muscle tone, patellar, flexor, perineal, and cutaneous trunci reflexes. Lesion localization can be effectively achieved performing only these reflexes.
7. Muscle tone (extensor tone)
   a. Extensor tone is one of the most reliable spinal reflexes. It can be performed with the patient standing or in lateral recumbency. Testing should be performed by gently applying pressure to the plantar or palmar surface of the pelvic or thoracic limbs, respectively (Fig. 2.26).

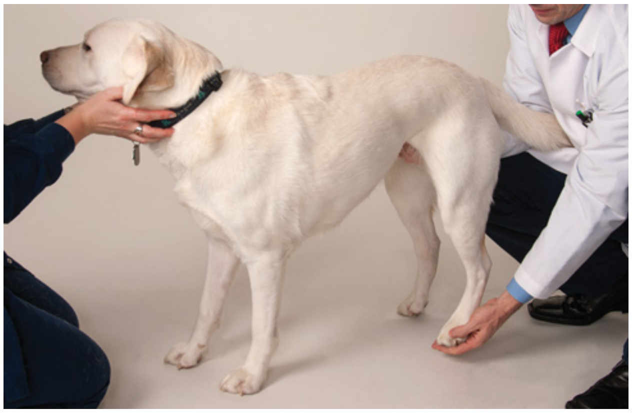


Figure 2.26 Evaluation of extensor tone is performed by applying pressure to the plantar or palmar surfaces with the patient standing in lateral recumbency.

   b. In normal dogs it should be easy to flex the limb when pressure is applied. When pressure is applied and the extensor tone becomes increased (hypertonic or spastic), this is an indication of a UMN lesion.
   c. Extensor tone is a more reliable indicator of a UMN lesion, as it is not as dependent on the sensory component to be elicited as the patellar reflex is.
8. Patellar reflex
   a. With the patient in lateral recumbency, place one hand under the thigh to support the limb with the stifle in a partially flexed position. With the other hand, briskly strike the patellar ligament (located between the patella and tibial tuberosity) with a reflex hammer. An alternative to see and "feel" the patellar reflex is to hold the limb and extend the digits. This may be useful to adjust the degree of limb flexion and extension in cases where the patellar reflex appears decreased (Fig. 2.27). In small dogs and cats, an alternative to test the patellar reflex quickly is to have the patient be

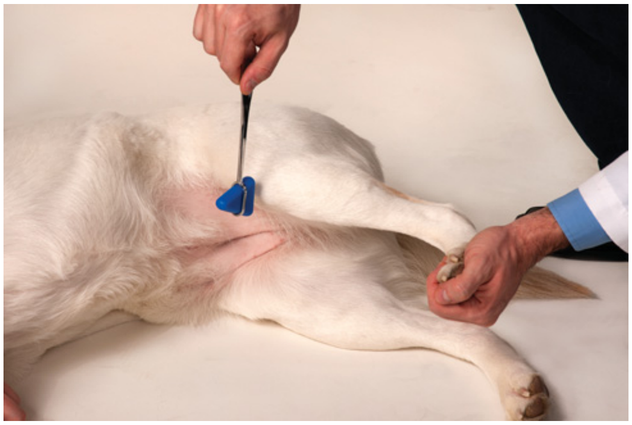


Figure 2.27 The patellar reflex is elicited by percussing the patellar tendon between the patella and tibial tuberosity.

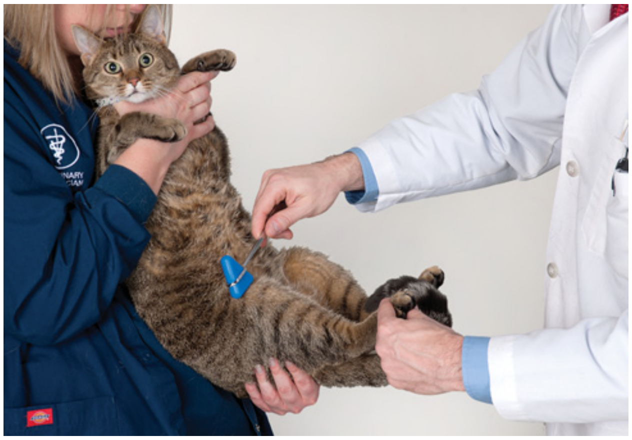


Figure 2.28 The patellar reflex (as well as the other spinal reflexes) can be tested quickly in small dogs and cats with the patient positioned in a "sitting" position. Comparison of left- and right-sided limbs is also easily performed.

supported by the caudal lumbar region as shown on Fig. 2.28.

  b. The normal response is a single, quick extension of the stifle.
  c. Before testing the patellar reflex, always palpate the stifle to make sure that the patient does not have severe medial patellar luxation. In cases of patellar luxation, the patellar tendon is not under enough tension and the patellar reflex may be decreased or absent.
  d. The patellar reflex assesses the integrity of the femoral nerve and L4–L6 spinal cord segments.
  e. As discussed in Chapter 3, unilateral or bilateral loss of the patellar reflex in older (> 10-yr-old) dogs is a nonspecific age-related phenomenon.
  f. The patellar reflex is the most reliable myotatic reflex among all the reflexes described in this section.

9. Gastrocnemius reflex
  a. Grasp the metatarsal area, extend the stifle, and flex the hock. Strike the common calcaneal tendon above the calcaneus.
  b. A normal response is contraction of the caudal thigh muscles.
  c. The recumbent leg tends to have a better response than the nonrecumbent leg.
  d. The gastrocnemius reflex assesses the integrity of the sciatic nerve and the L6–S2 spinal cord segments (primarily L7, S1 segments).
  e. The gastrocnemius reflex may be difficult to elicit in normal animals.

10. Cranial tibial reflex
  a. Hold the limb of the patient in lateral recumbency and strike the belly of the cranial tibial muscle midway through its length (Fig. 2.29).
  b. A normal response is flexion of the tibiotarsal (hock) joint.

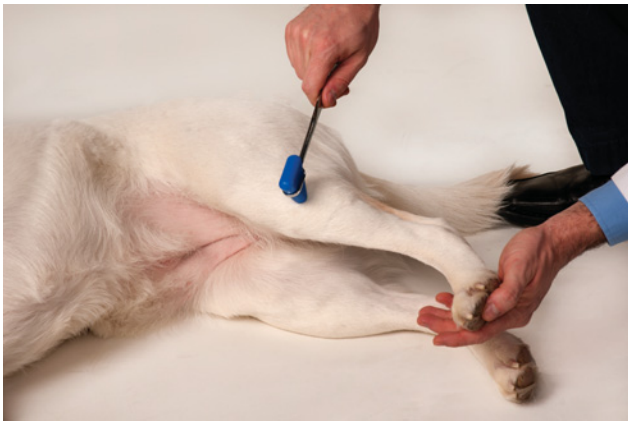


Figure 2.29 Cranial tibial reflex. This reflex is tested by percussing the belly of the cranial tibial muscle.

  c. The cranial tibial reflex assesses the integrity of the fibular (peroneal) branch of the sciatic nerve and primarily the L6 and L7 spinal cord segments.
  d. The cranial tibial reflex is easier to be elicited than the gastrocnemius reflex, but it may actually not be a true myotatic reflex, and be just a muscular response because it has been seen in limbs with a transected sciatic nerve.

11. Biceps reflex
  a. Grasp the antebrachium, extend the elbow (forelimb pulled caudally), and place your index finger on the tendinous insertion of the biceps on the radius. Lightly tap the dorsum of your finger (Fig. 2.30).
  b. A normal response is contraction of the biceps brachii muscle. If this is difficult to appreciate (e.g. long-haired patient), let up with your left hand and observe for elbow flexion as you tap the tendon.
  c. It is easier to test the recumbent leg.
  d. The biceps reflex assesses the integrity of the musculocutaneous nerve and the C6–C8 spinal cord segments.

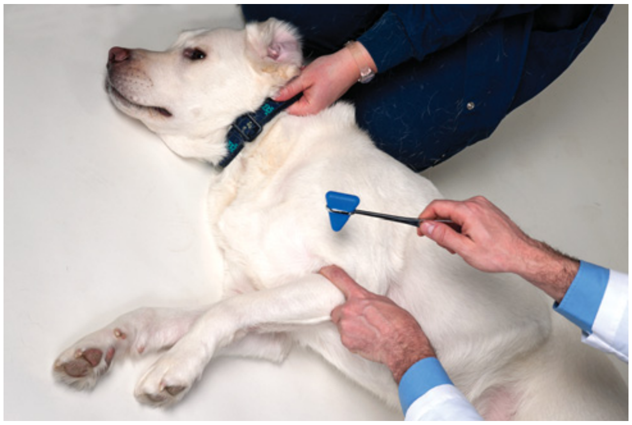


Figure 2.30 The biceps reflex is elicited by striking the examiner's finger placed over the biceps tendon just proximal to the elbow.

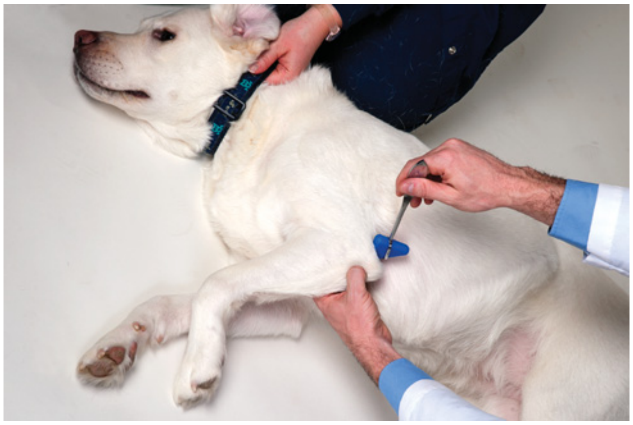


Figure 2.31 The triceps reflex is elicited by percussing the triceps tendon just proximal to the olecranon.

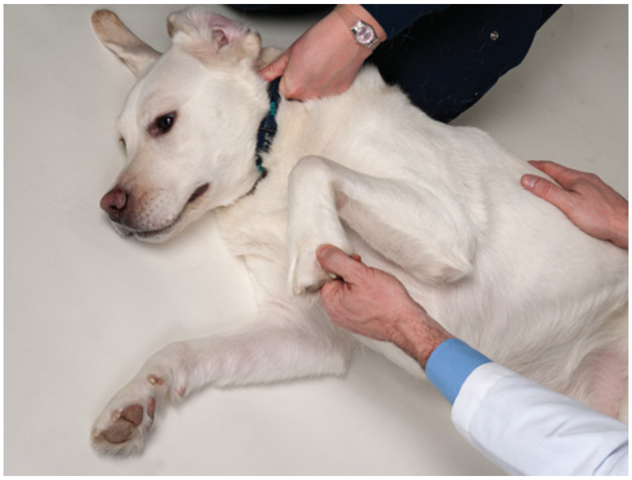


Figure 2.32 The flexor reflex is tested by pinching the skin between the digits. Normal response is flexion of the hip, stifle, and hock in the pelvic limbs, and carpus, elbow and shoulder in the thoracic limbs. This is a reflex mediated at the level of the spinal cord and does not indicate the conscious perception of pain (which happens at a cortical level).

12. Triceps reflex
    a. Grasp the antebrachium, flex the elbow, and rotate the shoulder medially (inward), so that the elbow joint is abducted. Strike the triceps tendon on the medial surface, above the olecranon (Fig. 2.31).
    b. A normal response is contraction of the triceps muscle mass.
    c. The triceps reflex assesses the integrity of the radial nerve and the C7–T2 spinal cord segments.
    d. The triceps reflex may be difficult to elicit in normal animals.
13. Extensor carpi radialis reflex
    a. Hold the antebrachium, supporting the limb under the elbow, keeping the elbow flexed. Strike the belly of the carpi radialis muscle just distal to the elbow.
    b. A normal response is extension of the carpus.
    c. The extensor carpi radialis assesses the integrity of the radial nerve and the C7–T1 spinal cord segments.
    d. This may not be a true myotatic reflex, and be just a muscular response because it can be elicited in dogs with a transected radial nerve.
14. Withdrawal (flexor) reflex
    a. With the limb extended, pinch the interdigital skin lightly with your finger (Fig. 2.32).
    b. The normal response is flexion of the hip, stifle, and hock (pelvic limb) and the shoulder, elbow, and carpus (thoracic limb).
    c. If pain perception is intact, this may also elicit a behavioral response.
    d. Observe the contralateral limb for extension (crossed-extensor reflex). A crossed-extensor reflex is abnormal in a recumbent animal and usually denotes UMN disease.
    e. The withdrawal reflex assesses the integrity of spinal cord segments C6–T2 for the thoracic limb, and L6–S2 (primarily L7, S1) for the pelvic limb. The specific nerves that are assessed depend upon the specific area of skin stimulated (see Chapter 17 for autonomous zones). The efferent arc of the thoracic limb withdrawal reflex is mediated by the musculocutaneous nerve (the most important nerve for biceps flexion), as well as the axillary, median, ulnar, and radial nerves. In the pelvic limb, the efferent arc is mediated by the sciatic nerve.
15. Perineal (anal) reflex
    a. Lightly touch or stroke the perineum (Fig. 2.33). The left and right sides should be tested.
    b. The normal response is contraction of the anal sphincter and tail flexion.
    c. The perineal reflex assesses the integrity of sacral (S1–S3) and caudal (tail flexion) spinal cord segments, as well as perineal and caudal rectal nerve branches (both are branches of the pudendal nerve).
16. Cutaneous trunci (formerly panniculus) reflex
    a. With the patient standing or in straight sternal recumbency, lightly pinch the skin just lateral to the vertebral column (Fig. 2.34A). Start just cranial to the lumbosacral region and proceed cranially, one vertebral level at a time. The opposite side is tested similarly.
    b. The normal response is a bilateral contraction of the cutaneous trunci muscle, resulting in a twitch of the skin over the thorax and abdomen. This reflex is present in the thoracolumbar region and is absent in the neck and sacral regions.
    c. An obvious cutoff point suggests a spinal cord lesion 1–4 cord segments cranial to the level of cutoff (the rule of thumb is approximately two vertebral bodies cranial to the cutoff point).

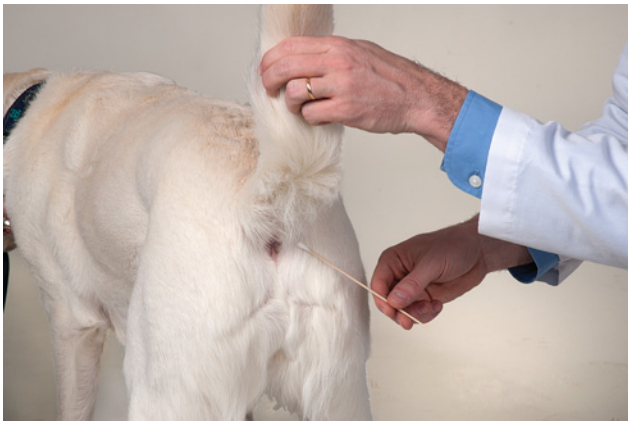


Figure 2.33 Gently stroking or pinching the perineum tests the perineal reflex. The normal response is flexion of the tail and contraction of the external anal sphincter.

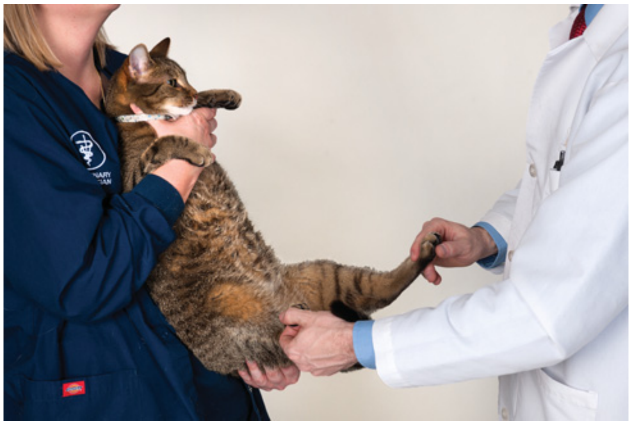


Figure 2.35 Representation of the crossed extensor reflex. With flexion of one pelvic or thoracic limb, the opposite limb extends. This is an upper motor neuron reflex.

   d. A lesion affecting the brachial plexus may cause a loss of the ipsilateral cutaneous trunci reflex with a normal response on the other side, regardless of the level at which the skin is stimulated. Thoracotomies typically transect the lateral thoracic nerve, also causing ipsilateral loss of the cutaneous trunci reflex.
   e. The cutaneous trunci reflex assesses the sensory integrity of all dermatomes over the thoracolumbar vertebral column (with their corresponding spinal cord segments and nerves). The efferent component is mediated by the lateral thoracic nerve and C8–T1 spinal cord segments (Fig. 2.34B).

17. Pathological reflexes.
   a. Crossed-extensor reflex—a crossed-extensor reflex is typically seen with chronic myelopathies. It indicates a UMN lesion. Crossed-extensor reflex is observed when the patient shows contralateral extension of the thoracic or pelvic limb after pinching the opposite limb for evaluation of flexor reflex (Fig. 2.35). In order to ensure that the patient is displaying a true crossed-extensor reflex and not simply moving the opposite limb, it is recommended to flex the digits and push the limb close toward the body. Patients with true crossed-extensor reflex will then extend the opposite limb.

G. Palpation
   1. Light palpation helps detect swelling or atrophy. Light palpation is also useful to evaluate the vertebral column for areas of luxation or crepitus.
   2. Deep palpation and manipulation detect painful regions. If crying, whimpering, or muscle tensing occurs on palpation, more vigorous maneuvers, such as manipulation, are unnecessary and may be dangerous in patients with

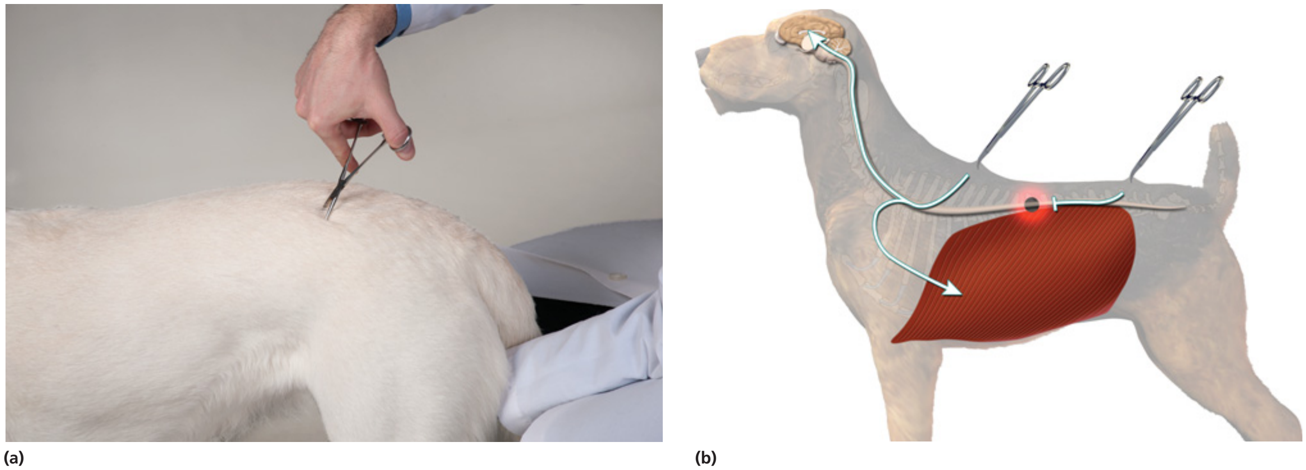


Figure 2.34 (A) The cutaneous trunci reflex is evaluated by lightly pinching the skin just lateral to the vertebral column, starting over the lumbosacral region and proceeding cranially, one vertebral level at a time. The normal response is a bilateral contraction of the cutaneous trunci muscle, resulting in a twitch of the skin over the thorax and abdomen. (B) With spinal cord lesions along the thoracolumbar region, the ascending pathway of the cutaneous trunci reflex is interrupted and the reflex is absent approximately two vertebral bodies caudal to the lesion. Testing the reflex cranial to the lesion point will elicit a response. (The Ohio State University. Reproduced with permission.)

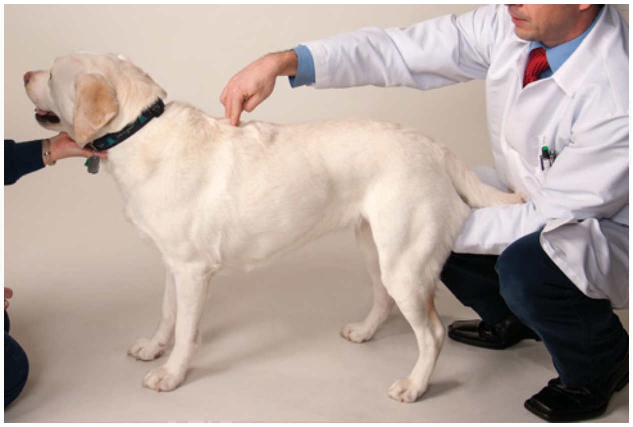


Figure 2.36 Palpation of the thoracolumbar vertebral column is performed applying direct pressure ventrally, starting in the cranial thoracic region and moving caudally until reaching the lumbosacral region.

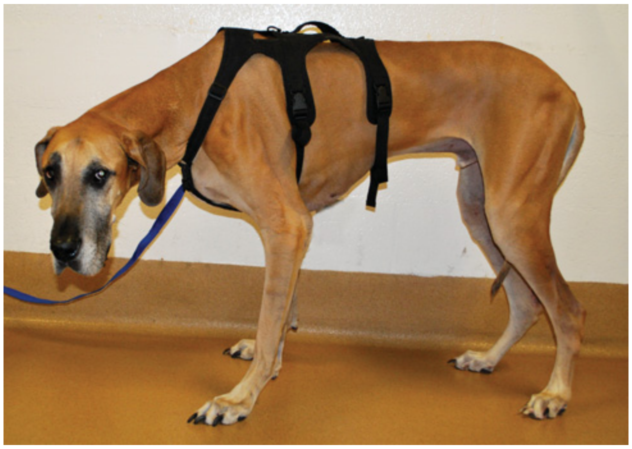


Figure 2.38 Great Dane dog demonstrating a guarded neck posture indicative of cervical pain.

unstable fractures or luxations. Also, palpation is usually more specific because the manipulation of one region often produces movement in other areas.

3. Head
   a. Check the calvarium for masses, defects, or persistent fontanelles.
   b. After palpating the muscles of mastication, gently open the mouth to detect pain or reduced range of motion of the temporomandibular joints.
   c. Retropulse the globe by gently pressing on the closed eyelids to detect pain or a retrobulbar mass.
   d. The authors have found that lightly squeezing the head by grasping above the zygomatic arch often elicits a painful response in dogs and cats with structural brain disease.
4. Vertebral column (Video 6)
   a. Lightly palpate the vertebral column to detect any curvature, displacement, atrophy, masses, or swelling.
   b. Deeply palpate the paraspinal muscle for pain. To be effective the palpation should be performed with the correct technique (Fig. 2.36 and Fig. 2.37).
   c. Palpate, extend, and flex the tail.
   d. Downward pressure on the sacrum often elicits pain in animals with lumbosacral lesions.
   e. When palpating the thoracolumbar vertebral column, lightly place one hand on the abdomen to detect tensing of the abdominal muscles as the affected area is palpated. Avoid applying pressure in the abdomen as it can elicit abdominal pain, which can be confused with spinal pain.
   f. The spinous processes, articular processes, and transverse processes or ribs are palpated separately.
   g. If palpation is not painful, the vertebral column can be gently manipulated by applying ventral and lateral pressure to extend and flex the vertebral column, respectively. To extend the lumbosacral joint, place one hand under the pelvis while the animal is standing. Raise the pelvis and press downward on the seventh lumbar vertebra with the other hand.
   h. Obvious cervical pain can be readily appreciated on posture examination (Fig. 2.38) and it is unnecessary to further palpate or manipulate the area. In less

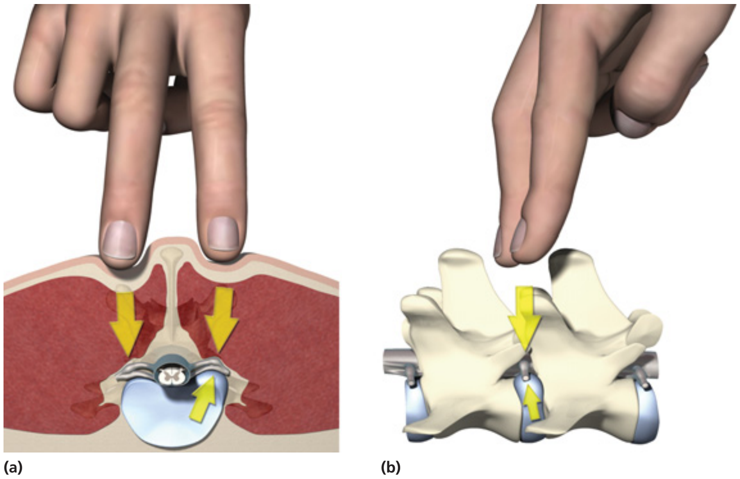


Figure 2.37 Diagram illustrating the position of the fingers in relation to the spinous processes for palpation. The fingers should be kept relatively close to each other and pressure should be performed between the spinous processes because most disease processes involve the intervertebral discs. (The Ohio State University. Reproduced with permission.)

obvious cases, cervical pain is often manifested by tensing of the cervical muscles and twitching of the ears during palpation or manipulation. If palpation does not induce pain, gently extend and flex the head with one hand while placing the other hand on the cervical muscles to detect muscle tensing. This has to be done carefully and avoiding forcing it excessively as severe neurologic deterioration can ensue if the patient has potentially unstable vertebral conditions (such as atlantoaxial subluxation). A safer method is to use a food treat and make the dog follow it in all directions. This would more closely assess the natural cervical range of motion and the patient will stop if the movement becomes painful. The main advantage of this technique is that it does not carry the risk of neurologic worsening. Caudal neck pain can often be detected by gently rocking the large transverse processes of the sixth cervical vertebra. A very sensitive method for detecting cervical pain is by gently pushing aside the soft tissues of the ventral neck (trachea, esophagus, etc.) and pressing against the ventral aspect of the vertebral column while supporting the dorsal neck with the opposite hand (Fig. 2.39). The advantages of this technique are that subtle pain can be detected, presumably by applying pressure more directly to the problem area, and anatomic landmarks (e.g. caudal ventral midline protuberances, transverse processes of C6) can be readily palpated.

5. Limbs
   a. Limbs are initially palpated with the patient standing. Contralateral limbs are compared for symmetry.
   b. The limbs are more closely examined with the animal in lateral recumbency, when the spinal reflexes are tested.

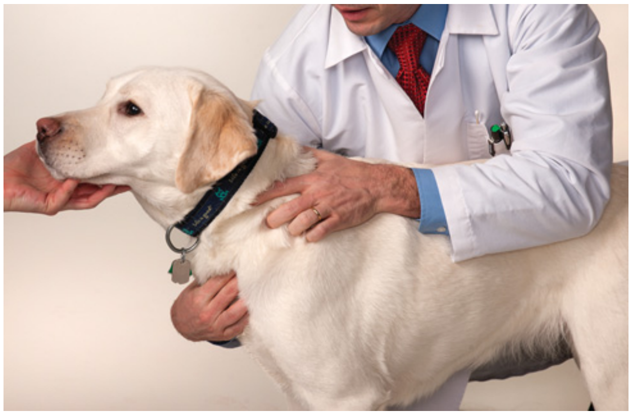
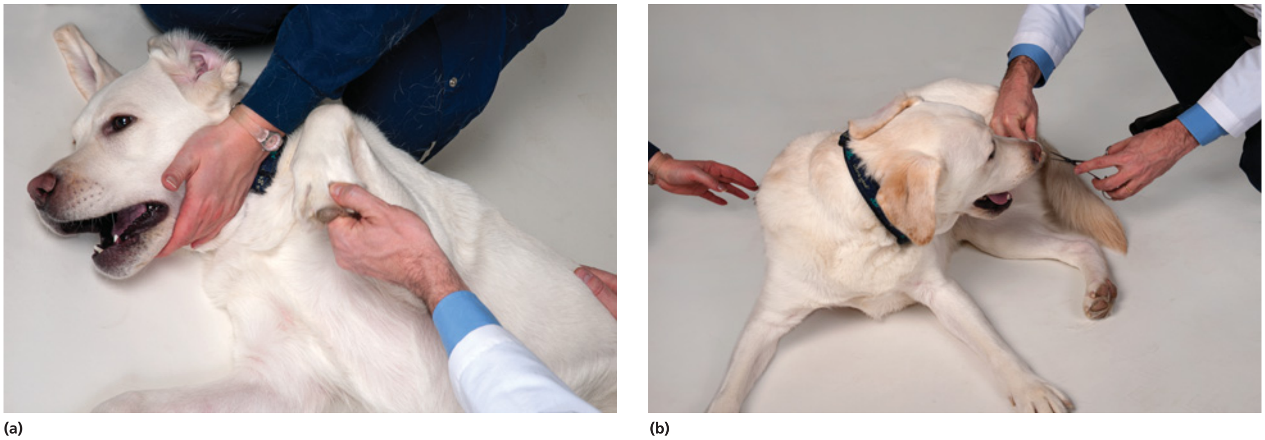


Figure 2.39 Direct application of pressure to the ventral aspect of the vertebrae or the intervertebral spaces is a sensitive method of detecting and localizing cervical hyperesthesia in dogs and cats.

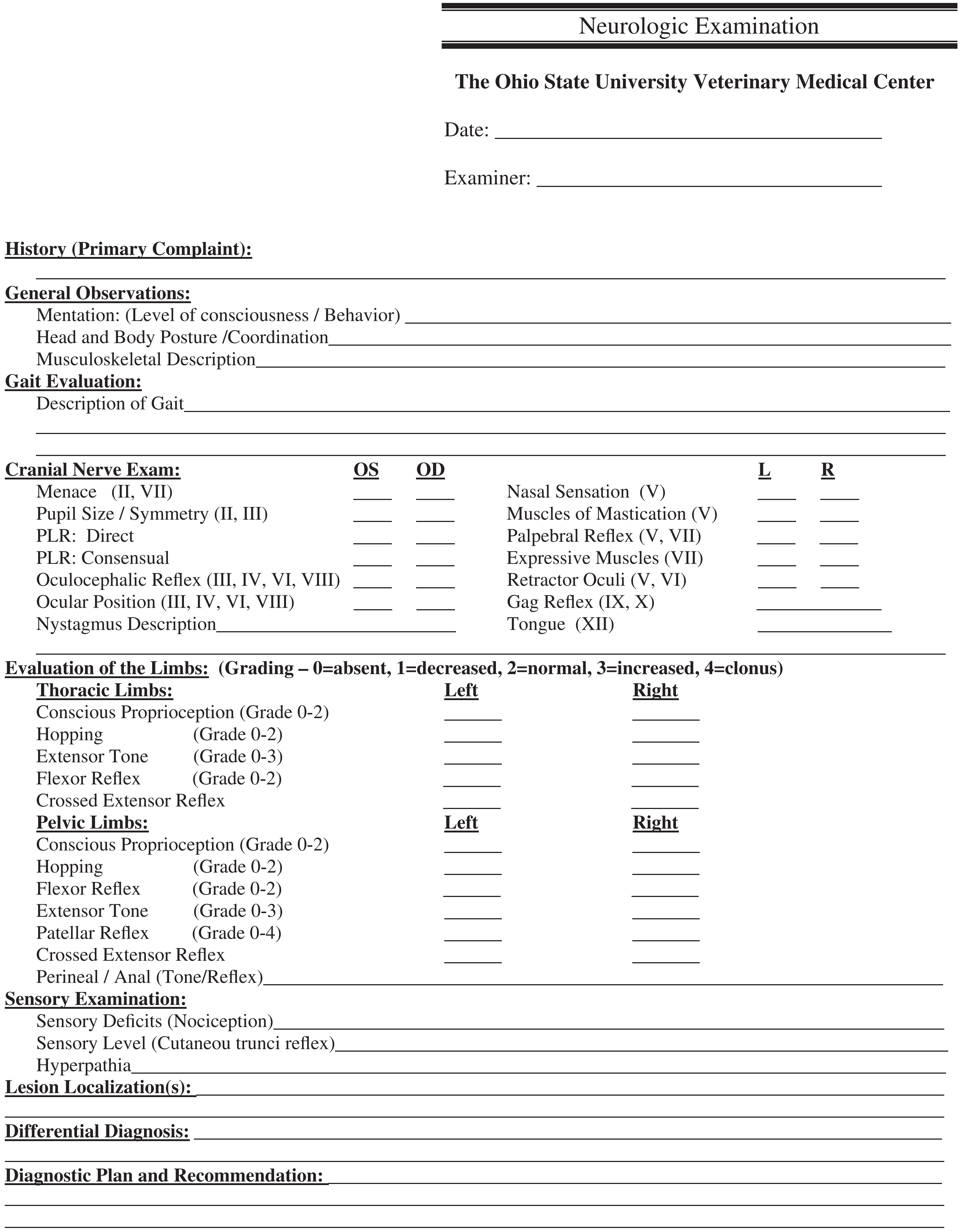
   c. Palpate specific structures, not general regions. Carefully move overlying muscles to palpate bones without compressing adjacent structures. Palpate muscles without compressing or moving adjacent bones and joints.

H. Pain perception (nociception)
   1. In addition to evaluating the patient for areas of hypersensitivity (hyperesthesia), it is important, especially in nonambulatory patients, to determine whether noxious stimuli applied to the limbs are traversing the damaged segment of spinal cord to reach the brain for conscious perception. Nociception has been classically divided into superficial and deep. This division has been questioned because the pathways responsible for these two degrees of noxious stimuli are poorly divided. Superficial pain, also called fast pain, is sharp, well-localized pain most commonly originating in the skin. Deep pain, also called slow



(a) (b)

Figure 2.40 Testing nociception can be performed manually (A) or with a hemostat (B). If the patient does not respond to manual pressure, a hemostat must be used before calling the nociception absent. In the pelvic limbs it is recommended to test the lateral and medial digits as the sensory innervation is mediated by the sciatic and femoral nerves, respectively. A conscious response, such as crying or turning the head, indicates that nociception is present. Simple flexion of the limb without a conscious response means that the flexor reflex is present but nociception is absent.



Neurologic Examination

The Ohio State University Veterinary Medical Center

Date: ______________________________

Examiner: ___________________________

History (Primary Complaint):

____

General Observations:

Mentation: (Level of consciousness / Behavior) ______________________
Head and Body Posture /Coordination______________________
Musculoskeletal Description______________________

Gait Evaluation:

Description of Gait______________________
____
____

Cranial Nerve Exam:	**OS**	**OD**		**L**	**R**
Menace (II, VII)	____	____	Nasal Sensation (V)	____	____
Pupil Size / Symmetry (II, III)	____	____	Muscles of Mastication (V)	____	____
PLR: Direct	____	____	Palpebral Reflex (V, VII)	____	____
PLR: Consensual	____	____	Expressive Muscles (VII)	____	____
Oculocephalic Reflex (III, IV, VI, VIII)	____	____	Retractor Oculi (V, VI)	____	____
Ocular Position (III, IV, VI, VIII)	____	____	Gag Reflex (IX, X)	__________	
Nystagmus Description__________			Tongue (XII)	__________	

____

Evaluation of the Limbs: **(Grading – 0=absent, 1=decreased, 2=normal, 3=increased, 4=clonus)**

Thoracic Limbs:		**Left**	**Right**
Conscious Proprioception	(Grade 0-2)	______	______
Hopping	(Grade 0-2)	______	______
Extensor Tone	(Grade 0-3)	______	______
Flexor Reflex	(Grade 0-2)	______	______
Crossed Extensor Reflex		______	______
Pelvic Limbs:		**Left**	**Right**
Conscious Proprioception	(Grade 0-2)	______	______
Hopping	(Grade 0-2)	______	______
Flexor Reflex	(Grade 0-2)	______	______
Extensor Tone	(Grade 0-3)	______	______
Patellar Reflex	(Grade 0-4)	______	______
Crossed Extensor Reflex		______	______

Perineal / Anal (Tone/Reflex)______________________

Sensory Examination:

Sensory Deficits (Nociception)______________________
Sensory Level (Cutaneou trunci reflex)______________________
Hyperpathia______________________

Lesion Localization(s): ______________________
____

Differential Diagnosis: ______________________
____

Diagnostic Plan and Recommendation: ______________________
____
____

Figure 2.40 Example of a neurologic examination form.

pain, is felt as burning, aching, poorly localized pain originating from the skin or deeper structures.

- **a.** The pathways that carry “deep” nociception (spinothalamic tracts) are more resistant to damage than other pathways, including those responsible for proprioception, motor function, and superficial pain. Therefore, testing deep pain perception is necessary only if superficial pain is absent.
- **b.** When there is no response to pinching with the fingers, use a hemostat to compress the digits or tail (Fig. 2.40). The degree of compression is gradually increased until a response is elicited. Always test both the medial and lateral digits of the pelvic limbs. If no response is seen, evaluate the tail.
- **c.** Withdrawal of the limb indicates only an intact reflex arc (peripheral nerve and spinal segments). A behavioral response such as turning the head or vocalization indicates conscious perception.
- **d.** In patients with severe spinal cord injuries, the presence or absence of deep pain perception is important in assessing prognosis for recovery. It is critical not to confuse reflex withdrawal with conscious perception. As a rule of thumb, perform this test watching the head of the patient for reaction. As long as the patient does not have an LMN injury, a flexor reflex will always be present. The key point is to see a conscious behavioral response involving head movement or vocalization.

Conclusion

The task of performing a neurologic examination can be very intimidating. An important concept to keep in mind is that it is more important to perform fewer tests with a correct technique than several tests with a sloppy technique. This will lead to unreliable and unusable results. We outlined all tests that can be performed, pointing to the most reliable and essential tests. The basis of clinical neurology is lesion localization. The list of differential diagnoses and the diagnostic approach are completely dependent on lesion localization. And lesion localization can only be achieved with a good neurologic examination.

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Video Resources

Video resources are available on the companion website: www.wiley.com/go/dewey/neurology

See videos 1, 2, 3, 4, 5 and 6.

CHAPTER 3

Lesion Localization: Functional and Dysfunctional Neuroanatomy

Curtis W. Dewey

Introduction

Mastering canine and feline neuroanatomy is a formidable task. The complexity of the subject matter often discourages the veterinary student, as well as the clinician, from becoming proficient in clinical neurology. Although understanding clinical neurology depends upon a working knowledge of neuroanatomy, an intricate knowledge of neuroanatomy is not necessary. This chapter reviews the basic functional and dysfunctional neuroanatomy necessary to understand the neurologic examination (discussed in Chapter 2) and to interpret clinical signs of neurologic dysfunction. Normal functions of specific areas of the nervous system, as well as clinical signs of dysfunction, are described concurrently.

Fundamentals of lesion localization

The brain

The brain includes the cerebrum, the brain stem, and the cerebellum (Fig. 3.1). The brain stem includes the diencephalon (thalamus, hypothalamus), the midbrain (mesencephalon), the pons (ventral metencephalon), and the medulla oblongata (myelencephalon). Although the diencephalon is technically the rostral-most aspect of the brain stem, it is functionally (and dysfunctionally) more similar to the cerebrum than the remainder of the brain stem (midbrain through medulla). In this text, the term “forebrain” will be used to describe the combination of cerebrum and diencephalon, which is also known as the prosencephalon or thalamocortex. The cerebellum (dorsal metencephalon) is the final brain subdivision and will be discussed in more detail in Chapter 12. The upper motor neurons originate from various regions of the brain. The term “upper motor neuron” (UMN) refers to the neurons of the brain that control motor activity of the body. The UMNs exert their effects by stimulating or inhibiting the neurons that directly innervate the muscles. The actual neurons that innervate the muscles are lower motor neurons (LMNs). In other words, the UMN “tells” the LMN what to do (Fig. 3.2). The UMN system is responsible for (1) initiation of voluntary movement, (2) maintenance of muscle tone for support against gravity, and (3) the regulation of posture. The UMN system is often divided into pyramidal (mainly located in the motor area of the cerebral cortex) and extrapyramidal (mainly located in the brain-stem nuclei) neurons. In primates, the pyramidal system plays a very important role in control over the LMN and thus voluntary motor activity, whereas the extrapyramidal system is the predominant UMN system in dogs and cats. Gait is generated in the brain stem of dogs and cats. The exact location of the brain-stem center for gait generation in dogs and cats is unknown, but the midbrain is thought to play a major role.

A. Cerebrum (Fig. 3.3; see Table 3.1 for clinical signs of forebrain dysfunction)[2, 5, 6, 9, 16, 18, 26, 36] (Video 7)
   1. Functional regions of the cerebrum can be conceptually divided into lobes (Fig. 3.4). These include frontal lobe (motor area, origin of corticospinal and corticonuclear tracts), parietal lobe (somatosensory area or somesthetic area, receives afferent conscious proprioceptive and nociceptive information), temporal lobe (receives afferent input from both auditory and vestibular systems), occipital lobe (termination of optic tract fibers for visual interpretation), and pyriform lobe (termination of olfactory tract axons for perception of smell). This is an oversimplification (e.g. the motor area of the cerebral cortex is actually partially represented in the parietal lobe as well as the frontal lobe), but is often helpful in understanding cerebral function or dysfunction in the clinical patient. In addition to these general functions, the cerebrum is the seat of consciousness and is important for cognition, interpretation of afferent input, and memory.

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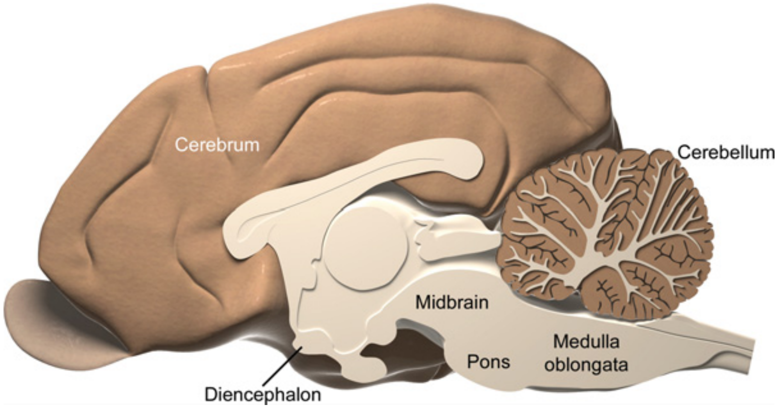

Figure 3.1 Schematic midsagittal illustration of the brain, depicting major anatomical landmarks. (The Ohio State University. Reproduced with permission.)

2. The descending tracts to the limbs (corticospinal tracts) are mainly (about 75%) contralateral (Fig. 3.5), and are located primarily in the dorsolateral funiculus of the spinal cord (lateral corticospinal tract). Similarly, cerebral cortical influence over cranial nerve nuclei (corticonuclear or corticobulbar tracts) is predominantly contralateral. These cerebral cortical tracts are of minor importance in dogs and cats, in comparison with humans. However, damage to cerebral cortical neurons or their associated white matter tracts may result in subtle, contralateral hemiparesis.
3. Conscious proprioception (position sense), tactile sensation, and some nociception (deep pain perception; face) are represented in the contralateral cerebral hemisphere. Conscious proprioception refers to position sense as perceived at the cerebral level. The modality of conscious proprioception is conveyed to the cerebrum primarily via the dorsal column/medial lemniscus pathways (e.g. fasciculus cuneatus for thoracic limb, spinomedullary tract for pelvic limb; Fig. 3.6) and is best evaluated with the animal in a standing position (i.e. proprioceptive positioning; see Chapter 2). Note that some texts attribute the sense of pelvic limb conscious proprioception to the fasciculus gracilis and associated nucleus gracilis. There is evidence that the fasciculus gracilis conveys primarily discriminative touch perception, whereas the spinomedullary tract (whose afferent axons synapse on nucleus Z, rostromedial to the nucleus gracilis) is responsible for conveying the modality of conscious proprioception.
4. The combination of conscious proprioceptive deficits (usually contralateral to a cerebral lesion) with a normal or near-normal gait is a hallmark of cerebral dysfunction.

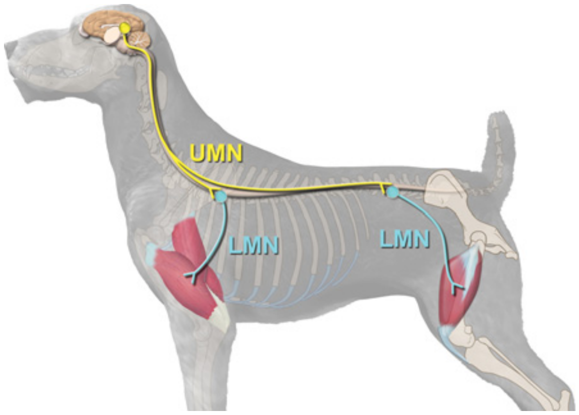

Figure 3.2 Schematic representation of the association between the upper motor neuron and the lower motor neuron. (The Ohio State University. Reproduced with permission.)

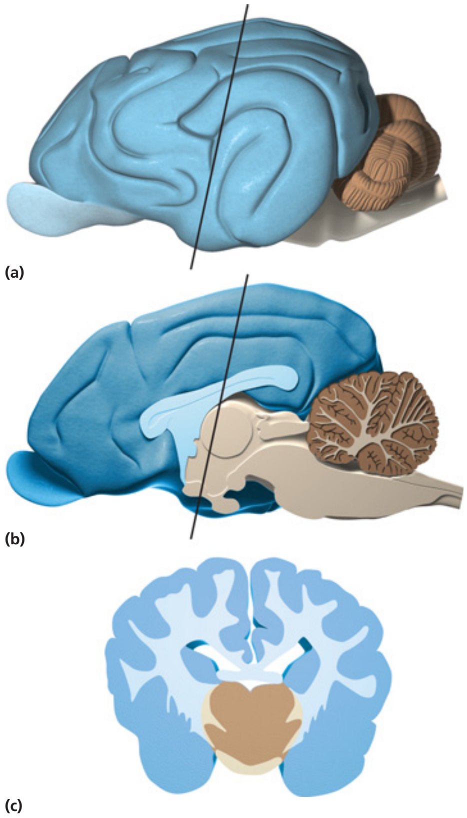

Figure 3.3 The cerebrum (blue), depicted in (A) lateral, (B) sagittal, and (C) cross-sectional (transverse) views. (The Ohio State University. Reproduced with permission.)

Table 3.1 Neurologic signs of forebrain dysfunction.

Evaluations	Clinical signs
Mental status	Normal, obtunded, demented, stupor (less likely)
Behavior	Normal, hemi-inattention, wandering, vocalizing, dull
Seizures	Present or absent
Posture	Normal, ipsilateral head turn (yaw), horizontal neck carriage, head-pressing
Gait	Normal, circling (usually ipsilateral), movements with lack of purpose
Cranial nerve evaluation	Normal, contralateral perceptual deficits (i.e. menace response, nasal/facial sensation)
Postural reactions/voluntary	Contralateral postural reaction deficits; +/– mild motor abilities contralateral hemiparesis
Spinal reflexes	Intact
Spinal hyperesthesia	Present or absent, especially in the cervical spine
Pain perception	Usually normal; may see mild contralateral sensory loss
Micturition	May show inappropriate urination

Source: J. Coates, University of Missouri, Columbia, MO, 2014. Reproduced with permission of J. Coates.

5. Lesions of the cerebrum often cause behavior change, altered mental status (e.g. obtundation), seizure activity, walking in circles (usually in the direction of the lesion), head pressing, and menace deficits. The deficits in the menace response are primarily contralateral. Contralateral deficits of facial sensation may also be appreciated.

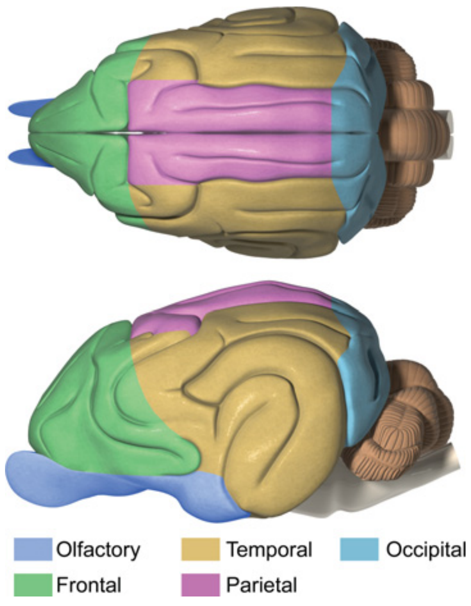

Figure 3.4 Schematic representation of functional "lobes" of the cerebrum. (The Ohio State University. Reproduced with permission.)

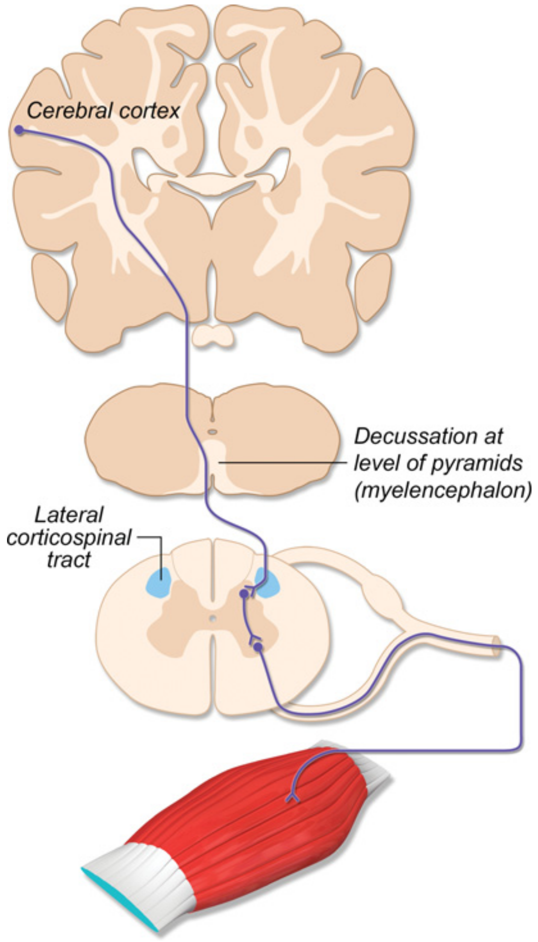
Cerebral cortex
Decussation at level of pyramids (myelencephalon)
Lateral corticospinal tract

Figure 3.5 Schematic representation of the corticospinal pathway motor tracts to the limbs traversing via the lateral corticospinal tract. The majority of these axonal processes (75%) cross in the medulla (myelencephalon) in the pyramidal decussation. (The Ohio State University. Reproduced with permission.)

Note: Patients with structural lesions of the cerebrum occasionally exhibit anisocoria, which may be subtle. They may also exhibit mild facial muscle paresis, often demonstrated best by observing asymmetry of the lip commissures with the patient's nose held in a vertical position. The cerebral cortex normally has a facilitatory influence over the contralateral facial nucleus and an inhibitory influence over the contralateral parasympathetic oculomotor nucleus. Therefore, a unilateral cerebral lesion may cause contralateral miosis (disinhibition of the oculomotor nucleus), and contralateral facial paresis.

6. Patients with structural disease (e.g. tumors) of the cerebrum, or any area of the brain, may exhibit neck pain (thalamic pain syndrome). This phenomenon is thought to be due to factors such as meningeal stretching and referred pain. It is important that the clinician realize that structural brain disease can cause neck pain, and that this clinical finding does not necessarily indicate multifocal or

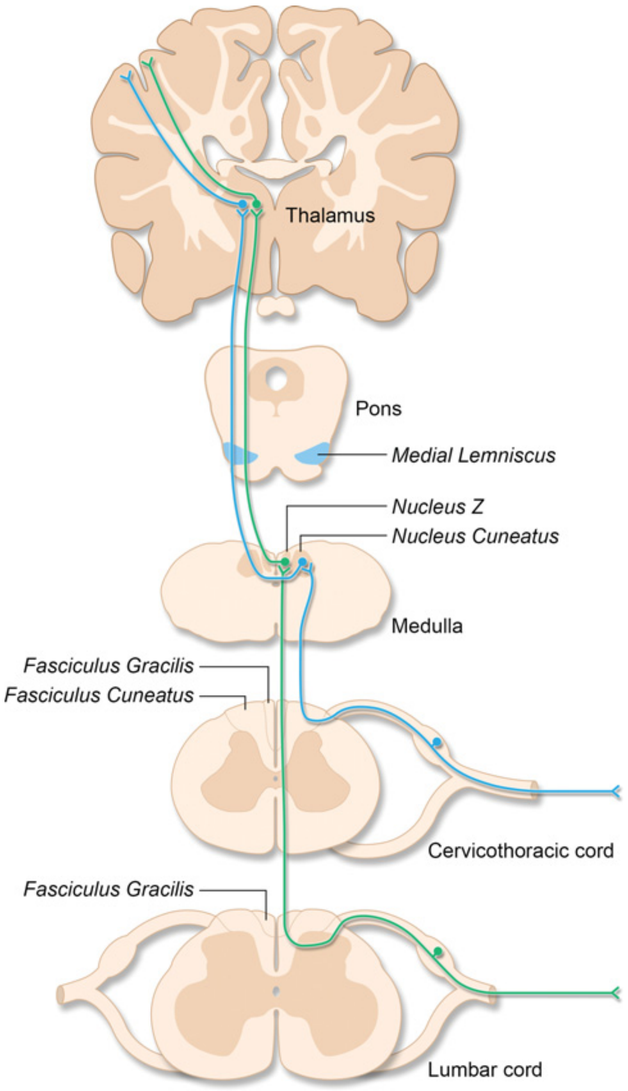

Figure 3.6 Conscious proprioceptive pathways from thoracic (fasciculus cuneatus) and pelvic (spinomedullary tract and fasciculus gracilis) pathways. (The Ohio State University. Reproduced with permission.)

diffuse disease (i.e. another lesion in the cervical spinal cord area).

7. "Hemi-inattention syndrome," or "hemineglect syndrome," refers to a phenomenon in which a patient with a structural forebrain lesion ignores input from one-half of his or her environment. Since most sensory stimuli are interpreted primarily in the cerebral hemisphere contralateral to the stimulus side, the side that the patient ignores is contralateral to the side of the lesion. These patients may eat from only one-half of the food bowl, turn the opposite direction when called by name (i.e. when called from the ignored side), and ignore or have difficulty localizing nociceptive (e.g. skin pinch) stimuli when applied contralateral to the side of the brain lesion.

B Diencephalon (Fig. 3.7)[2, 5, 13, 28, 34]

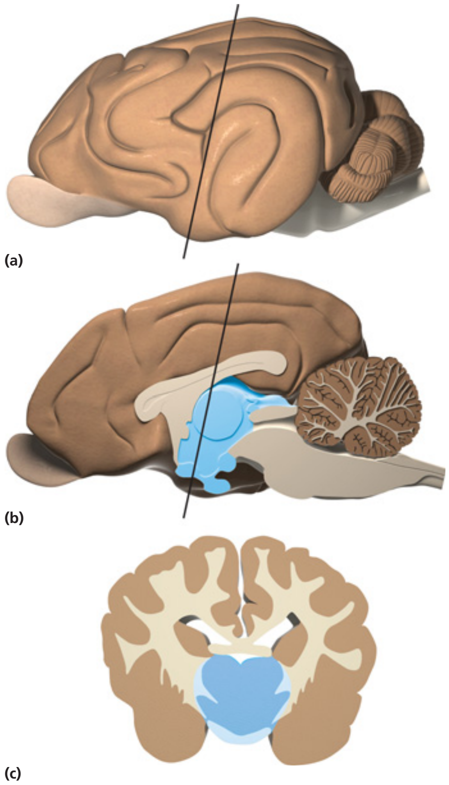

Figure 3.7 The diencephalon, depicted in (A) lateral (covered by the cerebrum), (B) sagittal (blue), and (C) cross-sectional (transverse) views. (The Ohio State University. Reproduced with permission.)

1. Signs of dysfunction are often similar to those associated with cerebral disease. In fact, all of the clinical signs of dysfunction listed for cerebral disease may be observed in patients with diencephalic disease (Table 3.1). One fairly consistent feature of patients with diencephalic disease is that they often will circle to either side. If a patient alternates which side he/she circles to, based either on hospital observation or owner-supplied history, this may point to a diencephalic lesion vs. a cerebral lesion.
2. Patients with diencephalic dysfunction may also exhibit evidence of endocrine dysfunction (e.g. PU/PD), abnormal eating patterns, and problems with temperature regulation. Uncommonly, animals with diencephalic disease act nonspecifically painful (thalamic syndrome). Absence of these signs does not rule out a diencephalic lesion, however.
3. The optic nerves or their relays with lateral geniculate nuclei may be affected, resulting in visual impairment and deficient menace responses.
4. Large lesions of the diencephalon may produce stupor and coma as the diencephalon is part of the ascending reticular activating system (ARAS) projecting to the cerebral cortex. The ARAS is responsible for maintaining the awake state in normal animals.

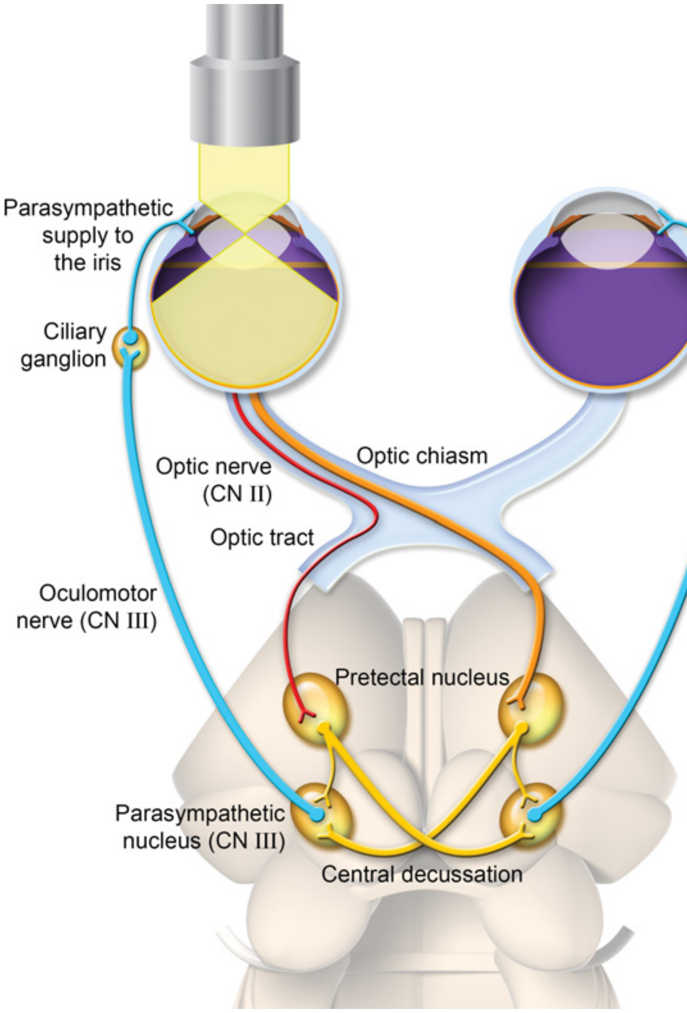

Figure 3.8 Neuroanatomic pathways for vision and pupillary constriction. Pretectal nucleus, parasympathetic nucleus of CN III, oculomotor nerve (CN III). (The Ohio State University. Reproduced with permission.)

5. Although uncommon, peracute and acute diencephalon and midbrain lesions may cause a head tilt. (See Chapter 7.)

Note: The sensory modality of vision (Fig. 3.8) is carried by the optic nerves (CN II), which are associated with the forebrain (cerebrum and diencephalon). Axons of the optic nerve arise from the ganglion neurons of the retina. The majority of axons in each optic nerve carrying visual information for cerebral cortical recognition cross to the opposite side at the level of the optic chiasm (65% crossing in the cat; 75% in the dog). These axons then synapse on neurons in the lateral geniculate nucleus (LGN) of the diencephalon. These LGN neurons, in turn, relay information to the occipital area of the cerebral cortex for the perception of sight. Focal lesions of the diencephalon and/or cerebrum may result in menace response deficits that are primarily contralateral to the lesion. It is important to note that the menace response involves cerebral cortical integration and interpretation, and therefore is not a reflex. The pupillary light reflex (PLR) involves optic nerve axons not destined for cerebral cortical recognition and is discussed in the following section, concerning the midbrain.

C Midbrain (Fig. 3.9; see Table 3.2 for clinical signs of brain-stem [caudal to the diencephalon] dysfunction)[2, 5, 8, 10, 16, 18, 20, 28, 36, 42, 44, 45]

1. Lesions from the midbrain through the medulla are more likely to produce severe disturbances of consciousness (stupor, coma) due to impairment of the ARAS.
2. Lesions from the midbrain through the medulla typically cause obvious gait abnormalities (UMN paresis or plegia). These can be unilateral or bilateral, depending on the size and rate of development of the lesion. On each side of the midbrain, ventrolateral to the mesencephalic aqueduct, is a collection of neurons called the red nucleus. Each red nucleus gives rise to axons that cross the midline and become the rubrospinal tract (Fig. 3.10). The rubrospinal tracts are thought to be important in gait generation in dogs and cats. If the midbrain lesion is focal enough (unlikely, due to the small size of the midbrain), an ipsilateral (caudal midbrain) or contralateral (rostral midbrain) hemiparesis with postural reaction deficits may predominate. The anatomic landmark for focal lesions that will produce ipsilateral gait and postural

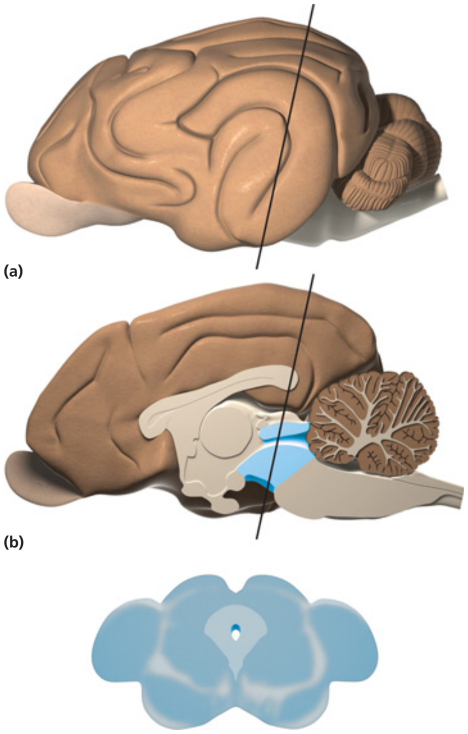

Figure 3.9 The mesencephalon (midbrain), depicted in (A) lateral (covered by the cerebrum), (B) sagittal (blue), and (C) cross-sectional (transverse) views. (The Ohio State University. Reproduced with permission.)

reaction deficits appears to be in the vicinity of the caudal midbrain and rostral pons. Lesions rostral to the midbrain cause contralateral postural reaction deficits and mild or inapparent contralateral paresis. Midbrain lesions seen in clinical practice are often large enough that the signs are bilateral and severe (e.g. decerebrate rigidity in brain-stem herniation).

3. The oculomotor nuclei (motor to extraocular muscles and parasympathetic to pupil) and trochlear nuclei are located in the midbrain. Axons from these nuclei comprise cranial nerves (CN) III and IV, respectively. CN III and IV indent and traverse across the cavernous sinus at the base of the brain. Other cranial nerves that traverse through the connective tissue overlying this sinus include the ophthalmic and maxillary branches of CN V (from the pons) and CN VI (from the medulla). Cavernous sinus syndrome refers to dysfunction of more than one of these aforementioned cranial nerves. In addition to these cranial nerves, the sympathetic pathway to the eye courses in the vicinity of the cavernous sinus for a short distance, before exiting through the orbital fissure with the ophthalmic branch of CN V. Therefore, Horner's syndrome may also occur with lesions in the region of the cavernous sinus.

Table 3.2 Neurologic signs of brain-stem dysfunction (midbrain through medulla).

Evaluations	Clinical signs
Mental status	Normal, obtunded, stupor, coma
Posture	Normal, head tilt (ipsilateral/contralateral), wide-base stance; recumbent patients may manifest decerebrate or decerebellate rigidity
Gait	Normal, mild-severe ipsilateral tetraparesis/ hemiparesis, spastic gait
Cranial nerve evaluation	Ipsilateral deficits; CN III–XII may be affected depending upon lesion extent (vestibular signs common); ipsilateral or bilateral Horner's syndrome possible but uncommon
Postural reactions	Mild–severe ipsilateral deficits
Spinal reflexes	Intact; may have ipsilateral hyperreflexia
Spinal hyperesthesia	Present (inflammatory disorders) or absent
Pain perception	Usually intact; dependent upon mental status
Micturition	Usually intact; severe lesions may manifest absent micturition reflex

Source: J. Coates, University of Missouri, Columbia, MO, 2014. Reproduced with permission of J. Coates.

4. The origin of the tectotegmentospinal tract (sympathetic innervation of the eye) is in the midbrain (tectum refers to the dorsal aspect or roof of the midbrain; tegmentum refers to the body of the midbrain). The diencephalon has influence over this part of the midbrain.

Note: Axons of CN II that are involved in reflex activity (rather than cerebral cortical recognition) do not synapse at the level of the LGN of the diencephalon (Fig. 3.8). Those axons involved in the PLR bypass the LGN and synapse on neurons in the pretectal nuclei (PTN). These nuclei are located in the transition zone between the diencephalon and midbrain. The majority of the axons from each PTN will cross to the opposite side and synapse on neurons of the parasympathetic oculomotor nucleus (CN III). These latter neurons give rise to the parasympathetic portion of the oculomotor nerve, which mediates pupillary constriction. Since there are two levels of crossing in this pathway (chiasm level and pretectal level), the direct PLR (pupillary constriction on the side in which the light is shone) tends to be a bit stronger than the indirect (pupillary constriction on the opposite side in which the light is shone). The other reflex pathway for CN II axons also involves the midbrain. Some of the axons that bypass the LGN will synapse on neurons in the rostral colliculus, located in the roof (tectum) of the midbrain. These neurons project to various areas of the brain stem to mediate reflex movements of the eyes, neck, head, and limbs in response to visual stimuli.

D Pons (Fig. 3.11)[2,8,9,14,18,25,28,36,43,44]

1. The motor nucleus of CN V (trigeminal nerve) is located here. The sensory nuclei and tract of CN V are located from the midbrain to the cranial cervical spinal cord.

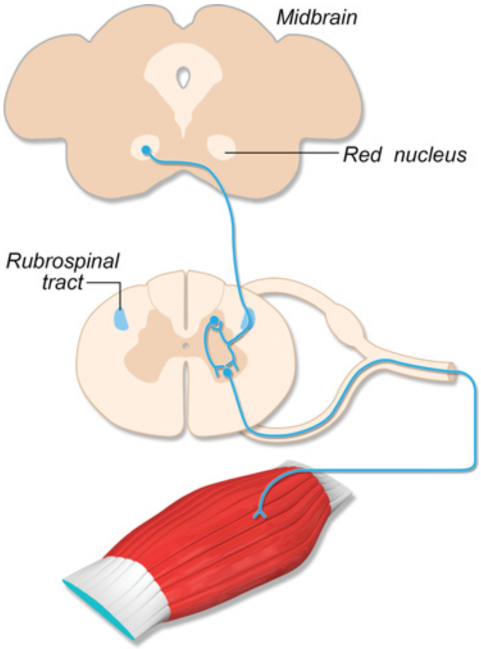

Figure 3.10 The rubrospinal tract, an important pathway for gait generation in dogs and cats. (The Ohio State University. Reproduced with permission.)

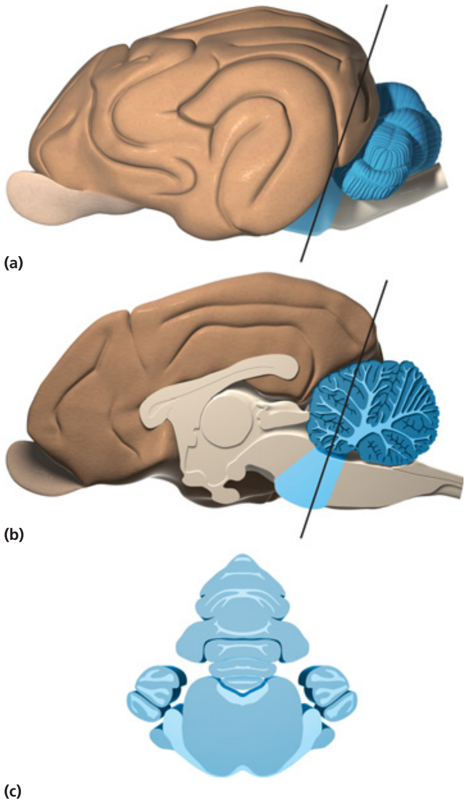

Figure 3.11 The metencephalon (pons and cerebellum), depicted in (A) lateral (blue), (B) sagittal (blue), and (C) cross-sectional (transverse) views. (The Ohio State University. Reproduced with permission.)

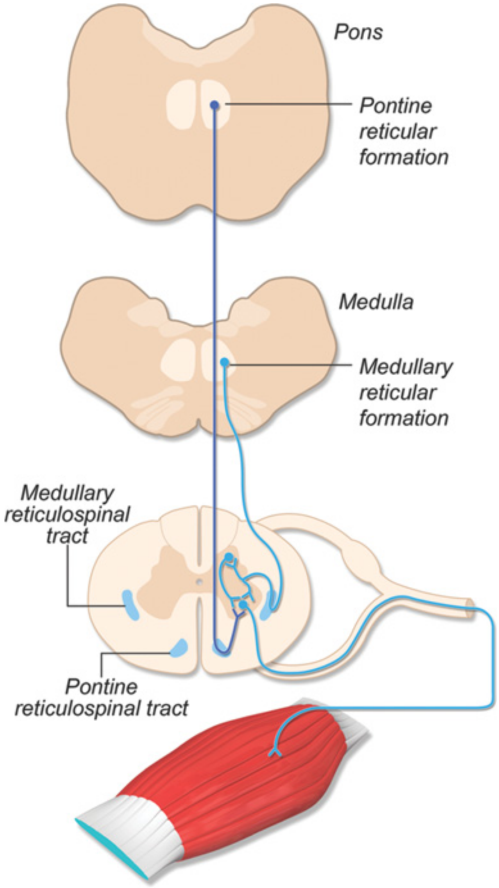
Pons
Pontine reticular formation
Medulla
Medullary reticular formation
Medullary reticulospinal tract
Pontine reticulospinal tract

Figure 3.12 Pontine and medullary reticulospinal tracts, important pathways for gait generation in dogs and cats. (The Ohio State University. Reproduced with permission.)

2. Lesions of the pons typically cause severe disturbances of consciousness and UMN paresis/plegia. Axons from the reticular formation of the pons give rise to the pontine reticulospinal tracts (Fig. 3.12).
3. The major respiratory centers are located in the pons and medulla (mainly), so abnormal respiratory activity may be apparent with damage to the pons.

Note: Sensory information from the face (Fig. 3.13) travels to the brain via branches of the trigeminal nerve (CN V). The cell bodies (first-order neurons) of these afferent nerves are located in the trigeminal ganglion within the petrous temporal bone of the skull. Once these axons traverse the trigeminal canal of the petrous temporal bone to reach the brain stem, they form the sensory tract of CN V, which extends from the midbrain level through the remainder of the brain stem, to reach the most cranial aspect of the cervical spinal cord. Medial to the spinal tract of CN V is the nucleus of the spinal tract of CN V. The axons of the spinal tract of CN V synapse somatotopically on this nucleus. The neurons from this nucleus (second-order neurons) project axons to neurons of the contralateral thalamus (quintothalamic tract). These thalamic

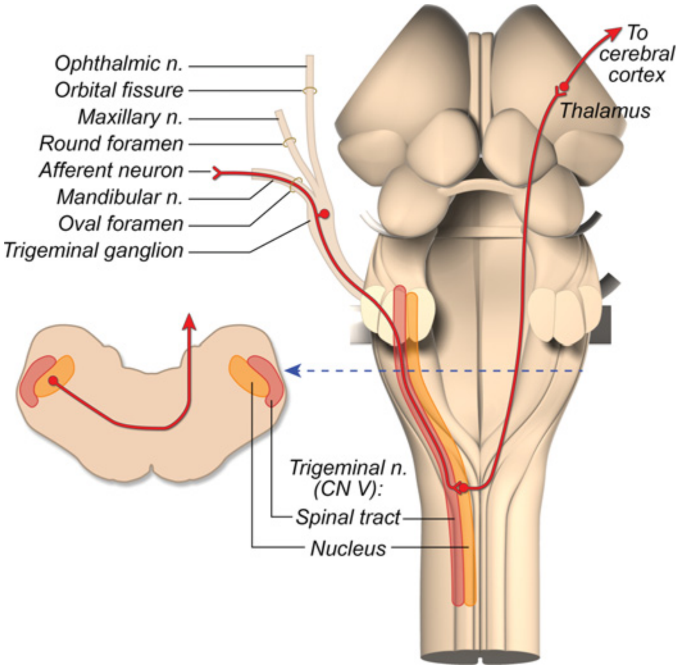

Figure 3.13 Neuroanatomic pathway for facial sensation. Spinal tract of trigeminal nerve (red); nucleus of spinal tract of trigeminal nerve (orange). The inset represents a cross-sectional view of the nuclei and tract at the indicated level. (The Ohio State University. Reproduced with permission.)

third-order neurons then project axons to the cerebral cortex for conscious recognition. Brain-stem lesions caudal to the diencephalon therefore may lead to ipsilateral deficits in facial sensation, whereas forebrain lesions produce contralateral deficits.

E Medulla (Fig. 3.14)[2, 8, 18, 24, 25, 28, 31, 36, 43, 44, 46] (Video 8)

1. The nuclei of CN V (trigeminal, sensory portion only), VI (abducent nerve), VII (facial nerve), IX (glossopharyngeal nerve), X (vagus nerve), XI (accessory nerve), and XII (hypoglossal nerve) are located in the medulla, so dysfunction of one or more of these cranial nerves (discussed in Chapter 2) may be evident.
2. This is also the location of the vestibular nuclei (rostral, medial, caudal, lateral). The functional neuroanatomy associated with the vestibular system is discussed in more detail in Chapter 11.
3. Clinically the medulla can be divided into rostral and caudal medulla. Lesions in the rostral medulla will frequently cause central vestibular signs, with or without facial nerve deficits. Lesions in caudal medulla will cause dysphonia, dysphagia, and occasionally tongue paresis.
4. Lesions of the medulla can cause alterations of consciousness, respiratory disturbance, and autonomic dysfunction (heart rate and blood pressure).
5. Axons from the medullary reticular formation give rise to the medullary reticulospinal tracts (Fig. 3.12). Damage to the medulla often results in UMN paresis/plegia from interference with these and other UMN tracts from the brain stem.

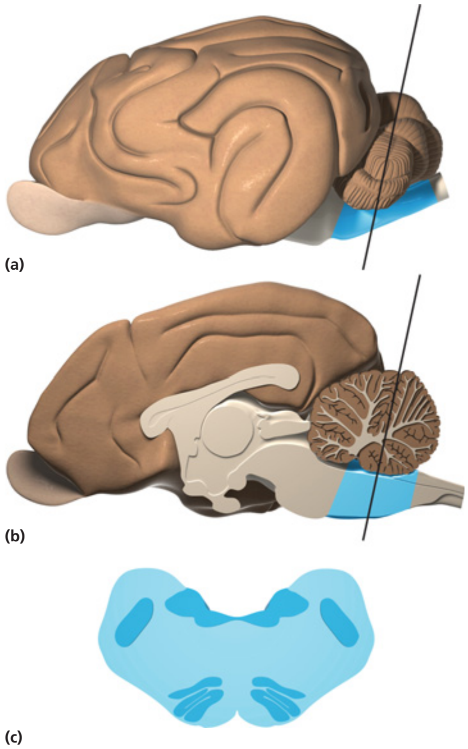

Figure 3.14 The myelencephalon (medulla), depicted in (A) lateral (blue), (B) sagittal (blue), and (C) cross-sectional (transverse) views. (The Ohio State University. Reproduced with permission.)

6. Abnormal respiration is possible, since the major respiratory centers are located in the medulla. The neurons of the medullary respiratory centers can be thought of as the UMNs of respiration, which send axons to the LMNs. The LMNs for respiration are located in the gray matter of the caudal cervical (C5–C7, phrenic nerve) and thoracic (intercostal nerves) spinal cord segments.

Note: Connections between the extraocular nuclei (III, IV, VI) and vestibular input (VIII) are essential for appropriate ocular movements when the head is moved. The connections are maintained by a tract in the brain stem called the medial longitudinal fasciculus (MLF).

F Cerebellum (see more in Chapter 12)[2,7,18,27,28,32,36,43]

1. The cerebellum does not initiate movement. It coordinates and regulates the rate and range of movement by acting as a comparator. Lesions here tend to cause exaggerated movements (e.g. hypermetria).
2. Lesions of the cerebellum can cause ataxia (unconscious proprioceptive loss) without paresis (Videos 9 and 21).
3. Intention tremors, which are tremors initiated by a voluntary movement (e.g. reaching for a treat) may occur, and are often most notable in the head region.
4. There are direct connections of the cerebellum with the vestibular system, so evidence of vestibular dysfunction may accompany cerebellar disease.
5. Lesions of the cerebellum can cause ipsilateral menace deficits with normal vision. The anatomic pathway responsible for this phenomenon is unknown.
6. Cerebellar lesions may also lead to anisocoria. In this scenario, the abnormal pupil is dilated with a sluggish pupillary light reflex. Other associated ocular abnormalities (in addition to mydriasis) may include a widened palpebral fissure and protrusion of the third eyelid. These ocular abnormalities can be either ipsilateral (interpositus nucleus) or contralateral (fastigial nucleus) to the lesion.

Note: Innervation of the striated muscle of the larynx, pharynx, and esophagus is provided by neurons in the nucleus ambiguus (Fig. 3.15). This is a large, poorly demarcated nucleus in the ventrolateral medulla containing somatic motor neuron contributions to CN IX (glossopharyngeal), X (vagus), and XI (accessory). All of these cranial nerves exit the skull via the tympano-occipital fissure. The nucleus ambiguus fibers in the glossopharyngeal nerve primarily innervate pharyngeal muscles. The nucleus ambiguus fibers in the vagus nerve have a variable distribution. Some leave the vagus nerve shortly after its emergence from the skull to innervate one of three structures (pharyngeal, palatal, cervical esophageal musculature), whereas some axons form the cranial laryngeal nerve, which innervates the cricothyroid muscle of the larynx. The remainder of the vagal somatic efferents travels with somatic efferents from the nucleus ambiguus contributions to the accessory nerve (internal branch of CN XI) distally in the vagosympathetic trunk in the neck. At the level of the aortic arch and right subclavian arteries, these axons leave the vagosympathetic trunk to form the left and right recurrent laryngeal nerves, respectively. The recurrent laryngeal nerves ascend the neck region in close proximity to the trachea. The recurrent laryngeal nerves innervate the entire esophagus (striated musculature), as well as the remainder of the laryngeal musculature (including the cricoarytenoideus dorsalis, which is necessary for inspiratory function). The external branch of CN XI is of minimal clinical importance. Axons of this external branch are not supplied by the nucleus ambiguus, but by neuronal cell bodies in the lateral region of the ventral gray column (motor nucleus of the accessory nerve) from the cervical spinal cord segments (up to the C6 or C7 segment). Axons from these neurons leave the cord laterally and ascend in the external branch of CN XI. This branch enters the cranial vault and briefly joins the internal branch from which it separates before exiting the skull as the only contribution to CN XI as it emerges from the tympano-occipital fissure. The external branch of CN XI innervates the trapezius muscle, and parts of the sternocephalicus and brachiocephalicus muscles.

The spinal cord[4,9,11,16,17,19,28,33,36,48]

With the exception of the first one or two cervical segments, and a few segments at the thoracolumbar junction level, most spinal cord segments are positioned cranial in the vertebral canal relative to the vertebra of the same number (Fig. 3.16). In medium- to large-breed dogs, the spinal cord terminates at the L6–L7 vertebral level. In small-breed dogs this spatial relationship is shifted caudally by one-half to one vertebral segment. The termination of the spinal cord in cats is usually over the body of S1. Clinically it is useful to remember that, in approximately two-thirds of dogs, the sacral spinal cord segments (S1–S3) are housed within the 5th lumbar vertebra (L5). Vertebral lesions caudal to L5 (i.e. at L6, L7, or sacral vertebrae) will typically damage spinal cord segments responsible for tail innervation or the spinal nerves. In general, the prognosis for caudal lumbar or lumbosacral vertebral diseases is typically better compared with lesions of similar severity at thoracolumbar or L4–L5 vertebral regions.

The spinal cord white matter is conceptually divided into dorsal, lateral, and ventral funiculi (Fig. 3.17). The axons or tracts of brain UMNs descend through the spinal cord, synapsing on LMNs of the spinal cord gray matter. The UMN tracts, mainly facilitory to limb flexor muscles and inhibitory to extensors, are located in lateral funiculi of the cord (corticospinal, rubrospinal, medullary reticulospinal). Those facilitory to limb extensors and inhibitory to flexors are located in the ventral funiculus (pontine reticulospinal, vestibulospinal). Ascending sensory tracts for proprioception (spinocerebellar tracts, spinomedullary tract, fasciculus cuneatus, gracilis) and nociception (spinothalamic

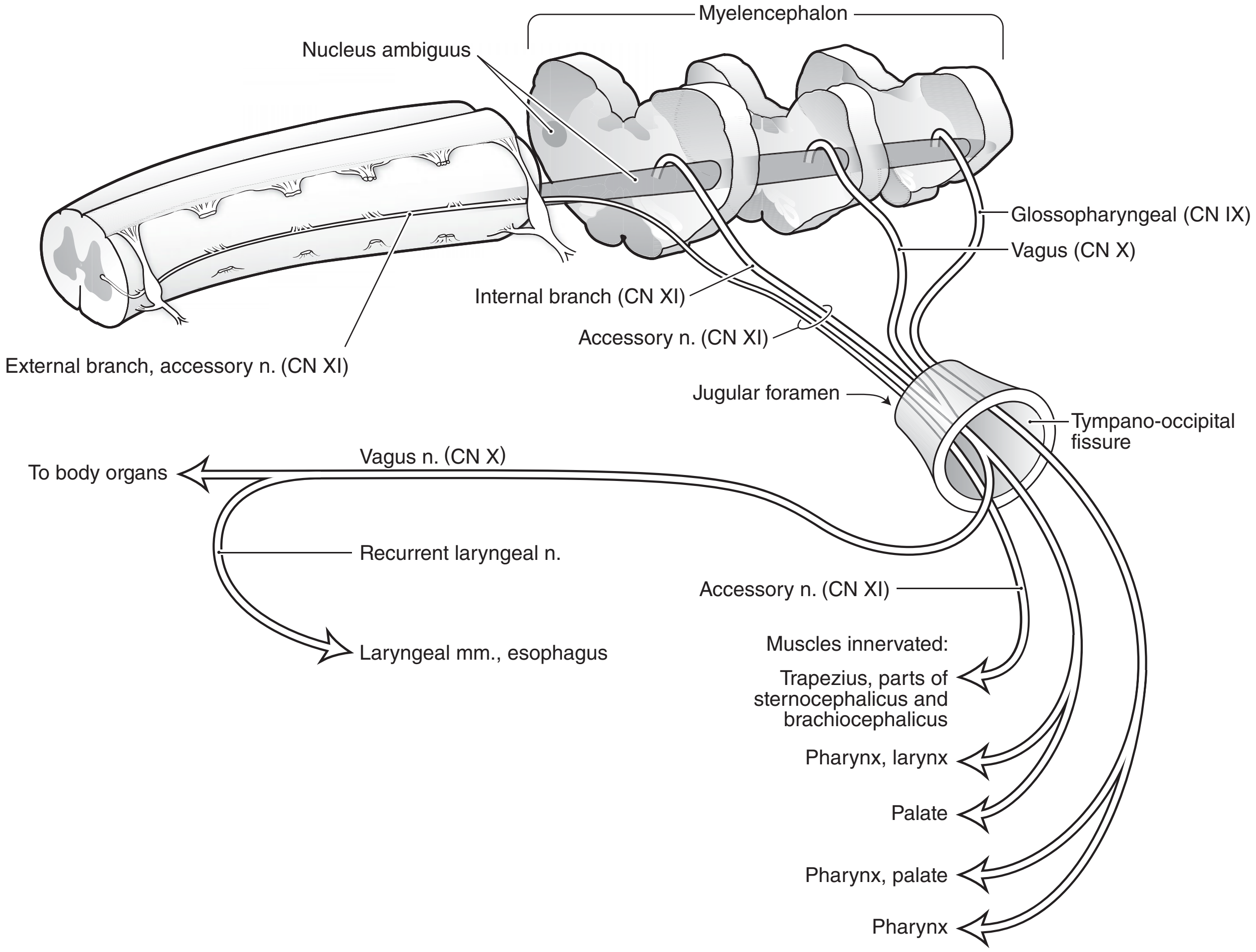
Myelencephalon
Nucleus ambiguus
Glossopharyngeal (CN IX)
Vagus (CN X)
Internal branch (CN XI)
Accessory n. (CN XI)
External branch, accessory n. (CN XI)
Jugular foramen
Tympano-occipital fissure
To body organs
Vagus n. (CN X)
Recurrent laryngeal n.
Accessory n. (CN XI)
Laryngeal mm., esophagus
Muscles innervated:
Trapezius, parts of sternocephalicus and brachiocephalicus
Pharynx, larynx
Palate
Pharynx, palate
Pharynx

Figure 3.15 Schematic illustration of the nucleus ambiguus and its innervation of the striated muscle of the larynx, pharynx, and esophagus.

tract, spinocervicothalamic tract) are located mainly in the dorsal and lateral funiculi (Fig. 3.18). Interference of the UMN influence over the LMN (i.e. the UMN lesion) typically results in a "release" of muscle inhibition (disinhibition), usually more apparent in the extensor muscles (Table 3.3). The result is paresis with normal to increased reflex activity and increased extensor muscle tone. Occasionally, a patient is encountered with decreased muscle tone (hypotonia) and intact reflexes; this may represent a relatively greater disturbance to UMN facilitory pathways versus inhibitory pathways. The reflex activity is at least normal if not hyperactive because the reflex arc is not affected by the UMN lesion. Sensory pathways travel cranially up the spinal cord to the brain mainly in dorsal and lateral funiculi. Conscious proprioception is represented in the contralateral cerebral cortex, and unconscious proprioception (spinocerebellar tracts) is mainly ipsilateral. Pain sensation is functionally bilateral. Although the terminal spinal cord segments are technically part of the spinal cord, they also supply the nerve roots of the cauda equina. In this text, the cauda equina will be defined as the nerve roots derived from the cord segments L7 and caudally.

It is of vital importance to understand that pain perception means cerebral cortical recognition and response to a noxious stimulus. The withdrawal reflex is not pain perception. The patient must show some behavioral response to the noxious stimulus (e.g. vocalization, attempting to bite) for pain perception to be judged intact.

The spinal cord is divided conceptually into segments, primarily based upon the location of LMNs supplying appendicular (limb) musculature. Although there are LMNs throughout the length of the spinal cord, the LMNs of clinical importance are those supplying the limbs, urinary bladder, as well as anal and urethral sphincters. The LMNs of clinical importance are located in the cervical intumescence (C6–T2 segments) and the lumbosacral intumescence (L4–S3 segments) of the spinal cord. Damage to these segments will cause LMN paresis or plegia, characterized by weak to absent reflexes and decreased tone in the associated muscle groups (Fig. 3.19). Damage to areas of the cord without LMNs of clinical significance (C1–C5 and T3–L3) will interrupt descending UMN control over the LMNs, leading to UMN paresis or plegia. With UMN paresis/plegia, reflexes and muscle tone will remain either normal or exaggerated.

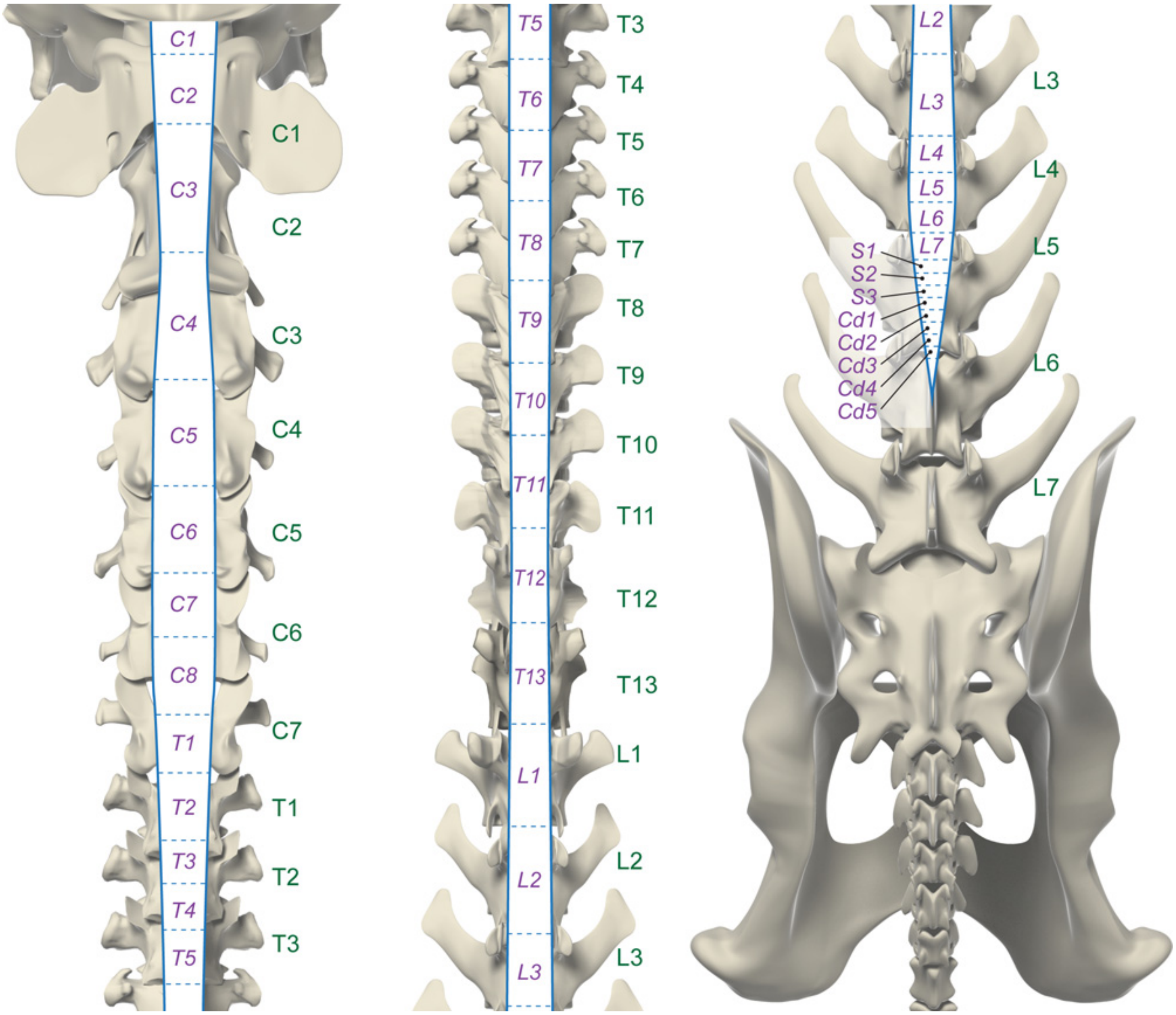
C1
C2
C3
C4
C5
C6
C7
C8
T1
T2
T3
T4
T5
C1
C2
C3
C4
C5
C6
C7
T1
T2
T3
T5
T6
T7
T8
T9
T10
T11
T12
T13
L1
L2
L3
T3
T4
T5
T6
T7
T8
T9
T10
T11
T12
T13
L1
L2
L3
L2
L3
L4
L5
L6
L7
S1
S2
S3
Cd1
Cd2
Cd3
Cd4
Cd5
L3
L4
L5
L6
L7

Figure 3.16 Spinal cord segments and their locations relative to vertebral levels in the dog at the cervical, thoracic, and lumbar regions. Note that the spinal cord ends at the level of the sixth lumbar vertebra. (The Ohio State University. Reproduced with permission.)

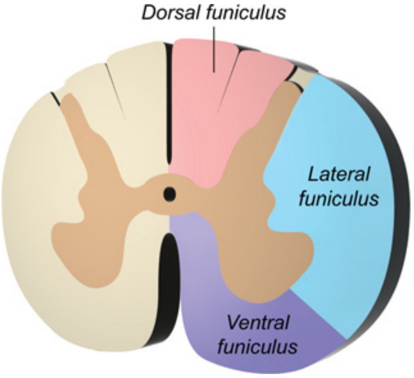
Dorsal funiculus
Lateral funiculus
Ventral funiculus

Figure 3.17 Schematic representation of spinal cord funiculi: dorsal funiculus, lateral funiculus, and ventral funiculus. (The Ohio State University. Reproduced with permission.)

A. Cervical and cervicothoracic spinal cord (C1–C5 and C6–T2; see Table 3.4 for clinical signs of spinal cord dysfunction)[15,31,34] (Videos 10, 25, 27, and 30)

1. This area of the spinal cord can be divided into cranial (C1–C5) and caudal (C6–T2) cord segments. Lesions in this area of the spinal cord can cause hemiparesis, hemiplegia, tetraparesis, or tetraplegia. Some patients exhibit neck pain only, with no proprioceptive or motor deficits. The clinical signs depend both on the location (i.e. unilateral, dorsal, ventral) and on the extent of the lesion.
2. C1–C5 lesions should cause UMN signs to the thoracic limbs and pelvic limbs; C6–T2 lesions can cause LMN signs in thoracic limbs (if involving the gray matter of C6–T2) and UMN signs in the pelvic limbs.

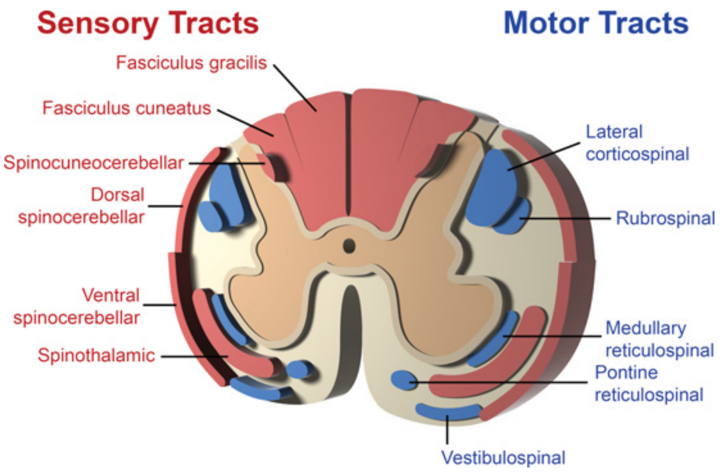

Figure 3.18 Important ascending/sensory (red) and descending/motor (blue) spinal cord tracts. (The Ohio State University. Reproduced with permission.)

3. The lateral tectotegmentospinal tract (sympathetic fibers) travels through the lateral funiculus of the cervical cord and synapses occur with neurons of the intermediolateral gray column nuclei at cord levels T1–T3. Damage to this tract or the cranial thoracic gray matter may result in a Horner's syndrome ipsilateral to the lesion.
4. The phrenic nerve is formed from neurons in cord segments C5–C7, so damage to these segments may compromise respiratory function.
5. The lateral thoracic nerve (efferent arm of the cutaneous trunci reflex) is derived from neurons in cord segments C8–T1, so damage to this area of the spinal cord may result in a decreased or absent cutaneous trunci (panniculus) reflex.
6. Cranial nerves are normal (as opposed to brain-stem disease), with the possible exception of sympathetic dysfunction of the eye(s).
7. Lesions of this area of the spinal cord may result in an "UMN bladder" (see Chapter 16).
8. A common location for lesions in the cervical spine is the C6–C8 spinal cord lesion with compressions in the caudal cervical region. Lesions in this location cause a decreased flexor reflex by affecting the musculocutaneous nerve (C6–C8), and an increase in extensor tone by releasing the spinal cord segments for the radial nerve (C7, C8, T1 and T2). The gait is abnormal in all four limbs but the ataxia and paresis are more evident in the pelvic limbs.

Note: The sympathetic innervation to the eye (Fig. 3.20) continues from the synapses at T1–T3 (the preganglionic nuclei). The axons of these nuclei join the vagosympathetic trunk in the dorsal thorax, travel up the neck with the vagosympathetic trunk, and leave the trunk near the base of the skull to synapse in the cranial cervical ganglion. Axons from these postganglionic neurons project from here through the tympano-occipital fissure, subsequently travel through the petrous temporal bone in the vicinity of the middle ear cavity, and exit the skull as components of the ophthalmic nerve, a branch of the trigeminal (CN V). The pathway followed by the postganglionic sympathetic axons in the petrous temporal bone is not well defined, but does not appear to involve these axons directly entering the middle ear cavity as commonly believed. Nonetheless, disorders involving the middle ear (e.g. otitis media/interna) do tend to involve this pathway, so there is likely very little tissue physically dividing these sympathetic fibers from the middle ear cavity. Another important point is that, as these postganglionic sympathetic axons pass through the petrous temporal bone, they follow a brief intracranial course before joining the ophthalmic branch of CN V and exiting the skull through the orbital fissure. So, from the level of the cranial cervical ganglion, postganglionic sympathetic axons to the eye are initially extracranial, then intracranial, and then extracranial. A Horner's syndrome (ptosis, miosis, enophthalmos) can be caused by damaging the sympathetic system at a number of locations.

Table 3.3 Comparison of upper and lower motor neuron signs.

	Upper motor neuron (UMN)	Lower motor neuron (LMN)
Motor function	Paresis or paralysis	Paresis or paralysis
Reflexes	Normal to increased	Decreased to absent
Extensor muscle tone	Normal to increased	Decreased to absent
Muscle atrophy	Mild/chronic	Severe/fast

B Thoracolumbar spinal cord (T3–L3)[4, 15, 34] (Videos 11, 23 and 26)

1. This area of the spinal cord can be conceptually divided into T3–L3 segments.
2. The thoracic limbs are neurologically normal. T3–L3 lesions cause signs of UMN dysfunction in the pelvic limbs.
3. Border cells in the dorsolateral border of the ventral gray column of L1–L7 (mainly L2–L4) are neurons that project to the cervical intumescence, providing tonic inhibitory activity to muscles of the thoracic limbs.

Disruption of these neurons or their ascending processes can result in disinhibition, usually manifested as thoracic limb extensor rigidity. This posture is known as the "Schiff–Sherrington" phenomenon (Fig. 2.2 and Fig. 3.21). It is important to note that a patient with Schiff–Sherrington posture has normally functioning thoracic limbs that have increased extensor tone (most readily appreciated when in lateral recumbency). The two most common clinical errors made when this phenomenon is encountered are (1) to incorrectly assume a C1–C5 lesion based on the increased thoracic limb extensor tone and (2) to assume a poor prognosis based on the presence of Schiff–Sherrington posture; this is an anatomic phenomenon and does not connote anything regarding prognosis for return to function. The only reliable clinical assessment that dictates prognosis for myelopathies is the presence or absence of nociception in the limbs and tail.

4. Lesions of this area of the spinal cord may result in a "UMN bladder" (see Chapter 16).

C Lumbosacral and caudal spinal cord (L4–Cd5)[11,15,19,31,34] (Video 31)

1. This section of the spinal cord comprises the L4–caudal (Cd) segments. Lesions anywhere along this large area will lead to signs of LMN dysfunction. Because lesions in particular areas of this large region can lead to distinctively different types of neurologic dysfunction, there is some clinical utility in dividing this area into L4–L6, L7–S3, and caudal (Cd1–Cd5) segments.
   a. L4–L6 lesions cause signs of LMN dysfunction in the pelvic limbs, as the neurons in these segments give rise to the femoral nerve. Decreased to absent patellar reflexes, and intact to diminished withdrawal and gastrocnemius reflexes, may be observed. The L6 spinal segment contributes to the

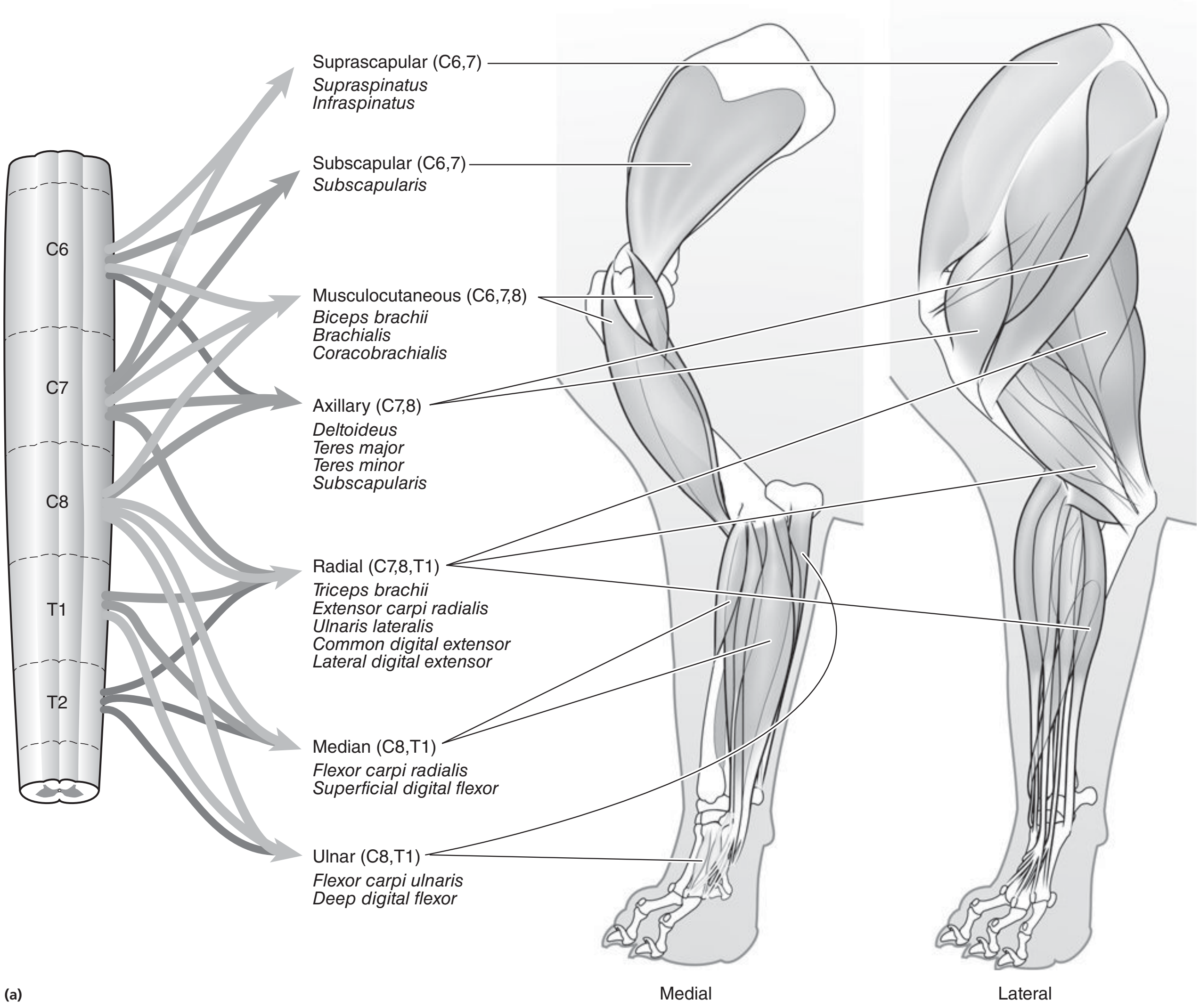
C6
C7
C8
T1
T2
Suprascapular (C6,7)
Supraspinatus
Infraspinatus
Subscapular (C6,7)
Subscapularis
Musculocutaneous (C6,7,8)
Biceps brachii
Brachialis
Coracobrachialis
Axillary (C7,8)
Deltoideus
Teres major
Teres minor
Subscapularis
Radial (C7,8,T1)
Triceps brachii
Extensor carpi radialis
Ulnaris lateralis
Common digital extensor
Lateral digital extensor
Median (C8,T1)
Flexor carpi radialis
Superficial digital flexor
Ulnar (C8,T1)
Flexor carpi ulnaris
Deep digital flexor
(a)
Medial
Lateral

Figure 3.19 Schematic illustration of important muscles innervated by the cervical and lumbosacral intumescences and the spinal cord segments contributing to their respective innervations.

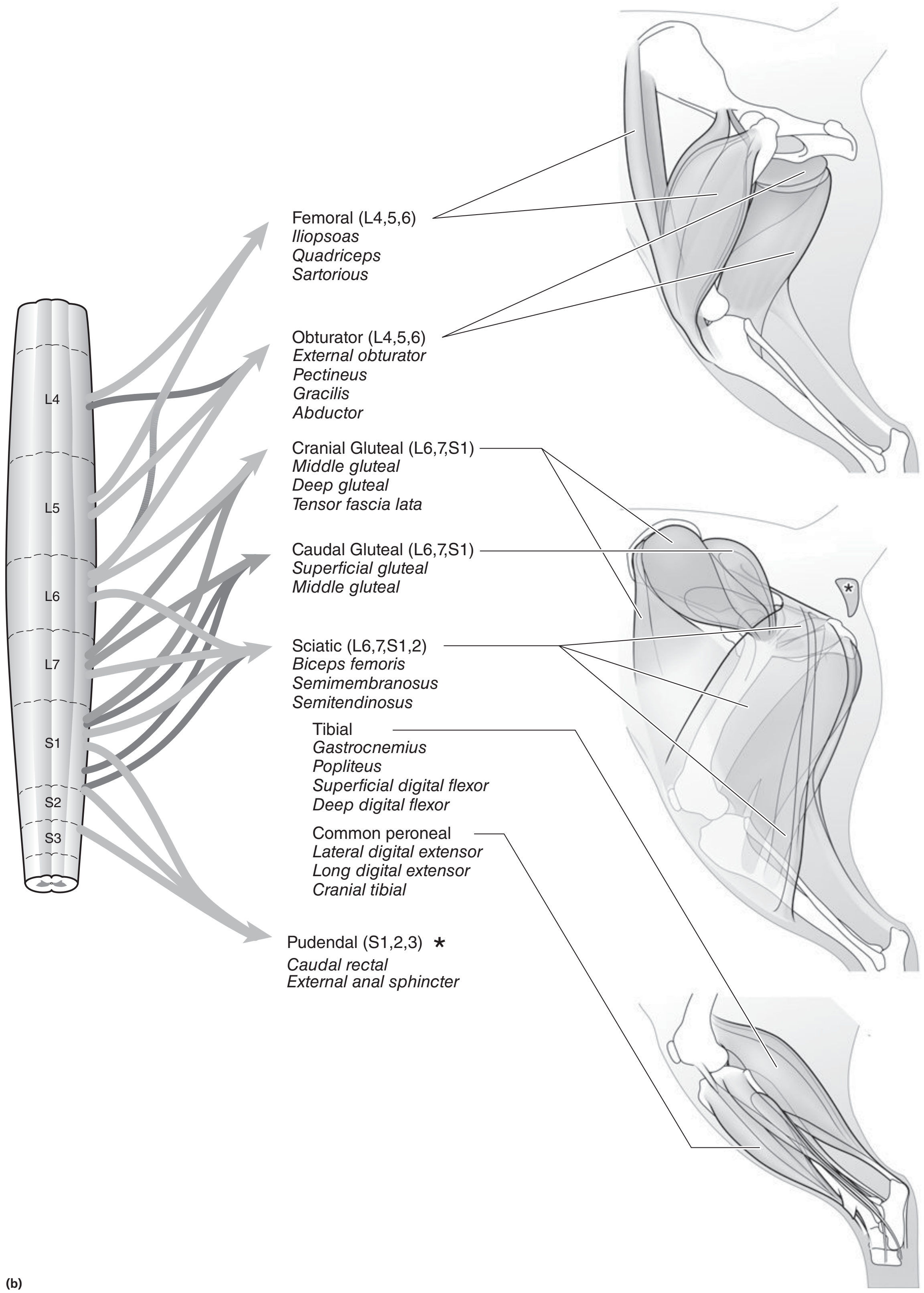
L4
L5
L6
L7
S1
S2
S3
Femoral (L4,5,6)
Iliopsoas
Quadriceps
Sartorious
Obturator (L4,5,6)
External obturator
Pectineus
Gracilis
Abductor
Cranial Gluteal (L6,7,S1)
Middle gluteal
Deep gluteal
Tensor fascia lata
Caudal Gluteal (L6,7,S1)
Superficial gluteal
Middle gluteal
Sciatic (L6,7,S1,2)
Biceps femoris
Semimembranosus
Semitendinosus
Tibial
Gastrocnemius
Popliteus
Superficial digital flexor
Deep digital flexor
Common peroneal
Lateral digital extensor
Long digital extensor
Cranial tibial
Pudendal (S1,2,3) *
Caudal rectal
External anal sphincter
*
(b)

Figure 3.19 (*Continued*)

Table 3.4 Neurologic signs of spinal cord dysfunction.

Evaluations	C1–C5*	C6–T2	T3–L3	L4–caudal segments
Mental status	Normal	Normal	Normal	Normal
Posture	Normal; wide-base stance Lateral recumbency with severe lesions Normal or guarded neck posture	Normal; wide-base stance Lateral recumbency with severe lesions Normal or guarded neck posture	Normal or kyphotic posture with painful lesions	Normal or kyphotic posture with painful lesions
Gait	Proprioceptive ataxia, typically TL = PL), spastic (long-strided) tetraparesis/plegia Ipsilateral hemiparesis/plegia	Proprioceptive ataxia, typically PL > TL), tetraparesis/plegia Ipsilateral hemiparesis/plegia	Normal TLs Proprioceptive ataxia in the PLs Paraparesis or paraplegia	Paraparesis or paraplegia (with spinal cord lesions) Mild proprioceptive ataxia PLs (with cord lesions) Lesions affecting the cauda equina nerves (L6-L7-S1 vertebrae) will only cause paraparesis without ataxia
Cranial nerves	Typically normal May see Horner's syndrome with severe lesions	Typically normal May see Horner's syndrome with severe lesions	Normal	Normal
Spinal reflexes	Normal Hyperreflexia all limbs	Hyporeflexia or absent reflexes TLs Normal to hyperreflexia in PLs	Normal Hyperreflexia PLs	Decreased to absent reflexes PLs May see pseudohyperreflexia patellar reflex with sciatic lesions
Spinal hyperesthesia	None or pain on palpation or movements	None or pain on palpation or movements	None or pain on palpation	None or pain on palpation
Nociception (pain perception)	Normal Tetraplegic dogs may show decreased or absent nociception	Normal Tetraplegic dogs may show decreased or absent nociception	Normal Paraplegic dogs may show decreased or absent nociception	Normal Paraplegic dogs may show decreased or absent nociception
Micturition	Usually normal May have detrusor areflexia-sphincter hypertonia	Usually normal May have detrusor areflexia-sphincter hypertonia	Usually normal Plegic patients may have detrusor areflexia-sphincter hypertonia	Normal or detrusor areflexia-sphincter hypotonia

*These locations reflect spinal cord regions, not vertebral column regions.
TL = thoracic limbs, PL = pelvic limbs.
Source: Courtesy of Dr. Joan Coates (with modifications).

sciatic nerve (L6, L7, S1, variable S2), so decreased withdrawal and gastrocnemius reflexes are also possible.

b. Lesions primarily of the L7–S3 area of the spinal cord cause signs of LMN dysfunction in distribution sites of sciatic (decreased to absent withdrawal and gastrocnemius reflexes), pudendal (decreased to absent perineal [anal] reflex, poor anal tone), and pelvic (atonic "LMN bladder") nerves. Patellar reflexes may appear hyperactive (pseudohyperreflexia) if the sciatic nerve or its contributing cell bodies are compromised, but the segments supplying the femoral nerve are not damaged (e.g. degenerative lumbosacral stenosis). The quadriceps muscle group is usually opposed by the caudal thigh muscles; the latter tend to dampen the patellar reflex (they cause stifle flexion) in the normal dog and cat.

c. The terminal spinal cord segments are referred to as caudal or coccygeal segments (Cd1–Cd5). These segments contain the LMNs supplying tail musculature, so their dysfunction is manifested by paresis or plegia of the tail.

The peripheral nervous system

This neuroanatomic localization includes peripheral nerve, skeletal muscle, and neuromuscular junction (NMJ). Neuronopathies are diseases in which premature degeneration of neuronal cell bodies occurs. Since dogs and cats with neuronopathies display clinical signs similar to or indistinguishable from animals with neuropathies, this disease category is included under peripheral nerve disorders in this text. While disorders of this category are not as common as brain and spinal cord disorders, they are not rare as a group. Many of these disorders have a diffuse distribution (e.g. polyradiculoneuritis), whereas others may appear relatively focal (e.g. idiopathic facial paralysis/paresis). These disorders are usually readily distinguishable from brain and spinal cord problems. One key clinical feature that assists in this distinction is *the lack of ataxia* with peripheral nervous system diseases. It may be difficult to distinguish neuropathy from myopathy from neuromuscular junction disorders. This is not of major importance, as the diagnostic tests used to further characterize all of these disorders are similar. Refer to Table 3.5 for clinical signs of peripheral nervous system dysfunction.

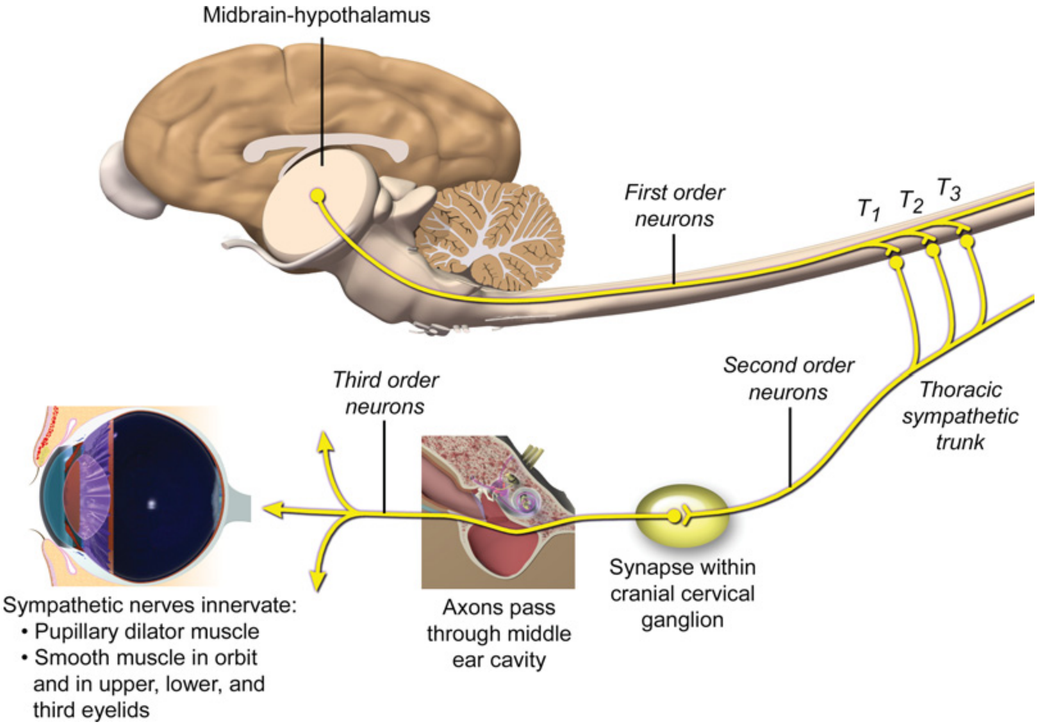
Midbrain-hypothalamus
First order neurons
T1
T2
T3
Second order neurons
Thoracic sympathetic trunk
Third order neurons
Sympathetic nerves innervate:
• Pupillary dilator muscle
• Smooth muscle in orbit and in upper, lower, and third eyelids
Axons pass through middle ear cavity
Synapse within cranial cervical ganglion

Figure 3.20 Neuroanatomic pathway for sympathetic innervation of the eye. (The Ohio State University. Reproduced with permission.)

A. Peripheral nerve[11,29] (Videos 13, 33, 34, 36)

1. There are often markedly reduced or absent reflexes, primarily the patellar reflex, with variable proprioceptive deficits.
2. There is often reduced or absent muscle tone.
3. Depending on the specific disorder, there is a variable distribution of deficits; both mononeuropathies and polyneuropathies are possible (see Chapter 17).
4. Neurogenic muscle atrophy is common. This is rapidly developing muscle atrophy (over 1–2 wks) due to disruption of nerve supply to the muscle.
5. It may be difficult to discern peripheral nerve disorders from some NMJ disorders.

B. Skeletal muscle[3,21,40] (Video 39)

1. Patellar reflexes and proprioception are usually normal. Flexor reflexes may be decreased.

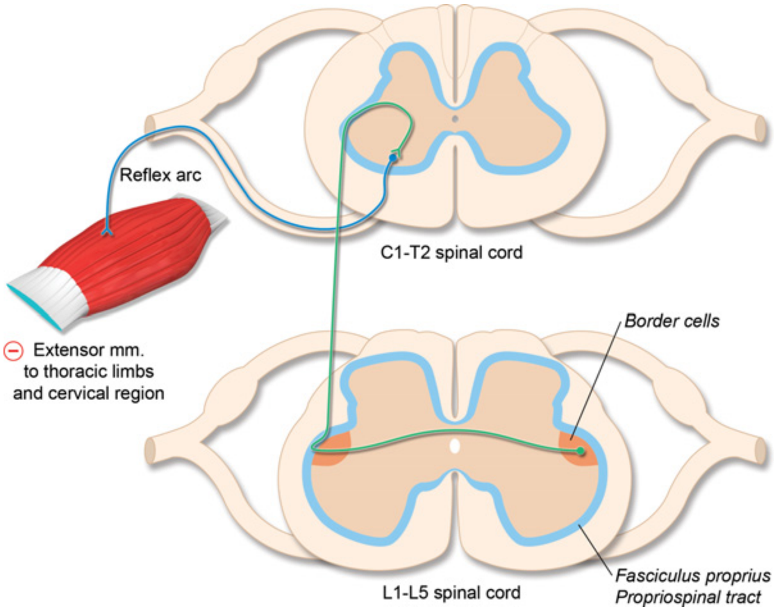
Reflex arc
C1-T2 spinal cord
⊖ Extensor mm. to thoracic limbs and cervical region
Border cells
L1-L5 spinal cord
Fasciculus proprius Propriospinal tract

Figure 3.21 Fasciculus proprius or propriospinal tract is the ascending inhibitory pathway to cervicothoracic lower motor neurons, the interruption of which leads to the Schiff–Sherrington phenomenon. (The Ohio State University. Reproduced with permission.)

Table 3.5 Neurologic signs of peripheral nerve, neuromuscular junction, and muscle dysfunction.

	Specific signs seen with lesions in each location				
Evaluations	**Neuronopathy**	**Mononeuropathy**	**Polyneuropathy**	**Junctionopathy**	**Myopathy**
Mental status	Usually normal May be obtunded if brain-stem nuclei are affected	Normal	Normal	Normal	Normal
Posture	Progressively unable to support trunk and head	Varies according to location of affected nerve	May be unable to support trunk or head	May be unable to support trunk or head may show generalized or focal involvement	Stiff May hold head/cervical spine horizontal
Muscle mass/tone	Usually proximal mm, atrophy progressing to distal mm	Asymmetric limb involvement Rapid and severe atrophy of affected mm	Generalized and symmetrical rapid and severe atrophy Distal > proximal mm ± mm flaccidity	Muscle mass usually normal Muscle tone may be flaccid	Usually bilateral, symmetrical generalized atrophy May have bulk muscles May have asymmetry Joint contracture
Gait	Tetraparesis Variations in severity of thoracic vs. pelvic limb involvement	Monoparesis/plegia	May be stilted Tetraparesis/plegia	Episodic paresis Pelvic limbs may be more severely affected, stilted	Tetraparesis; episodic Exercise intolerance Stilted gait
Cranial nerves	May be affected May manifest dysphonia, megaesophagus	May be affected	May be affected Facial paresis, dysphonia	May be affected Facial paresis, megaesophagus, dysphonia	May observe severe loss muscle mass of masticatory mm
Postural reactions	Decreased/absent Limb involvement may vary	Decreased/absent in affected limb	Decreased-absent in all limbs	Normal if patient not weak May be decreased/absent depending on degree of weakness	Normal, decreased/absent
Spinal hyperesthesia	None	None	None (except in rare cases of polyradiculoneuritis)	None	Pain may be present upon palpation with some disorders
Pain perception	Normal	Dermatomal hypoesthesia or analgesia	Usually normal, ± paresthesia	Normal	Normal
Micturition	Usually normal until late in disease course	Usually not affected unless S1–S3 spinal nerves are involved	May manifest detrusor/sphincter hypotonia	Usually normal	Usually normal

Note: mm. = muscles.
Source: J. Coates, University of Missouri, Columbia, MO, 2014. Reproduced with permission of J. Coates.

2. Generalized weakness is frequently evident, often with exercise intolerance.
3. There is usually a bilaterally symmetrical distribution of clinical signs (see Chapter 18 for specific myopathies).
4. Muscle pain on palpation (myalgia) may be appreciated with some myopathies.

C. Neuromuscular junction[47] (Video 40)
1. Clinical signs of weakness are due to interference of nerve–muscle communication at the level of the neuromuscular junction (see Chapter 19).
2. Reflexes may be normal, depressed, or absent, depending on the specific disorder and severity.
3. In ambulatory dogs, the patellar reflex and proprioceptive positioning are usually normal.
4. There is a tendency for diffuse distribution of signs.
5. Exercise intolerance may be noted.
6. Some NMJ disorders may be indistinguishable clinically from a neuropathy or myopathy without further diagnostics.

Anatomy of the spinal reflexes

In the normal animal, spinal reflexes operate under the influence of descending UMN influence from the brain. However, spinal reflexes remain intact, and are sometimes even exaggerated, if UMN influence is attenuated or abolished. An extreme example of this concept is spinal walking. Occasionally, weeks to months after a complete transection injury to the T3–L3 region of the spinal cord in a dog or cat, the patient will develop rhythmic walking movements in the pelvic limbs. The walking movements are due to coordinated reflex patterns that develop within

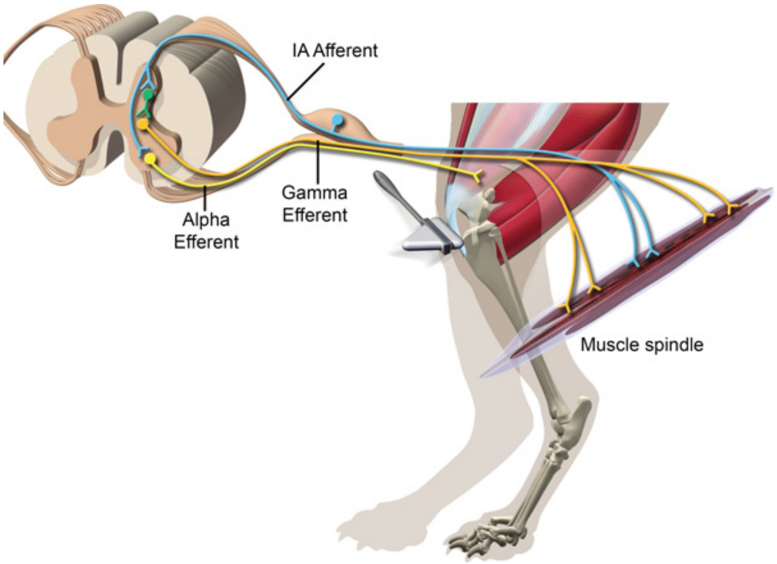

Figure 3.22 Schematic representation of the tendon/patellar (stretch) reflex. (The Ohio State University. Reproduced with permission.)

the spinal cord, without any input to or information from UMNs. This "walking" can be induced by stimulating the patient's pelvic limbs, and sometimes by stimulating nearby areas (e.g. tail, perineum). These animals have no nociception to the pelvic limbs, and the pelvic limb movements are not coordinated with the thoracic limbs.[38] The following is a simplified description of the anatomy involved in withdrawal and tendon (stretch) reflexes.

A. Withdrawal reflex[39]
  1. The withdrawal reflex is a coordinated polysynaptic reflex, in which all the flexor muscles of a limb contract in response to a noxious stimulus.
  2. During the withdrawal reflex, alpha motor neurons to the limb flexor muscles are stimulated, while those to extensor muscles are inhibited. This phenomenon is called reciprocal innervation.
  3. The force and duration of the withdrawal reflex are proportional to the intensity of the noxious stimulus applied.

B. Tendon (stretch) reflex[35, 39]
  1. The stretch reflex (e.g. patellar reflex) is primarily a monosynaptic reflex. Afferent axons from a muscle stretch receptor directly synapse with spinal cord alpha motor neurons, which cause contraction of that same muscle (Fig. 3.22).
  2. The stretch receptor for the tendon reflex is a structure called the muscle spindle, located deep within the main muscle belly. The muscle spindle contains specialized muscle fibers called intrafusal fibers, which are arranged in parallel with the main muscle (extrafusal) fibers.
  3. The intrafusal muscle fibers of the muscle spindle are made up of polar contractile ends and a central, noncontractile region. Sensory endings of Ia afferent axons contact the central regions of the intrafusal fibers. When the central region is stretched (i.e. striking the tendon), action potentials are generated in the Ia axons. The Ia axons enter the spinal cord synapsing with, and exciting, alpha motor neurons innervating the extrafusal muscle fibers. Collaterals of Ia axons within the spinal cord also excite Ia inhibitory interneurons. These interneurons synapse with, and decrease activity of, alpha motor neurons that innervate antagonistic muscle groups. When the muscle contracts, the central region of the intrafusal fibers relaxes, decreasing the firing rate of Ia axons.
  4. The sensitivity of the muscle spindle can be altered by UMN input to gamma motor neurons. Gamma motor neurons are excitatory neurons that directly innervate the contractile ends of intrafusal muscle fibers. UMN excitation or inhibition of gamma motor neurons can increase or decrease sensitivity of the muscle spindle to stretch, respectively.
  5. The duration and force of muscle contraction associated with a tendon reflex is mitigated to some degree by another receptor called the Golgi tendon organ. The Golgi tendon organ is a group of sensory nerve endings intertwined with collagen fibers at the musculotendinous junction. These sensory nerve endings give rise to an Ib afferent axon. The sensory endings are sensitive to muscle tension, increasing their firing rate when the muscle contracts. The Ib afferent axon stimulates a spinal cord Ib inhibitory interneuron, which inhibits the alpha motor neuron causing the muscle contraction.
  6. It has been demonstrated that older dogs (>10 yrs old) are significantly more likely to lose their patellar reflex in one or both limbs, in the absence of any other sign of neurologic disease, than younger (< 10 yrs old) dogs. This is considered an age-related phenomenon, rather than an indication of spinal cord disease. Hypotheses for this age-related finding include degeneration/atrophy of extrafusal muscle fibers, degeneration of intrafusal muscle fibers (responsible for the afferent impulse propagation via Ia afferents), and degenerative changes of the

lumbar spinal nerves. The finding of decreased to absent patellar reflexes in an older dog could be considered normal in the absence of any other signs of neurologic dysfunction.

The autonomic nervous system and associated visceral functions[1, 10, 12, 22–24, 30, 41]

The anatomical and functional complexity of the autonomic nervous system often causes clinical evidence of its dysfunction to be misunderstood or ignored. A basic understanding of this involuntary "visceral" system and associated structures is more than sufficient for clinical application. (See Chapter 16 for a fuller discussion of autonomic function and dysfunction associated with bladder control.) The autonomic nervous system is functionally and structurally divided into parasympathetic (cholinergic) and sympathetic (adrenergic) systems. Because the preganglionic neurons of the parasympathetic system are found primarily in the brain stem and sacral spinal cord, this system is sometimes referred to as the "craniosacral" component of the autonomic nervous system. The preganglionic neurons of the sympathetic nervous system are found primarily in the thoracic and lumbar spinal cord (from approximately T1–L5 segments), which explains why this aspect of the autonomic nervous system is called the "thoracolumbar" component. Although organs are generally innervated by both systems, sympathetic output is the controlling influence facilitating cardiac output and blood pressure, whereas parasympathetic output predominantly opposes these sympathetic effects and promotes gastrointestinal and glandular (e.g. lacrimation, salivation) function. It should be noted that the gastrointestinal tract has its own intrinsic and somewhat autonomous nervous system. Although a gross oversimplification, the sympathetic nervous system has been referred to as the "fight or flight" division of the autonomic nervous system, with the parasympathetic system occupying the role of the "rest and digest" division. As with other functional divisions of the nervous system, the autonomic nervous system normally maintains a state of visceral homeostatic equilibrium by adjusting efferent output in accordance with afferent input.

Afferent input

In general, afferent input from the periphery to brain-stem centers for autonomic control are transmitted via the solitary tract (ST) in the medulla oblongata (Fig. 3.23). This sensory tract is organized similarly to the sensory tract for the trigeminal nerve (quintothalamic tract). Surrounding the solitary tract is the nucleus of the solitary tract (NST). Afferents from the peripheral nerves (CN VII, IX, and X) travel to the ST, synapse on neurons in the NST, and these neurons will subsequently synapse either on brain-stem or spinal cord centers for involuntary visceral functions (see the next section, Efferent output), or project to the thalamus for conscious perception (solitariothalamic tract). The solitary tract conveys information regarding blood pressure and tissue oxygenation levels from baroreceptors and chemoreceptors in large arteries (e.g. carotid, aortic arch) via CN IX and X, and the modality of taste from gustatory nerves via CN VII (CN V in the periphery), IX and X. In addition, sensory input to the ST from the olfactory and limbic portions of the brain allow for autonomic responses to smells and emotional reactions, respectively. Reflex functions associated with the viscera also involve afferent input into the solitary tract.

Visceral pain does not appear to be primarily represented in the solitary tract. Rather, this mode of visceral sensation travels retrograde via sympathetic nerves (Fig. 3.24). Once at the spinal cord level, this visceral nociceptive pathway follows a route similar to that for somatic pain perception (spinothalamic tract). At the dorsal horn level of the spinal cord, there are interneurons that receive input from both visceral and somatic afferent nerves. In essence, these interneuron relays for pain sensation are shared by somatic and visceral structures; this anatomic organization may be a potential explanation for the clinical phenomenon of referred pain.

Efferent output

The hypothalamus influences both parasympathetic and sympathetic output centers in the medulla oblongata, with the rostral hypothalamus facilitating parasympathetic output, and the caudal hypothalamus facilitating sympathetic output. The hypothalamus probably plays an integrative role in autonomic responses, rather than providing the primary efferent output for these responses.

Both parasympathetic and sympathetic efferent systems consist of a two-neuron pathway, with a preganglionic and postganglionic neuron. In the sympathetic system, the preganglionic neuron is located in the intermediolateral gray substance of the thoracic and lumbar spinal cord. The axons of these neurons leave via ventral rootlets, join the spinal nerve of that cord segment and then travel to synapse in a ganglion (the postganglionic neuron) via one of three routes: a sympathetic chain ganglion along the lateral aspect of the vertebral column; via splanchnic nerves to a visceral ganglion in the thoracic or abdominal cavities (e.g. celiac, cranial, and caudal mesenteric ganglia); or the adrenal medulla, which is structurally and functionally a large collection of postganglionic sympathetic neurons. With some notable exceptions (e.g. adrenal medulla), preganglionic sympathetic axons synapse some distance from the ultimate target organ or structure. In contrast, preganglionic parasympathetic neurons generally have long axonal processes that synapse on postganglionic neurons either very close to or within the target organ or structure. Within the medulla, there are three clinically important parasympathetic nuclei that contain the preganglionic neurons which project to parasympathetic ganglia to regions other than those associated with bladder function (this topic is covered in detail in Chapter 16)—the parasympathetic nuclei of CN VII, IX, and X (Fig. 3.25). These parasympathetic nuclei are located dorsolateral to their

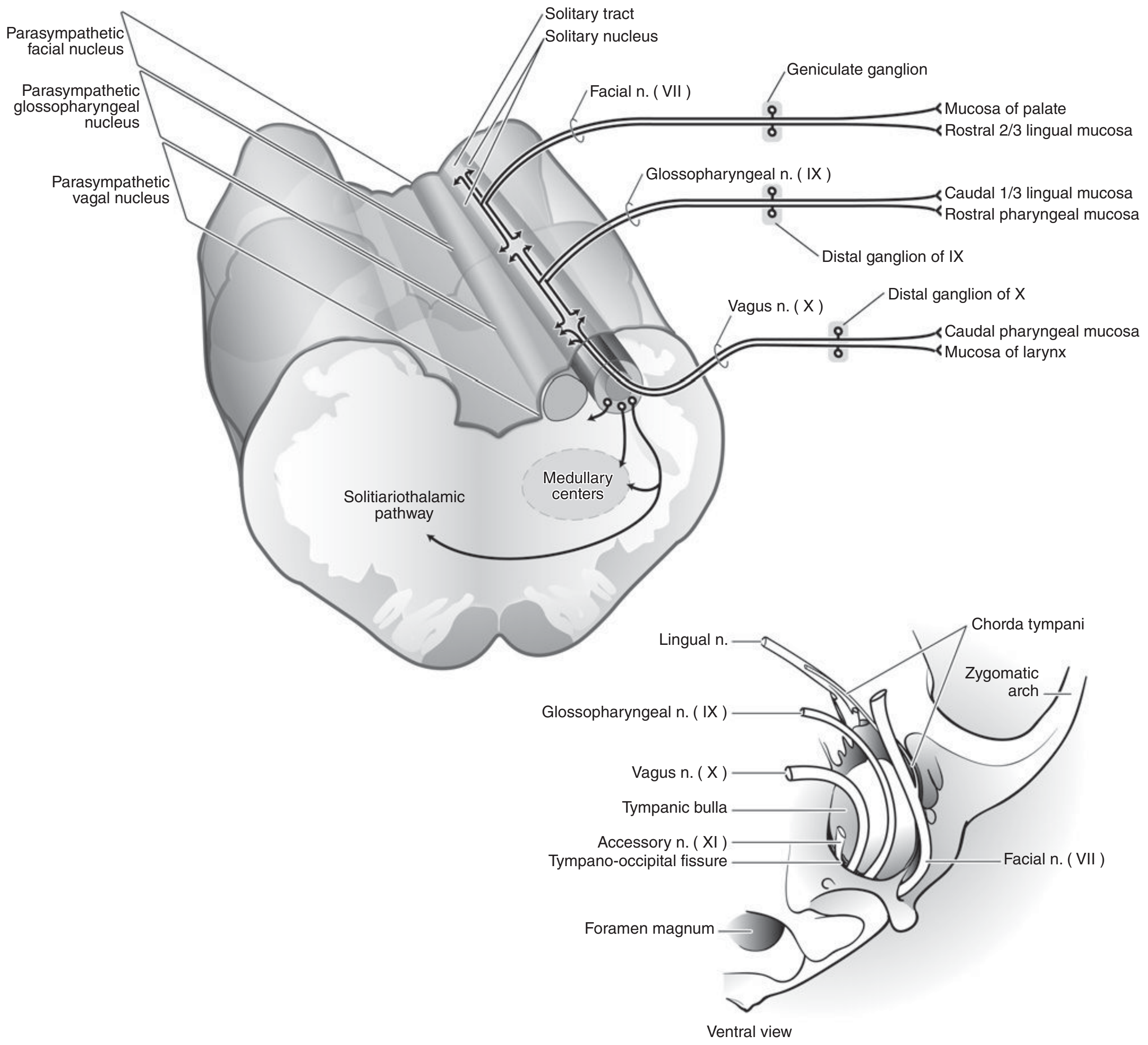
Parasympathetic facial nucleus
Parasympathetic glossopharyngeal nucleus
Parasympathetic vagal nucleus
Solitary tract
Solitary nucleus
Facial n. (VII)
Geniculate ganglion
Mucosa of palate
Rostral 2/3 lingual mucosa
Glossopharyngeal n. (IX)
Caudal 1/3 lingual mucosa
Rostral pharyngeal mucosa
Distal ganglion of IX
Vagus n. (X)
Distal ganglion of X
Caudal pharyngeal mucosa
Mucosa of larynx
Medullary centers
Solitiariothalamic pathway
Lingual n.
Chorda tympani
Zygomatic arch
Glossopharyngeal n. (IX)
Vagus n. (X)
Tympanic bulla
Accessory n. (XI)
Tympano-occipital fissure
Facial n. (VII)
Foramen magnum
Ventral view

Figure 3.23 Afferent input for autonomic functions and connections with the solitary tract.

somatic motor counterparts. This is an important distinction to make, especially for CN IX and X. The parasympathetic nuclei of CN IX and X are structurally and functionally distinct from those neurons found in the nucleus ambiguus. In some texts, the parasympathetic nuclei of CN VII and IX are referred to as rostral and caudal salivatory nuclei, respectively. The parasympathetic nucleus of CN X, or the parasympathetic nucleus of the vagus nerve, is referred to in some texts as the dorsal vagal nucleus. The parasympathetic nucleus of the facial nerve (VII) supplies preganglionic axonal input to the pterygopalatine ganglion as well as the mandibular and sublingual ganglia. Postganglionic axons from the pterygopalatine ganglion join the maxillary branch of CN V to supply the lacrimal glands, nasal glands, and palatine glands. Postganglionic axons from the mandibular and sublingual ganglia join the mandibular branch of CN V to supply the mandibular and sublingual salivary glands, respectively. Preganglionic input to the otic ganglion is provided by the parasympathetic nucleus of the glossopharyngeal nerve (CN IX). Postganglionic fibers from the otic ganglion join the mandibular branch of CN V to innervate parotid and zygomatic salivary glands. The parasympathetic nucleus of the vagus nerve (CN X) provides parasympathetic input to the heart, lungs, gastrointestinal smooth muscle and glands, as well as several other organs (e.g. gallbladder, pancreas, liver). The postganglionic neurons are located near or within the organs being innervated.

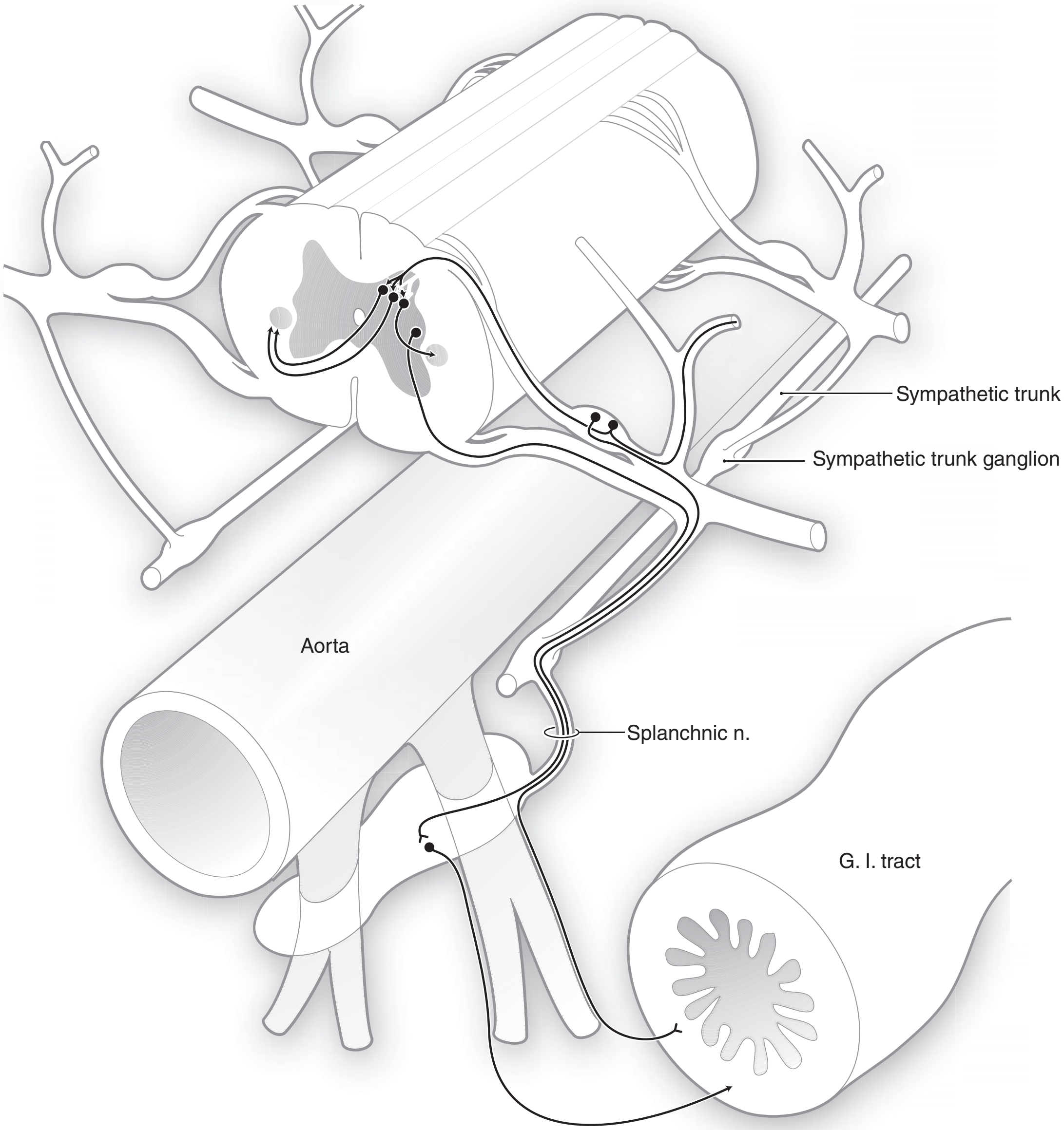

Figure 3.24 The pathway for visceral pain (nociception) sensation.

Blood pressure control and the "Cushing response"

Although the preceding discussion concerning autonomic functions should provide adequate understanding for application to clinical situations, one further level of complexity needs to be added to explain the interrelationships between the brain and blood pressure. Specific information regarding intracranial pressure (ICP) dynamics can be found in Chapter 8, and will not be discussed here. The sympathetic outflow from the preganglionic neurons in the intermediolateral gray column of the thoracolumbar spinal cord is the main driving force for maintaining normal blood pressure, as well as increasing systemic blood pressure as needed. The parasympathetic system plays a comparatively minor role in affecting vascular tone. The thoracolumbar sympathetic efferents are innervated and driven by higher brain centers, most importantly a vasomotor center in the rostral ventrolateral medulla (RVLM). The RVLM supplies constant facilitory input to the spinal cord preganglionic sympathetic neurons and can be thought of as the UMN of the sympathetic nervous system; these neurons have also been referred to as "presympathetic." A constant inhibitory influence to the RVLM is provided by a group of neurons in the caudal ventrolateral medulla (CVLM). As discussed, both baroreceptor and chemoreceptor afferents from the peripheral vasculature reach the medullary centers via the solitary tract and nucleus of the solitary tract; however, there are some important differences in

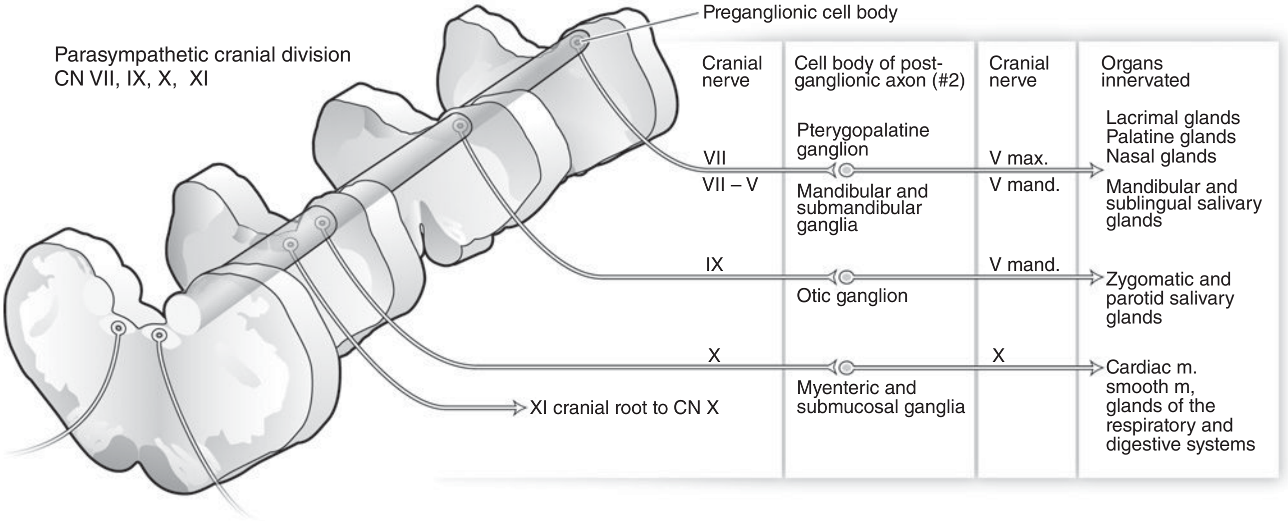
Parasympathetic cranial division
CN VII, IX, X, XI
Preganglionic cell body
Cranial nerve
Cell body of post-ganglionic axon (#2)
Cranial nerve
Organs innervated
VII
Pterygopalatine ganglion
V max.
Lacrimal glands
Palatine glands
Nasal glands
VII – V
Mandibular and submandibular ganglia
V mand.
Mandibular and sublingual salivary glands
IX
Otic ganglion
V mand.
Zygomatic and parotid salivary glands
X
Myenteric and submucosal ganglia
X
Cardiac m. smooth m, glands of the respiratory and digestive systems
XI cranial root to CN X

Figure 3.25 General organization of efferent parasympathetic pathways from the medulla.

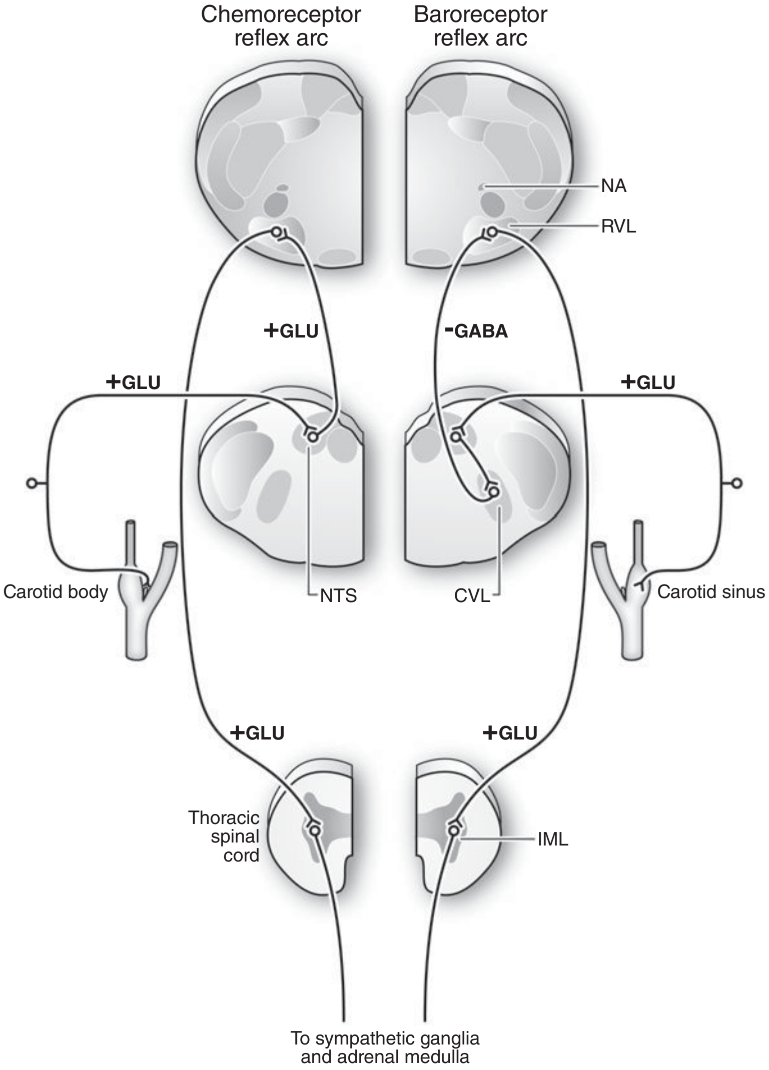
Chemoreceptor reflex arc
Baroreceptor reflex arc
NA
RVL
+GLU
-GABA
+GLU
+GLU
Carotid body
NTS
CVL
Carotid sinus
+GLU
+GLU
Thoracic spinal cord
IML
To sympathetic ganglia and adrenal medulla

Figure 3.26 Schematic representation of chemoreceptor (left side) and baroreceptor (right side) pathways: NA, nucleus ambiguus; RVL, rostral ventrolateral nucleus of the medulla; GLU, glutamate; GABA, gamma-aminobutyric acid; NTS, nucleus of the solitary tract (nucleus tractus solitarius); CVL, caudal ventrolateral nucleus of the medulla; IML, intermediolateral gray column. (Adapted from Reis *et al.*, 1994.)[41]

the organization of the medullary pathways for these two modalities (Fig. 3.26). In situations of mild hypoxemia and/or hypercarbia, afferents from chemoreceptors synapse on neurons in the NST. These NST neurons then directly synapse on and stimulate neurons of the RVLM, increasing sympathetic outflow. Baroreceptor afferents also synapse on neurons of the NST after joining the ST in the medulla. However, these afferents are stimulated by increased systemic blood pressure. The NST neurons stimulated by baroreceptor afferents then synapse on and excite neurons of the CVLM, which in turn provide inhibitory synaptic input to the neurons of the RVLM region. So, hypoxemia will have a fairly direct stimulatory effect on increasing medullary sympathetic outflow, whereas hypotension will have a more indirect, disinhibiting method of causing increased medullary sympathetic outflow (via decreasing baroreceptor input to the tonically inhibitory CVLM region). In addition to these peripheral inputs to the RVLM, the neurons of the RVLM also are able to directly sense and respond (by increasing sympathetic outflow to the periphery) to local brain ischemia/hypoxemia. In such ischemic situations, RVLM neurons have also been shown to cause regional vasodilation in cerebral arteries/arterioles in order to improve blood flow to the brain (mechanisms unclear). This *cerebral ischemic response* is a very effective and powerful mechanism to increase blood flow to the brain by simultaneously increasing local blood flow via vasodilation of cerebral vessels and increasing systemic blood pressure and causing vasoconstriction in peripheral vascular beds (e.g. skin, muscle, mesentery) not essential to survival. In general, the chemoreceptor pathway for sympathetic excitation and the cerebral ischemic response are more potent physiologic phenomena than the counterbalancing disinhibiting response from the baroreceptor system. In addition, the baroreceptor pathway is more effective in influencing cardiovagal responses to hypoxemia than counterbalancing sympathetic elevations of vasomotor tone. These various responses to brain ischemia help to understand the Cushing response. In cases of brain ischemia/hypoxemia, it is common to have the seemingly odd combination of systemic hypertension and bradycardia-the Cushing response. Although historically thought of as an invariably acute, typically fatal, “last-ditch” physiological response to brain ischemia (which it can be-in head trauma patients for example), it probably represents in many patients with more slowly progressive intracranial disease (e.g. intracranial meningioma), a tonic resetting of the vasomotor tone via the mechanisms previously discussed.

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Video Resources

Video resources are available on the companion website: www.wiley.com/go/dewey/neurology

See videos 1, 7, 8, 9, 10, 11, 12 and 13.

CHAPTER 4

Differential Diagnosis

Ronaldo C. da Costa & Curtis W. Dewey

Developing a comprehensive list of differential diagnosis is a key step in the diagnostic approach of patients with neurologic problems. This step is dependent on appropriate neurologic localization. For example, a dog with an abnormal gait in all four limbs could have a lesion in the cerebellum, brain stem, or cervical spinal cord. Obviously, the list of differential diagnoses and the approach for a patient with a cerebellar lesion will be quite different from one with a cervical spinal cord disease. Therefore to appropriately use the tables in this chapter, the clinician should complete a physical and neurologic examination to confirm that the patient has a neurologic problem and localize the lesion appropriately. When developing a list of differential diagnoses, the patient's signalment and history often provide important clues. The goal of this chapter is to bridge the process of localizing a lesion with the selection of the most likely diseases to develop a diagnostic plan. Only the key features of the common diseases will be listed; more detailed information about the differential diagnoses included herein can be found in other chapters. The chapters containing detailed information will be indicated in each table.

Diagnostic approach

The approach to patients with neurologic diseases includes a thorough physical and neurologic examination aimed at localizing the lesion. Proper lesion localization is paramount for the diagnostic approach, as differential diagnoses and ancillary diagnostic tests are dependent on proper lesion localization (Fig. 4.1 and Fig. 4.2).

In terms of lesion localization it may be helpful to localize the lesion to "big" regions first and then refine the process by narrowing the location to a specific brain or spinal cord region. For example, first establish whether the lesion is in the central (CNS) or peripheral (PNS) nervous system, then, if in the CNS, define whether it is the brain or spinal cord.

The brain can be functionally divided into forebrain (the same as thalamocortex, prosencephalon, or cerebrum), brain stem (mesencephalon or midbrain, pons and rostral and caudal medulla), and cerebellum. Vestibular signs are a very common manifestation of brain-stem disease. Vestibular disease can be a sign of a brain-stem problem (rostral medullary lesion) commonly known as central vestibular disease, or an inner ear problem (vestibulocochlear nerve or receptors), known as peripheral vestibular disease.

The spinal cord is divided into four major segments. It is important to remember that the spinal cord segments do not match up with the vertebrae in the cervical and lumbar regions and that there are seven cervical vertebrae but eight cervical spinal cord segments (Fig. 3.16). The main spinal cord divisions in terms of lesion localization are C1 to C5, C6 to T2, T3 to L3 and L4 to S3. In addition to these four classic spinal cord segments, there are three subdivisions that are clinically relevant and may assist the clinician in considering the appropriate differential diagnoses and select the most indicated ancillary tests. These subdivisions are the vertebral regions T2 to T10, and L6–L7–S1.

Finally, we have the neuromuscular diseases in a separate category. For detailed information on the clinical features seen with lesions in each specific brain, spinal, or neuromuscular region, the reader is referred to the specific chapters (Chapters 7, 13, 17, 18, and 19).

Differential diagnosis

The simplest approach to a case with neurologic signs, once the lesion is localized, is to consider differential diagnoses using the acronym lists based on pathophysiologic mechanisms. These acronyms are called either VITAMIN-D or DAMNIT-V and are very useful and practical ways to approach neurologic diseases. A list of common diseases according to the VITAMIN-D acronym is presented in Table 4.1 and Table 4.2, and Fig. 4.1 and Fig. 4.2. When using this acronym, it is useful to consider the signalment and history to develop appropriate differential diagnoses for the patient. For example, even though intervertebral

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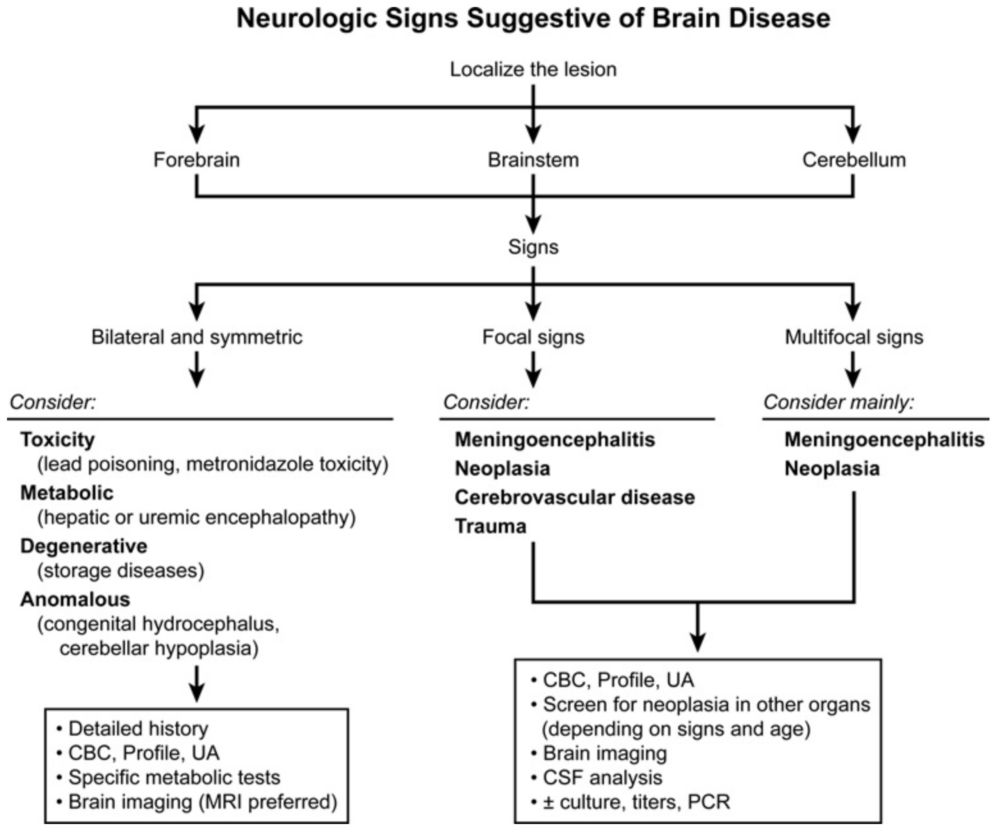
Neurologic Signs Suggestive of Brain Disease
Localize the lesion
Forebrain
Brainstem
Cerebellum
Signs
Bilateral and symmetric
Focal signs
Multifocal signs
Consider:
Toxicity
(lead poisoning, metronidazole toxicity)
Metabolic
(hepatic or uremic encephalopathy)
Degenerative
(storage diseases)
Anomalous
(congenital hydrocephalus, cerebellar hypoplasia)
• Detailed history
• CBC, Profile, UA
• Specific metabolic tests
• Brain imaging (MRI preferred)
Consider:
Meningoencephalitis
Neoplasia
Cerebrovascular disease
Trauma
Consider mainly:
Meningoencephalitis
Neoplasia
• CBC, Profile, UA
• Screen for neoplasia in other organs (depending on signs and age)
• Brain imaging
• CSF analysis
• ± culture, titers, PCR

Figure 4.1 Algorithm presenting the differential diagnoses and diagnostic approach to brain problems according to the lesion localization.
CSM = cervical spondylomyelopathy. IVDD = intervertebral disc disease. FCEM = fibrocartilaginous embolic myelopathy. MRI = magnetic resonance imaging. CT = computed tomography. PCR = polymerase chain reaction. CSF = cerebrospinal fluid analysis.

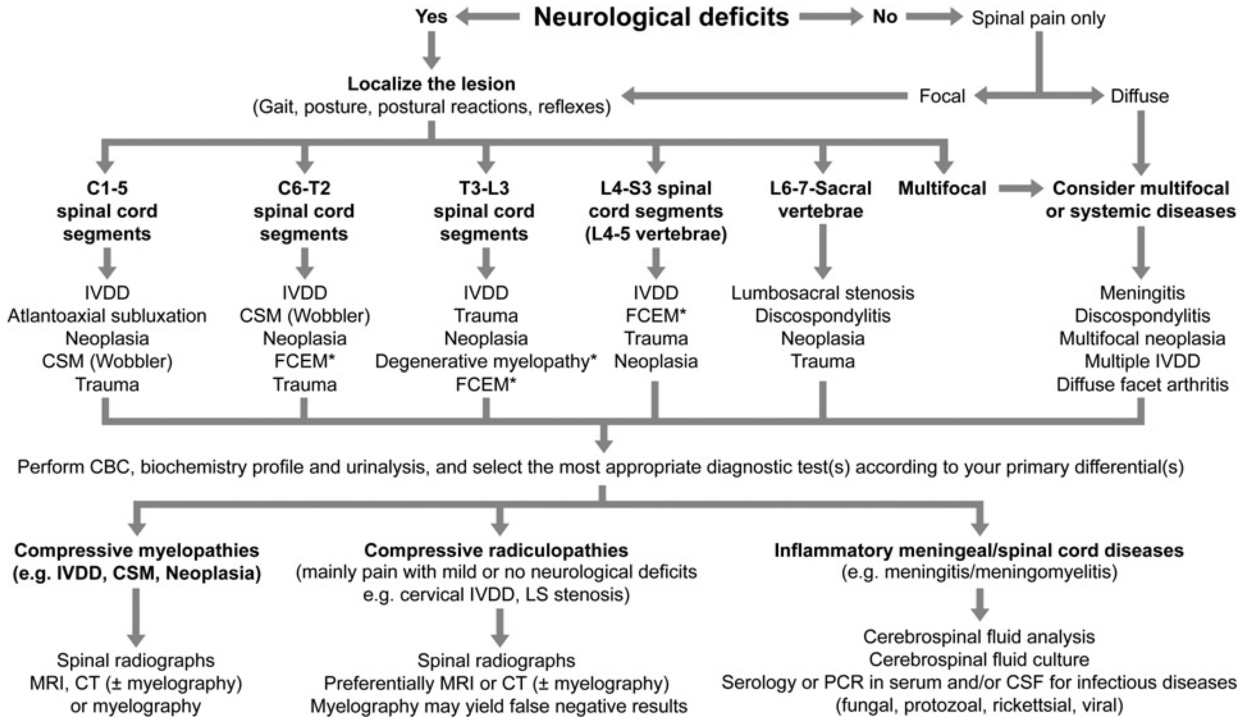
Yes
Neurological deficits
No
Spinal pain only
Localize the lesion
(Gait, posture, postural reactions, reflexes)
Focal
Diffuse
C1-5 spinal cord segments
C6-T2 spinal cord segments
T3-L3 spinal cord segments
L4-S3 spinal cord segments (L4-5 vertebrae)
L6-7-Sacral vertebrae
Multifocal
Consider multifocal or systemic diseases
IVDD
Atlantoaxial subluxation
Neoplasia
CSM (Wobbler)
Trauma
IVDD
CSM (Wobbler)
Neoplasia
FCEM*
Trauma
IVDD
Trauma
Neoplasia
Degenerative myelopathy*
FCEM*
IVDD
FCEM*
Trauma
Neoplasia
Lumbosacral stenosis
Discospondylitis
Neoplasia
Trauma
Meningitis
Discospondylitis
Multifocal neoplasia
Multiple IVDD
Diffuse facet arthritis
Perform CBC, biochemistry profile and urinalysis, and select the most appropriate diagnostic test(s) according to your primary differential(s)
Compressive myelopathies (e.g. IVDD, CSM, Neoplasia)
Compressive radiculopathies (mainly pain with mild or no neurological deficits e.g. cervical IVDD, LS stenosis)
Inflammatory meningeal/spinal cord diseases (e.g. meningitis/meningomyelitis)
Spinal radiographs
MRI, CT (± myelography)
or myelography
Spinal radiographs
Preferentially MRI or CT (± myelography)
Myelography may yield false negative results
Cerebrospinal fluid analysis
Cerebrospinal fluid culture
Serology or PCR in serum and/or CSF for infectious diseases
(fungal, protozoal, rickettsial, viral)

Figure 4.2 Algorithm presenting the differential diagnoses and diagnostic approach to spinal problems according to lesion localization. (The Ohio State University. Reproduced with permission.)
*indicates nonpainful spinal cord diseases. CSM = cervical spondylomyelopathy. IVDD = intervertebral disc disease. FCEM = fibrocartilaginous embolic myelopathy. MRI = magnetic resonance imaging. CT= computed tomography. PCR = polymerase chain reaction. CSF = cerebrospinal fluid analysis.

Table 4.1 Common brain diseases based on the VITAMIN-D acronym for dogs and cats.

Disease mechanism	Specific diseases
Vascular	**Canine or feline cerebrovascular disease (ischemic or hemorrhagic)**[*]
Inflammatory/Infectious	**Meningoencephalitis of unknown etiology** **Necrotizing meningoencephalitis** **Granulomatous meningoencephalitis** **Infectious meningoencephalitides (bacterial, fungal, rickettsial, viral [distemper])**
Trauma	**Craniocerebral trauma** (head trauma, injury) Traumatic vestibular disease (peripheral)
Toxic	**Lead poisoning** **Metronidazole toxicity** Multiple toxicities cause brain signs (see Chapter 23)
Anomalous	**Hydrocephalus** **Chiari-like malformation and syringomyelia** **Quadrigeminal (arachnoid) cysts** Cerebellar hypoplasia Cerebellar abiotrophy Polymicrogyria
Metabolic	**Hepatic encephalopathy** **Hypoglycemic encephalopathy** Uremic encephalopathy Electrolyte-associated encephalopathies
Idiopathic	**Idiopathic epilepsy** **Idiopathic vestibular disease**
Neoplastic	**Primary brain tumors** **Secondary (metastatic) brain tumors**
Nutritional	Thiamine deficiency
Degenerative	**Cognitive dysfunction** Lysosomal storage diseases Mitochondrial encephalopathies Organic acidurias

[*] Bold used to indicate common diseases.

Table 4.2 Common spinal diseases based on the VITAMIN-D acronym for dogs and cats.

Disease mechanism	Specific diseases
Vascular	**Fibrocartilaginous embolic myelopathy**[*] Epidural hemorrhage Spinal cord hemorrhage
Inflammatory/Infectious	**Discospondylitis** (bacterial or fungal) **Meningitis** (**steroid-responsive meningitis-arteritis** or bacterial meningitis) **Meningomyelitis infectious** (bacterial, fungal, rickettsial, viral) or **noninfectious** (unknown etiology, granulomatous meningoencephalomyelitis) Spinal empyema Vertebral osteomyelitis
Trauma	**Spinal trauma** (fracture/luxations) Traumatic disc extrusion Traumatic atlantoaxial subluxation
Toxic	None
Anomalous	**Atlantoaxial instability** **Chiari-like malformation and syringomyelia** **Hemivertebra** Arachnoid cysts Multiple cartilaginous exostoses Spinal bifida Spinal dysraphism
Metabolic	None
Idiopathic	Disseminated idiopathic skeletal hyperostosis (DISH)
Neoplastic	**Primary or secondary spinal tumors**
Nutritional	Pathologic fractures due to metabolic bone disease Hypervitaminosis A (cats)
Degenerative	**Intervertebral disc degeneration** **Degenerative myelopathy** **Degenerative lumbosacral stenosis** Degenerative osteoarthritis of articular facets Extradural synovial cysts
Developmental	**Cervical spondylomyelopathy**

[*] Bold used to indicate common diseases.

disc disease is the most common spinal disease of dogs, it is not a reasonable differential diagnosis for a 6-mo-old dog with chronic paraparesis. Some generalities should be considered when using the VITAMIN-D acronym. Young dogs are more likely to have congenital or inflammatory conditions. Acute presentations are usually caused by vascular or traumatic conditions. Chronic presentations are usually seen with degenerative or neoplastic processes. Another way to approach patients with neurologic problems is to develop a list of diseases that are known to affect specific regions of the brain and spine. This is useful mainly for spinal disorders, because although many diseases affect several spinal regions (e.g. intervertebral disc disease, discospondylitis, fibrocartilaginous embolic myelopathy), many are region-specific (e.g. atlantoaxial instability, cervical spondylomyelopathy, degenerative myelopathy). The primary differential diagnoses for the most common diseases affecting each region of the brain and spine are presented in Tables 4.3–4.9. Some of the diseases listed are presented in only one table but can affect any region. For example, discospondylitis is more commonly seen in the lumbosacral area, but can affect any vertebral region.

Once the list of differential diagnoses is prepared for the patient, the most probable causes should be ruled in or ruled out, based on appropriate diagnostic tests. The diagnostic approach exemplifying the diagnostic tests used to confirm common brain and spinal diseases is presented in Fig. 4.1 and 4.2.

Specific brain regions

Forebrain (thalamocortex, prosencephalon, cerebrum)

Common diseases affecting the forebrain region mainly in small-breed dogs are the meningoencephalitis (any form of

Table 4.3 Differential diagnoses for common diseases affecting the forebrain. These diseases will cause seizures, behavioral changes, and circling (without a head tilt).

	Breeds	Age	Onset	Neurologic deficits
Granulomatous meningoencephalitis (GME) (chapter 7)	Mainly small Terriers, Poodles	Typically middle age and young, but any age	Acute, subacute or chronic	Focal or multifocal Circling, seizures, blindness Common to see vestibular signs
Necrotizing meningoencephalitis (NME) (Ch 7)	Mainly small Pug, Maltese, Shih-Tzu	Usually young adult Mean age 2 yrs	Acute	Seizures are the most common sign Circling and central blindness also common
Meningoencephalitis of unknown etiology (MUE) (Ch 7)	Any, mainly small breeds	Any Young to middle age more common	Acute, subacute or chronic	Focal or multifocal Circling, seizures, blindness Additional signs if involving other brain regions
Infectious meningoencephalitis (Ch 7)	Depends on infectious agent, but no clear predisposition for most	Any	Bacterial diseases are typically acute or peracute, protracted course with other agents	Focal or multifocal Signs can progress quickly from focal to multifocal in bacterial meningoencephalitis
Neoplasia (Ch 7)	Golden retrievers and Boxers have a high predisposition Other brachycephalic and dolichocephalic breeds also affected	Dogs—vast majority over 5 yrs of age (mean age 9 yrs) Cats—typically older, mean age 12 yrs	Slowly chronic progressive course is typical Acute presentations are occasionally seen	Signs typically focal, with the majority fairly asymmetrical (circling, unilateral menace, nasal sensation and/or proprioceptive deficits) Behavioral changes very common Multifocal presentations can be seen with secondary neoplasia or primary multifocal neoplasia such as gliomatosis cerebri
Cerebrovascular disease (Ch 7)	Any breed but Cavaliers King Charles Spaniels and Greyhounds are overrepresented. Thalamic infarcts more common in large breeds	Commonly seen in middle-age to older dogs	Peracute or acute nonprogressive presentation onset is typical	Abnormal mentation, asymmetric deficits (circling, postural reactions, menace and nasal sensation)
Head trauma (Chapter 8)	Any	Any	Peracute or acute onset Progression varies with severity of trauma and secondary effects	Mentation changes are common Severity of trauma can be assessed based on level of consciousness, motor function, and cranial nerves reflexes (PLR and oculocephalic reflex)
Hydrocephalus	Mainly small breeds Chihuahua, Maltese, Yorkshire, Toy Poodle	Typically younger than 6 mos of age	Signs usually present at a young age, and may progress slowly	Behavioral abnormalities, circling, dome-shaped head, open fontanels, seizures
Cognitive dysfunction	Any breed	Elderly dogs (older than 9 yrs)	Slowly chronic progressive signs	Neurologic deficits (menace, nasal sensation) not expected Signs are behavioral, such as inattentiveness, pacing, demented behavior, failure to recognize people or places

PLR = pupillary light reflex.

Table 4.4 Differential diagnoses for common diseases affecting the brain stem. These diseases will cause cranial nerve deficits, such as head tilt, facial nerve paresis, or paralysis, changes in the level of consciousness, and postural reaction deficits.

	Breeds	Age	Onset	Neurologic deficits
Granulomatous meningoencephalitis (GME) (Chapter 7)	Mainly small Terriers, poodles	Typically middle age and young, but any age	Acute, subacute or chronic	Typically focal involving pons (trigeminal nerve paresis) and medulla (head tilt, nystagmus, facial paralysis)
Necrotizing leukoencephalitis (NLE) (Chapter 7)	Mainly small Yorkshire Terrier, Maltese, Shih-Tzu, French Bulldog	Usually young adult (mean age 4.5 yrs)	Acute or chronic progressive	Head tilt, circling, mentation changes, facial paresis/paralysis Circling also common
Meningoencephalitis of unknown etiology (MUE) (Chapter 7)	Any, mainly small breeds	Any age, but young to middle age more common	Acute, subacute or chronic	Focal or multifocal
Infectious meningoencephalitis (Chapter 7)	Any breed	Any	Bacterial diseases are typically acute or peracute, protracted course with other agents	Distemper and rickettsial agents (ehrlichiosis and RMSF) are known to frequently cause central vestibular dysfunction
Neoplasia (Chapter 7)	Golden Retrievers and Boxers overrepresented Other brachycephalic and dolichocephalic breeds also affected	Dogs—vast majority over 5 yrs of age (mean age 9 yrs) Cats—typically older (mean age 12 yrs)	Slowly chronic progressive course is typical Acute presentations are occasionally seen	Signs typically focal, many affecting cerebellomedullary angle causing a combination of brain-stem (head tilt, atrophy muscles mastication, facial paralysis) and cerebellar signs (hypermetria, tremors)

PLR = pupillary light reflex; RMSF = Rocky Mountain spotted fever.

encephalitis), typically the noninfectious meningoencephalitides (granulomatous meningoencephalitis, necrotizing meningoencephalitis, or those where a specific diagnosis cannot be reached, so-called meningoencephalitis of unknown etiology). Neoplasia is also a common disease, mainly in dogs older than 5 yrs of age. Most dogs and cats have primary brain tumors, but secondary (metastatic) brain tumors are also seen. Head trauma can affect dogs of any age and size, and typically leads to forebrain signs in mild to moderate cases. Cerebrovascular disease (CVD) is being recognized more commonly in both dogs and cats. CVD develops as a peracute onset of typically strongly asymmetric signs. Table 4.3 lists the main characteristics of the primary differentials.

Brain stem (mesencephalon, pons, and rostral/caudal medulla)

Most patients with brain-stem signs will have inflammatory or neoplastic diseases. Less frequent diseases affecting the brain stem are metabolic diseases such as hypothyroidism (causing central vestibular disease), nutritional diseases (e.g. thiamine deficiency), or toxic, such as caused by metronidazole toxicity. Table 4.4 lists the main characteristics of the primary differentials for brain-stem diseases.

Cerebellum

Cerebellar disease in young dogs is commonly caused by congenital diseases such as cerebellar hypoplasia or abiotrophy (degeneration). Inflammatory diseases also commonly affect the cerebellum. Idiopathic shaker syndrome (steroid responsive tremor syndrome, idiopathic cerebellitis, white dog shaker syndrome) is an inflammatory/immune-mediated disease that causes acute onset of tremors. Cerebellar infarcts are common and typically present as an acute, severe, central vestibular disease. Neoplastic diseases can also affect the cerebellum in both young and old dogs. The main differentials are presented in Table 4.5.

Specific spinal regions

C1–C5 spinal cord segments/C1–mid-C5 vertebrae

Common diseases affecting the C1–C5 spinal cord segments in small breeds are atlantoaxial subluxation and cervical intervertebral disc disease. Spinal pain is often present with these diseases. Primary differentials for large-breed dogs with C1–C5 lesions are intervertebral disc disease (IVDD), cervical spondylomyelopathy, and spinal neoplasia, mainly meningiomas. Trauma is also common and affects both small and large breeds. Cervical pain without neurologic deficits affecting the C1–C5 regions is usually caused by steroid-responsive meningitis arteritis, cervical intervertebral disc disease, or discospondylitis. More information for the main clinical characteristics of each disease is presented in Table 4.6.

Table 4.5 Differential diagnoses for common diseases affecting the cerebellum. These diseases will cause head and whole-body tremor, cerebellar ataxia, hypermetria, intentional tremors, and menace deficits.

	Breeds	Age	Onset	Neurologic deficits
Meningoencephalitis of unknown etiology (MUE) (Chapter 7)	Any, mainly small breeds	Any Young to middle age more common	Acute, subacute or chronic	Focal or multifocal
Neosporosis (necrotizing cerebellitis) (Chapter 7 and 12)	Any, but Labrador Retrievers are overrepresented	Adult dogs	Slowly chronic progressive course	Bilateral and symmetrical cerebellar signs (ataxia, head tremors, hypermetria)
Corticosteroid responsive tremor syndrome (idiopathic tremor syndrome, white dog shaker syndrome) (Chapter 12)	Any breed, but approximately 50% cases in white dogs	Majority younger than 4 yrs	Acute onset	High-frequency, low-amplitude generalized tremors involving head, trunk, and limbs May be seen associated with head tilt
Neoplasia (Chapter 7)	Golden Retrievers and Boxers overrepresented Other brachycephalic and dolichocephalic breeds also affected	Typically older dogs and cats Young dogs (1–4 yrs) can have a neuroectodermal tumor known as medulloblastoma	Slowly chronic progressive course is typical Acute presentations are occasionally seen	Signs typically focal, causing asymmetric cerebellar signs characterized mainly by cerebellar ataxia, asymmetric hypermetria, with or without brain-stem signs
Cerebrovascular disease (cerebellar infarcts) (Chapter 7)	Any breed but Cavalier King Charles Spaniels and Greyhounds are overrepresented Cerebellar infarcts more common in large breeds	Commonly seen in middle-age to older dogs	Peracute or acute nonprogressive presentation is typical	Asymmetric cerebellar ataxia, ipsi- or contralateral head tilt, ipsilateral hemiparesis with postural reaction deficits, opisthotonus, nystagmus, ipsilateral menace deficit
Intracranial arachnoid cyst (IAC) (Chapter 7)	Small-breed dogs, mainly brachycephalic Shih Tzu, Maltese, Pug, Yorkshire Terriers, and Bulldogs appear overrepresented	Young to young adult dogs (mean age 4 yrs)	Acute or chronic onset	Most dogs with IAC are clinically normal Cerebellar signs may be more common with more severe compressions Cerebellar ataxia, head swaying, nystagmus, and menace deficits were reported
Cerebellar hypoplasia (Chapter 12)	Any breed of dog or cat Genetic in Chow Chow, Irish Setter, Fox Terrier, Airedale Terrier, and Boston Terrier	Young dogs and cats (signs noticed first few weeks of life)	Static signs Animals can adapt over time and "improve"	Classic cerebellar signs Bilateral and symmetric Cerebellar ataxia with head and whole-body tremors Hypermetria, menace deficits

C6–T2 spinal cord segments (cervical enlargement) / vertebrae C5–T1

Frequent conditions seen at this region are cervical intervertebral disc disease in large-and small-breed dogs, and cervical spondylomyelopathy in large- and giant-breed dogs. Neoplasia, discospondylitis, osteomyelitis, trauma, and fibrocartilaginous embolic myelopathy can also occur in this region (Table 4.6).

T3–L3 spinal cord segments/T2–L3 vertebrae

Most spinal diseases in dogs and cats affect the T3–L3 spinal segments. Intervertebral disc disease (either extrusion or protrusion) is very common in this location. Other common diseases are degenerative myelopathy, spinal trauma, neoplasia, and fibrocartilaginous embolic myelopathy. If the lesion is localized to the mid- to cranial thoracic region, between T2 and T10 vertebrae (based on the cut-off of the cutaneous trunci reflex and/or spinal pain), then a few diseases can be considered more likely. It is important to mention that IVDD is rare at this region. The diseases that are more commonly seen between T2 and T10 are spinal neoplasia, discospondylitis, and hemivertebra. The differential diagnoses for the diseases affecting the T3–L3 spinal cord region are presented in Table 4.7.

L4–S3 spinal cord segments (lumbosacral enlargement)/L4–L5 vertebrae (dogs)

This is a small spinal cord region, and most diseases affecting the T3–L3 spinal cord region can also affect this region (e.g. IVDD, trauma, neoplasia). A disease that frequently affects this specific region is fibrocartilaginous embolic myelopathy. The main features of diseases affecting this region are shown on Table 4.8.

L6–L7 vertebrae and sacrum in dogs

Problems affecting the caudal lumbar region are very common in large-breed dogs. Spinal diseases affecting this region can appear similar to musculoskeletal disorders, as lameness may be the only clinical sign. The primary differential diagnoses

Table 4.6 Differential diagnoses for common diseases affecting the cervical spine (C1–C5 spinal cord segments and cervical enlargement). These diseases cause proprioceptive ataxia, tetraparesis, and/or neck pain. (All diseases of this chapter are discussed in detail in chapter 13).

	Breeds	Age	Onset	Neurologic deficits	Spinal pain
Atlantoaxial instability (subluxation)	Mainly toy or small Yorkshire Terriers, Poodles	Typically younger than 2 yrs	Acute or chronic	Common Obvious ataxia and tetraparesis	Present in the majority of cases
Arachnoid diverticulum ("cyst")	Rottweilers (cervical region) Pugs (TL region)	Most dogs are young adults. Median age 2.5 yrs. Pugs are older	Chronic progressive signs	Common—various degrees of proprioceptive ataxia and paresis	Uncommon. If noted usually mild on palpation
Cervical IVDD (extrusions)	Any, mainly small	Usually older than 2 yrs	Acute	Typically mild or not present	Severe
Cervical IVDD (protrusion)	Any, mainly large	Middle age to old	Chronic	Mild to moderate	Present, but mild to moderate
Cervical spondylomyelopathy (osseous-associated)	Giant breeds Great Danes, Mastiffs	Usually younger than 3–4 yrs	Usually chronic, but can be acute	Common Obvious ataxia and tetraparesis	Usually mild. Seen in 50% cases
Cervical spondylomyelopathy (disc-associated)	Large breeds Dobermans, Weimaraners	Middle age to old dogs	Usually chronic, but can be acute	Common Obvious ataxia and tetraparesis	Usually mild. Seen in 50–70% cases
Fibrocartilaginous embolic myelopathy (FCEM)	Any Usually large breeds	Any Commonly middle age	Acute	Common. Usually strongly asymmetric	Absent (after 12–24 hours)
Spinal trauma	Any	Any	Acute	Common	Common
Steroid-responsive meningitis arteritis (SRMA)	Boxers, Beagles, Berneses, English Pointers, Golden Retrievers	Young Usually younger than 2 yrs	Acute or subacute	Uncommon	Severe

for diseases affecting this region are degenerative lumbosacral stenosis, discospondylitis, neoplasia, and extradural synovial cysts. Spinal pain is often a consistent feature of diseases affecting the caudal lumbar/lumbosacral spine. The main clinical features of the diseases affecting this region are presented in Table 4.9.

It is important to have a methodical way to approach patients with neurologic problems. Always start by localizing the lesion. The VITAMIN-D system can be used to select the primary pathophysiologic mechanisms causing the patient's clinical signs. Remember that, generally speaking, each mechanism has a typical onset of signs (e.g. acute onset = vascular and

Table 4.7 Differential diagnoses for common diseases affecting the thoracolumbar spine (T3–L3 spinal cord segments). These diseases cause proprioceptive ataxia, paraparesis, or paraplegia, with normal to increased pelvic limb reflexes. (All diseases of this chapter are discussed in detail in chapter 13 and 15).

	Breeds	Age	Onset	Neurologic deficits	Spinal pain
Degenerative myelopathy	Mainly large German Shepherds, Boxers, Pembroke Welsh Corgis	Older than 5 yrs	Chronic (months)	Common Obvious ataxia and paraparesis	Absent
Fibrocartilaginous embolic myelopathy (FCEM)	Any Usually large breeds	Any Commonly middle age	Acute	Common Usually strongly asymmetric	Absent (after 12–24 hrs)
Hemivertebra	Screw-tailed breeds French Bulldogs, others	Young Usually younger than 1 yr	Chronic	Common Paraparesis and ataxia	Rare
IVDD (extrusions)	Any, mainly small	Usually older than 2 yrs	Acute	Typically moderate to severe	Moderate to severe
IVDD (protrusion)	Any, mainly large	Middle age to old	Chronic	Mild to moderate	Usually present but mild
Meningomyelitis	Any	Any	Usually subacute (few days)	Variable, but signs are often asymmetric	Variable, can wax and wane
Spinal neoplasia	Any Usually large breeds	Any Commonly middle age to older	Chronic or subacute (2–3 days)	Common	Variable, but usually present
Spinal trauma	Any	Any	Acute	Common	Common

Table 4.8 Differential diagnoses for common diseases affecting the lumbosacral (L4–S3) spinal cord segments or L4–5 vertebrae. These diseases cause mild proprioceptive ataxia, paraparesis, or paraplegia, with decreased to absent pelvic limb reflexes. (All diseases of this chapter are discussed in detail in chapter 13 and 15).

	Breeds	Age	Onset	Neurologic deficits	Spinal pain
Degenerative myelopathy	Mainly large German Shepherds, Boxers, Pembroke Welsh Corgis	Older than 5 yrs	Chronic (months)	Ataxia and paraparesis The decreased patellar reflex is usually a manifestation of a dorsal (sensory) radiculopathy, and not a LMN sign	Absent
Fibrocartilaginous embolic myelopathy (FCEM)	Any Usually large breeds	Any Commonly middle age	Acute	Common Usually strongly asymmetric	Absent (after 12–24 hours)
IVDD (extrusions)	Any Mainly small	Usually older than 2 yrs	Acute	Typically moderate to severe	Moderate to severe
IVDD (protrusion)	Any Mainly large	Middle aged to old	Chronic	Mild to moderate	Usually present but mild
Meningomyelitis	Any	Any	Usually subacute (few days)	Variable, but signs are often asymmetric	Variable, can wax and wane
Spinal neoplasia	Any Usually large breeds	Any Commonly middle age to older	Chronic or subacute (2–3 days)	Common	Variable, but usually present.
Spinal trauma	Any	Any	Acute	Common	Common

Table 4.9 Differential diagnoses for common diseases affecting the L6–7 vertebrae and sacrum. These diseases may cause paraparesis with or without proprioceptive deficits, but without proprioceptive ataxia because the spinal cord is not affected. Lameness is also frequently observed with asymmetric lesions in this area. (All diseases of this chapter are discussed in detail in chapter 13, 14 and 15).

	Breeds	Age	Onset	Neurologic deficits	Spinal pain
Lumbosacral stenosis (cauda equina syndrome)	Usually large breeds German Shepherds are overrepresented	Middle age to old	Chronic	Typically mild to moderate Can be severe in late stages Lameness may be the only sign	Often present, but may only be elicited with deep spinal palpation
Spinal neoplasia	Any Usually large breeds	Any Commonly middle age to older	Chronic or subacute (2–3 days)	Common	Variable, but usually present
Discospondylitis	Any Usually large and giant breeds	Any Commonly young to middle age	Usually acute	Usually not present initially	Severe pain, sometimes not localizable
Spinal trauma	Any	Any	Acute	Common	Common

trauma; chronic = degenerative, neoplastic). (Fig. 1.1). Using the acronym VITAMIN-D or the specific tables by lesion localization, the clinician may be able to go from a large list of diagnostic possibilities to a shorter list of diagnostic probabilities. Further information on each one of the diseases listed in the tables is provided in the specific chapters elsewhere in the book.

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CHAPTER 5

Neurodiagnostics

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Introduction

Once the neurologic examination is completed, a list of differential diagnoses is formed, based on the lesion localization, the signalment, and the history (e.g. onset, progression, painful vs. nonpainful). In order to rule in or out the differentials on this list, additional diagnostic tests are often required. These might include: a minimum database (e.g. complete blood count, biochemistry panel, urinalysis); radiographs; cerebrospinal fluid (CSF) analysis; contrast radiographic studies, such as myelography or epidurography; advanced imaging, such as computed tomography (CT) or magnetic resonance imaging (MRI); or electrodiagnostic studies, such as electromyography (EMG), nerve conduction velocity (NCV) studies, or brain-stem auditory evoked response (BAER) tests. Occasionally, muscle or nerve biopsy, or exploratory surgery, is indicated. Diagnostic tests commonly used to evaluate dogs and cats with suspected neurologic disease are discussed in this chapter and in Chapter 6. For purposes of both patient safety and diagnostic accuracy, the procedures described in this chapter should be performed by appropriately trained individuals or under the direct guidance of such individuals. Most general small-animal practitioners will not be performing the procedures described in this chapter. However, maintaining a general knowledge base in regard to these procedures will assist the primary clinician in communicating effectively with both clients and specialists involved in managing patients with neurologic disease. The chapter is meant, therefore, to provide the reader with a brief overview of neurodiagnostic procedures; more in-depth descriptions of individual tests can be found by consulting the references at the end of the chapter.

Cerebrospinal fluid (CSF) analysis[5, 7–10, 13–15, 17, 18, 20, 22, 31, 32, 36, 37, 51, 64, 84, 85, 93, 96, 97, 104, 110]

The CSF bathes the brain and spinal cord. It is produced mainly by the choroid plexus of the lateral, third, and fourth ventricles, but also by brain capillaries, parenchymal cells, and ependymal cells. Carbonic anhydrase is an enzyme important in the formation of CSF; drugs that inhibit carbonic anhydrase may decrease CSF production. The normal rate of CSF production in dogs ranges from 0.047 to 0.066 ml/min, and in cats from 0.020 to 0.022 ml/min. The CSF is drained by the arachnoid villi, which are small projections of specialized arachnoid cells, into the venous sinuses that surround the brain. Abnormalities in the color, cellularity, and protein level of the CSF may contribute to or, in rare cases, confirm the diagnosis. It is rare for tumor cells or organisms to be visualized in CSF samples, but when this does occur, a definitive diagnosis can be made. The cell count and protein level of the CSF can be thought of as the central nervous system (CNS) analog of the complete blood count (CBC) and serum protein level for the systemic circulation, respectively. Abnormal CBC and serum protein results often assist in the diagnosis of systemic illness when viewed in the context of other laboratory abnormalities, as well as historical complaints and clinical findings; such abnormalities are typically not indicative of any specific disease when viewed as isolated test results. Similarly, results of CSF analysis often contribute to a diagnosis, but rarely by themselves provide a specific diagnosis. CSF analysis is very sensitive, in that it is often abnormal in patients with neurologic disease; it is very nonspecific, however, in most cases.

A. Indications for CSF collection (CSF "tap")
   1. Encephalopathies often are an indication for CSF analysis. In particular, infectious and noninfectious inflammatory diseases can be best characterized by evaluating the cellularity and protein levels in the CSF. Different inflammatory diseases lead to an accumulation of different types of cells in the CSF, and variably affect the amount and type of protein that is present. Degenerative, metabolic, traumatic, and neoplastic brain lesions may also alter the normal CSF. Any disease affecting the brain, including seizure disorders, should lead the clinician to consider CSF analysis as part of the diagnostic plan.
   2. Any spinal cord lesion, or myelopathy, that is not readily diagnosed on spinal imaging, should be evaluated by CSF

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analysis. Focal, multifocal, and diffuse spinal cord lesions will lead to changes in the CSF. Cerebrospinal fluid collection should be done prior to myelography, since myelographic contrast agents will change the character of the CSF, and will frequently produce a mild inflammatory response. These changes are believed to influence CSF analysis for at least three to five days following the myelogram. In one study of normal dogs, the CSF white blood cell (WBC) count returned to normal within 72 hrs of myelography, and CSF protein elevation resolved by seven days post-myelography.

3. Lesions that affect the spinal nerve roots (radiculopathies) may be evaluated with CSF analysis. The meninges enclose the nerve roots distally until they become the peripheral nerves. Thus, any disease, especially one that is inflammatory in nature, that affects the spinal nerve roots may alter the CSF.

B. Relative contraindications and risks of performing a CSF tap

1. Elevated intracranial pressure (ICP) due to mass lesions or inflammatory disease increases the risk of brain herniation (and subsequent death) when a CSF tap is performed. Typically, this is herniation of the cerebellar vermis and brain stem caudally through the foramen magnum. Cerebral herniation past the osseous tentorium caudally, or past the falx cerebri laterally, may also occur. The incidence of brain herniation following a CSF tap has been found to be slightly higher in cats than in dogs. Mannitol, corticosteroids, and hyperventilation may be used to decrease the risk. Because of the increased risk of herniation, CT or MRI should be performed prior to a CSF tap when mass lesions are suspected. It is unknown whether there is any advantage of lumbar versus cerebellomedullary cisternal CSF collection in terms of brain herniation risk.
2. Inadvertent penetration of the parenchyma at the cerebellomedullary angle may lead to temporary signs of brainstem disease, such as vestibular abnormalities, or cessation of voluntary respiration and death. The vestibular dysfunction may take a long time to subside or be permanent.
3. Performing CSF collection in small animals requires general anesthesia, as a rule. If the patient is an unacceptable anesthetic risk, lumbar puncture may be attempted with sedation and local (epidural) anesthesia.

C. Areas of CSF procurement and collection technique

1. One milliliter per 5 kg body weight of CSF can be safely removed at one time for analysis. Usually, 1 to 1.5 ml are collected (about ten drops). The fluid should be collected in a sterile glass tube, preferably without EDTA (e.g. red-top tube). EDTA may cause falsely elevated protein concentrations, as well as falsely low cell concentrations in small samples. Since EDTA is bactericidal, it may interfere with CSF culture results in cases of CNS bacterial infections. However, EDTA may help preserve cellular morphology. The authors routinely collect both a red-top and purple-top (EDTA) sample for analysis.

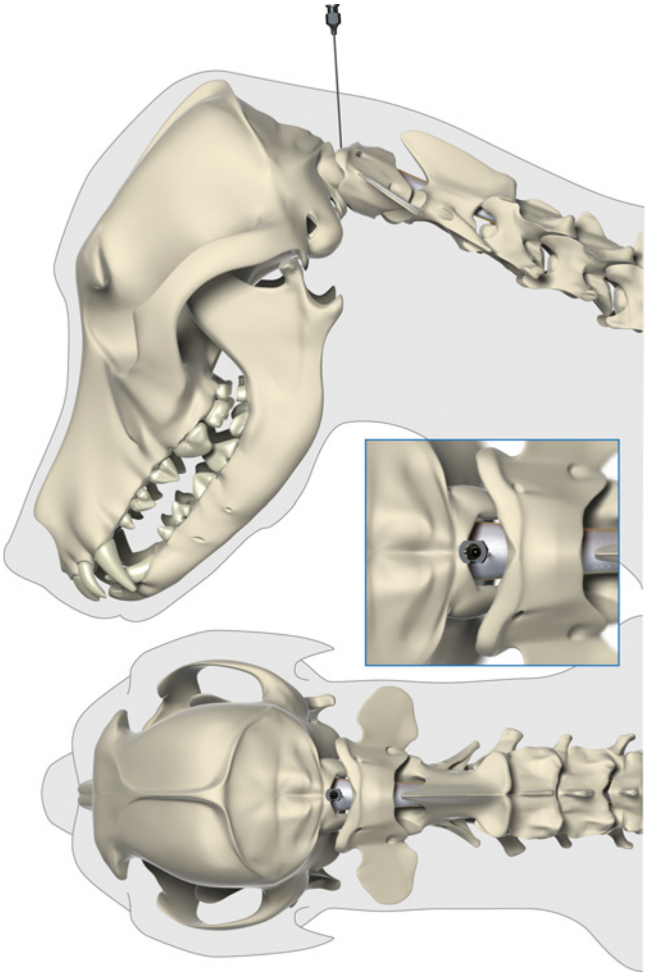


Figure 5.1 Anatomic landmarks for cerebellomedullary cisternal CSF collection in the dog, lateral, dorsoventral, and close-up views of the cerebellomedullary cistern region. (The Ohio State University. Reproduced with permission.)

CSF is most commonly obtained from the cerebellomedullary cistern (cisternal tap; Fig. 5.1). CSF collected from this site may be more representative of lesions involving the brain than CSF collected from a lumbar puncture. Anatomic landmarks useful in performing cisternal CSF taps include the external occipital protuberance, the cranial aspect of the dorsal spine of the axis (C2 cervical vertebra), and the transverse processes (“wings”) of the atlas (C1 cervical vertebra). The patient is placed in lateral recumbency and the neck is flexed by an assistant. The animal’s nose must be kept parallel with the table. A noncollapsing endotracheal tube should be used, to avoid occluding airflow during the procedure. Red rubber endotracheal tubes should be avoided, because it has been shown that these tubes are much more prone to complete kinking with neck flexion when compared with polyvinyl chloride (PVC) endotracheal tubes. The assistant should "tuck in" the animal's chin and push the external occipital protuberance toward the individual performing the tap. Placing some form of support under the neck (e.g. rolled-up paper towel) will help keep the spine of the axis and the external occipital protuberance in line.

The skin in the region of the tap is shaved and aseptically prepared, and a 22-gauge spinal needle with a stylet (20-gauge is acceptable in larger patients) is inserted on midline, directed toward the occipitoatlantal space. Sterile gloves are worn for the duration of the procedure. The proper location for needle insertion can be estimated in several ways. The authors prefer to locate the cranial aspect of the C2 spine with an index finger, then press firmly with the fingertip as the finger is simultaneously advanced cranially. In most patients, a ridge or "divot" can be palpated approximately one-third of the distance between the cranial aspect of the C2 spine and the external occipital protuberance. This ridge is the cranial aspect of the arch of C1. Inserting the needle just cranial to the ridge should allow entry into the occipitoatlantal space. An alternative method is to draw an imaginary line across the cranial limits of the wings of C1 and a perpendicular line from the external occipital protuberance caudally. The needle can be inserted at the intersection of these lines. The skin is punctured first, then the index finger and thumb of one hand (left hand for a right-handed person) is used to stabilize the needle against the skin surface, as the other hand is used to slowly advance the spinal needle. After every few millimeters of advancement, the stylet is removed to observe for CSF flow. Typically, the clinician will be able to feel the needle pass through fibrous tissue planes, producing a "popping" sensation. If the needle abuts bone, slight cranial or caudal redirection of the needle tip may allow entry into the dorsal subarachnoid space.

2. Lumbar puncture for CSF collection (lumbar tap) is usually performed at the L4/L5 space in large dogs or at the L5/L6 space in smaller dogs and cats (Fig. 5.2). Lumbar CSF may be more representative of lesions involving the thoracolumbar spinal cord than CSF from a cisternal puncture. The patient is placed in lateral recumbency and an area is shaved and aseptically prepared for CSF collection. The patient's pelvic limbs are advanced cranially, in order to open up the interarcuate space. The authors prefer to face the ventral aspect of the patient, and bend over the patient to insert the spinal needle. The spinal needle is inserted just lateral to midline, adjacent to the caudodorsal limit of a spinous process (L6 for L5/L6 puncture; L5 for L4/L5 puncture). The needle is inserted at a 30–60° angle from an imaginary line drawn perpendicular to the long axis of the spine.

   After the interarcuate space is entered, the needle will pass through the dorsal dura mater. Often, at this point, a twitch of the pelvic limbs and/or tail will be noted. The needle is advanced to the floor of the vertebral canal, and the stylet is withdrawn. CSF is allowed to drip into a collection tube. Although the spinal needle penetrates the spinal cord during a lumbar CSF tap, this does not appear to cause any clinical problems.

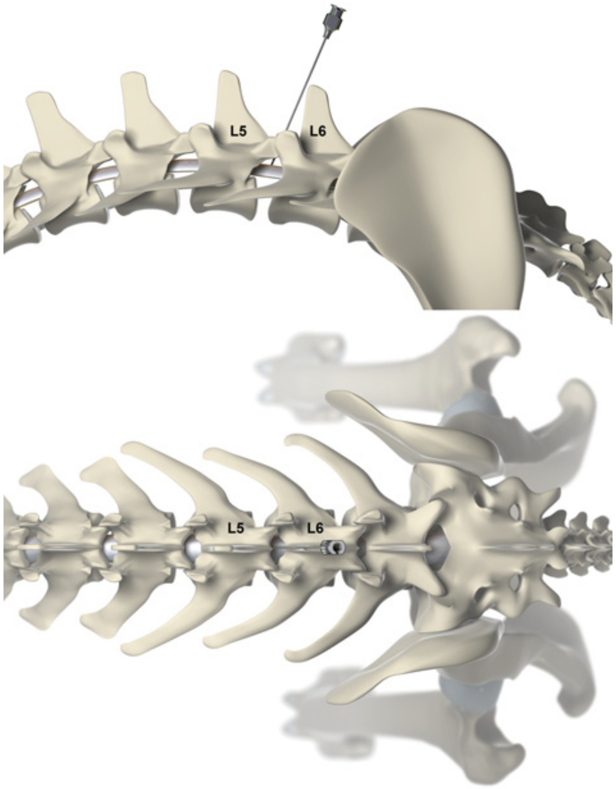


Figure 5.2 Anatomic landmarks for obtaining CSF via lumbar puncture in the dog, lateral and dorsoventral views. Collection should be preferably performed at L5–L6 intervertebral space. (The Ohio State University. Reproduced with permission.)

3. Collection site: CSF collection should be performed close to the location of the lesion or caudal to it. For brain and cervical diseases the cerebellomedullary region is appropriate. For thoracolumbar or lumbar lesions, CSF should preferably be collected in the lumbar region. In cases of multifocal disease, collection at both sites can be very valuable and is recommended.

D. CSF evaluation

There are a variety of tests that can be performed on CSF (Box 5.1). Typically, a total cell count, differential cell count (after cytocentrifugation), and a protein level are ascertained. A glucose level is occasionally obtained, and is normally 60–80% of the blood glucose level. If infectious disease is suspected, appropriate cultures or serology can be performed on the fluid. Electrophoresis of CSF may help to characterize the type(s) of protein present in the CSF. For some diseases (e.g. canine distemper virus, FIP [coronavirus] CNS infection in cats), amplification of genetic material via

Box 5.1 Guidelines for analysis and interpretation of cerebrospinal fluid (CSF)

Analysis

- CSF should be processed in 30 min.
- Acute and meningeal lesions will usually cause more severe changes.
- Corticosteroids can interfere with CSF results reducing the white blood cell (WBC) count and the percentage of neutrophils.

Interpretation

- Normal WBC count is usually < 5 cells/μl (< 3 cells/μl in some laboratories).
- Elevation of WBCs is called pleocytosis.
- Disproportionate increase in protein with normal or mild elevation in WBC count is called albuminocytologic dissociation.
- Normal protein concentration
  - Cerebellomedullary cistern < 25 mg/dl
  - Lumbar region < 45 mg/dl.
- Accounting for blood contamination on WBC count
  - Dogs 500 RBCs/μl = 1 WBC/μl
  - Cats 100 RBCs/μl = 1 WBC/μl.

polymerase chain reaction (PCR) may be indicated. When lymphoma is suspected (in cases of lymphocytic pleocytosis or possible neoplastic lymphocytes in the CSF), flow cytometry, or PCR for lymphocyte antigen receptor rearrangement (PARR) can be used to confirm the diagnosis. Testing for PARR requires a larger volume and higher concentration of lymphocytes than what is required for flow cytometry. Ideally, cell counts should be performed within 30 min of CSF collection; however, there is evidence that reliable cell counts may be obtained up to 48 hrs later when the CSF is preserved through the addition of autologous serum. Prior treatment may alter the expected results of CSF analysis, especially in patients with inflammatory disease treated with corticosteroids.

1. Color and clarity

   Normal CSF is clear and colorless, with the consistency of water. Prior hemorrhage (occurring a minimum of 10 hrs prior to CSF collection) in the CSF may result in a yellow tinge, referred to as xanthochromia. This discoloration can persist for 2–4 wks following hemorrhage into the subarachnoid space, but is usually resolved by four to eight days. Other potential causes for xanthochromia are severe icterus, and markedly elevated CSF protein levels.

   Gross blood contamination may be iatrogenic, or due to ongoing hemorrhage in the subarachnoid space. Iatrogenic hemorrhage is more common with lumbar taps, compared to cisternal taps. Although iatrogenic hemorrhage interferes with interpretation of CSF results, the extent to which it does so is controversial. It has been suggested that each 500 red blood cells (RBCs)/ml in a hemorrhagic CSF tap may account for one white blood cell (WBC)/ml in dogs, each 100 RBCs/ml accounting for one WBC/ml in cats. However, it has also been demonstrated that RBC counts in CSF as high as 15,000/ml can occur with minimal elevation of the WBC count. The effect of hemorrhage on CSF protein levels is typically low, with approximately 1200 RBCs/ml needed to increase the protein concentration by 1 mg/dl.

   Increased turbidity of CSF is usually due to an elevated number of cells (over 200 WBCs/ml, over 400 RBCs/ml), and occasionally due to increased protein levels. Elevated protein levels in CSF will also cause the fluid to be more viscous. CSF that tends to clot is rare, and is caused by markedly increased amounts of protein.

2. Total and differential WBC count

   Though the actual number may vary with the laboratory used, there are typically fewer than five nucleated cells/ml of CSF. In normal dogs and cats, lumbar CSF typically has fewer WBCs/ml than cisternal CSF. The distribution should be predominantly mononuclear cells with only occasional neutrophils.

3. Protein level

   Quantitative determinations are the most accurate. Although each laboratory will establish normal ranges, normal protein concentration for cisternal CSF is less than 27 mg/dl in dogs and cats. Normal protein levels will be higher when the CSF is collected from a lumbar puncture (approximately twice that of cisternal CSF, or less than 45 mg/dl).

E. CSF in disease

1. The greater the meningeal or ependymal involvement, in general, the greater the number of WBCs expected in the CSF. Deep-seated parenchymal lesions may be associated with mildly increased or normal cell counts, often with elevated protein levels. Increased nucleated cell counts in the CSF are referred to as pleocytosis. A normal cell count with an elevated protein level is often referred to as albuminocytologic dissociation.
2. Suppurative means a predominance of neutrophils. A neutrophilic pleocytosis is often associated with bacterial infections and corticosteroid-responsive (aseptic) meningitis. Other diseases in which neutrophils may predominate in CSF include some viral encephalitides (e.g. acute canine distemper infection, FIP meningoencephalitis in cats), fungal infections, meningiomas, and fibrocartilaginous embolic myelopathy (FCEM). Neutrophils associated with infectious diseases (e.g. bacterial meningoencephalitis) are more likely to be degenerate than those that occur in noninfectious (e.g. corticosteroid-responsive meningitis) disorders.
3. Mononuclear cell pleocytosis refers to a predominance of either lymphocytes or macrophages in the CSF. This is the most common pleocytosis encountered, and is usually associated with granulomatous meningoencephalomyelitis (GME) in dogs. The necrotizing encephalitides (Pug/Maltese encephalitis, Yorkshire Terrier encephalitis)

are usually characterized by primarily lymphocytic pleocytosis. Lymphosarcoma involving the CNS may also be associated with a lymphocytic pleocytosis. A predominantly mononuclear pleocytosis can be caused by fungal, viral (e.g. canine distemper virus), protozoal, rickettsial, and chronic bacterial infections.

4. Eosinophilic pleocytosis is rare. It has been associated with aberrant parasite migration in the CNS, rabies virus, and cryptococcal, protozoal, and protothecal infections. There is also a rare idiopathic condition called eosinophilic meningoencephalitis that is characterized by a substantial proportion of eosinophils in the CSF.

Neuroimaging[25–27, 34, 44, 49, 50, 52, 58, 75, 86, 88, 102, 103, 107]

The realm of neuroimaging typically includes survey ("plain") radiographs (e.g. skull, spine), myelography, epidurography, discography, computed tomography (CT), and magnetic resonance imaging (MRI). Due to the importance of MRI in the diagnosis of neurologic diseases, MRI is covered in detail in Chapter 6 and so is not discussed in this chapter. General anesthesia is often recommended for survey radiography, and is required for contrast radiography (e.g. myelography, epidurography), as well as CT and MRI studies. On some occasions, ultrasonography is also helpful. Ultrasonography can be used in the diagnosis of hydrocephalus and for intraoperative imaging of brain and spinal tumors. Ultrasonography can also be used to guide brain biopsies and fine needle biopsies of soft tissue masses in the paraspinal or plexus areas. Scintigraphy and angiography are no longer commonly performed for veterinary neurodiagnosis due to the wide availability of CT and MRI and the higher-quality images these tools provide. However, rectal scintigraphy is performed to diagnose portosystemic shunts. Occasionally, scintigraphy is used to evaluate esophageal function (e.g. patients with megaesophagus) and patency of surgically placed shunts in hydrocephalic patients.

A. Survey ("plain") radiographs[6, 57, 61, 76, 79, 91]

1. The main use of survey radiography is as a rapid screening tool for obvious bony abnormalities. Soft tissue structures of the CNS are poorly visualized, if at all, with survey radiographs. A minimum of two views (e.g. lateral and ventrodorsal) is required.
2. Survey radiographs of the skull may reveal fractures and osseous neoplasia, or may suggest soft tissue or fluid densities in the nasal passages, sinuses, or middle ear canals. Appropriate positioning for skull radiographs requires general anesthesia. In general, CT is preferable to radiographs for most of these purposes.
3. Survey spinal radiographs in the unanesthetized patient are often of questionable diagnostic quality due to poor patient positioning and patient movement. Obvious osseous tumors (Fig. 5.3), advanced discospondylitis (Fig. 5.4), displaced fractures or luxations (Fig. 5.5), and congenital vertebral anomalies (e.g. hemivertebrae), may be appreciated on survey spinal films in the unanesthetized patient. If the patient is likely to undergo anesthesia for myelography and/or surgery (e.g. acutely paralyzed Dachshund), performing survey radiographs on the unanesthetized patient is usually not justifiable.
4. High-quality spinal radiographs under anesthesia may reveal a number of abnormalities. In patients with intervertebral disc disease, collapsed disc spaces, decreased size of the intervertebral foraminae, or mineralized disc material within the vertebral canal or intervertebral foraminae may be appreciated (Fig. 5.6). Subtle vertebral fractures or subluxations with minimal displacement may be more readily apparent on radiographs performed with the patient anesthetized versus radiographs procured when the patient is awake. Other radiographic abnormalities that may be more evident in the anesthetized patient include subtle bony lesions associated with neoplasia (e.g. mild bone lysis), abnormalities associated with articular facets (including small fractures), and subtle bony changes suggestive of early discospondylitis (e.g. small regions of vertebral endplate lysis). In general, survey radiography is less sensitive than CT for identifying subtle bone lysis and small fractures.

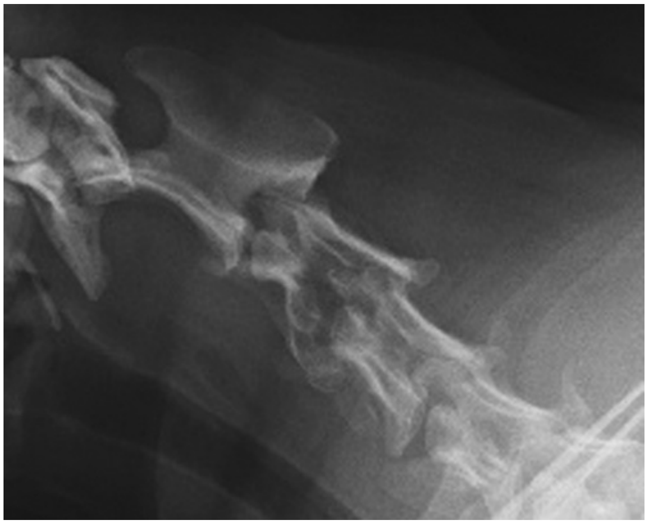


Figure 5.3 Lateral radiograph of a dog's cervical vertebral column, demonstrating a lytic vertebral lesion in the third cervical vertebra.

B. Myelography[11, 24, 40, 60, 62, 68, 70, 89, 108, 109]

1. Myelography is a procedure in which spinal radiographs are obtained following the injection of a radiopaque contrast agent into the subarachnoid space. Nonionic, iodinated, water-soluble contrast agents are used, iohexol and iopamidol being the most common.
2. The myelogram is performed via a cisternal or lumbar tap. CSF should be collected prior to contrast injection, as the contrast will change the composition of the CSF and may

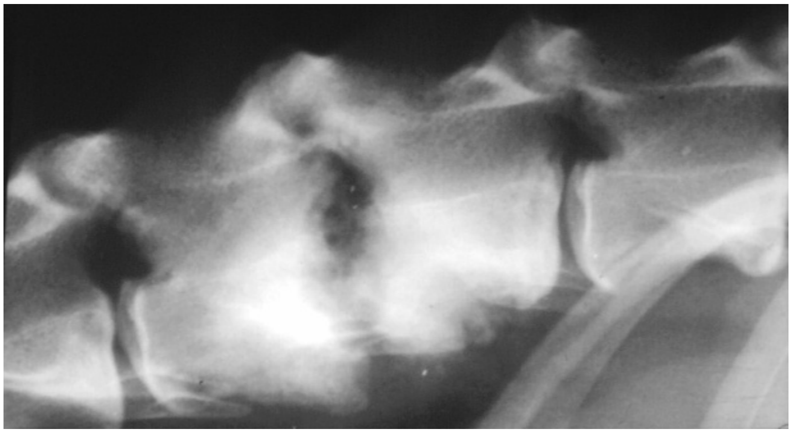


Figure 5.4 Lateral thoracolumbar radiograph of a dog with advanced discospondylitis.

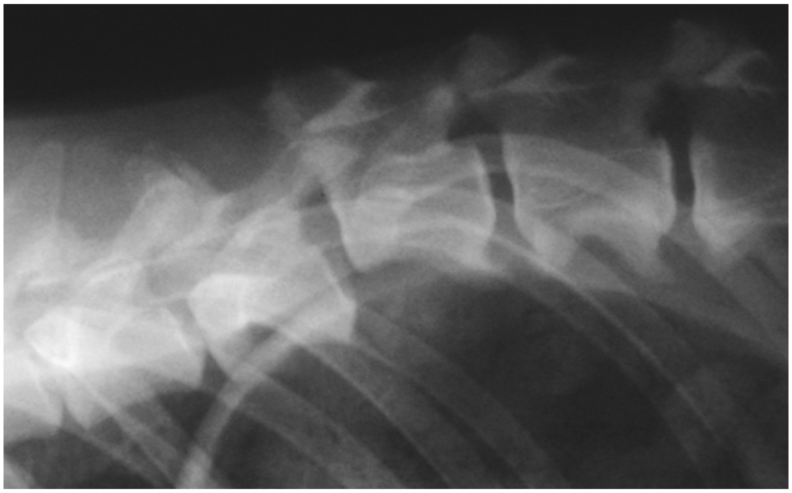


Figure 5.5 Lateral radiograph of a dog's spine with a traumatic luxation at the level of the T12 and T13 vertebrae.

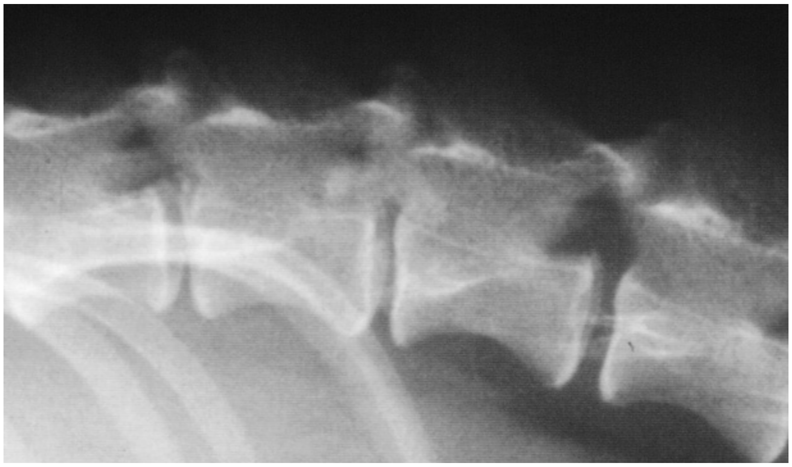


Figure 5.6 Lateral thoracolumbar radiograph of an anesthetized dog with acute thoracolumbar disc extrusion. A collapsed disc space, decreased size of the intervertebral foramen, and calcified material in the vertebral canal are apparent at the L1/L2 intervertebral disc space.

prevent accurate analysis for a minimum of three to five days. The authors prefer lumbar versus cisternal injection of contrast, regardless of the area of interest. Lumbar myelography often results in better image quality and is safer than cisternal myelography. The dosage of contrast used for a regional study (e.g. cervical myelogram with cisternal contrast injection) is 0.3 ml/kg body weight. For full studies (e.g. cervical myelogram with lumbar injection), the dose is 0.45 ml/kg body weight. The contrast is injected slowly, approximately 2–3 ml per minute. The authors prefer to administer a test injection (e.g. 0.5–1.0 ml, depending on patient size) to ensure the contrast is in the subarachnoid space, before administering the remainder of the calculated contrast dose.

3. Myelography is used to assist in the diagnosis of myelopathies. It is indicated for cases in which survey radiographs are either normal or inconclusive, despite neurologic evidence of myelopathy. Myelography is also often helpful in estimating the location, extent, and severity of spinal lesions. The ability to easily and rapidly visualize the entire spinal cord is an advantage of myelography over other imaging procedures (e.g. CT, MRI). Myelography is also generally less costly and may be more readily available than CT or MRI in certain situations (e.g. emergencies). As more veterinary referral centers acquire high-field MRI systems, myelography and other contrast radiographic procedures (e.g. epidurography, discography) are assuming a less important role in the neuroimaging of dogs and cats.
4. Despite the advantages of myelography, it is a somewhat invasive procedure and is associated with a low level of inherent risks. Overall, postmyelographic seizures occur in approximately 3–20% of dogs undergoing the procedure; this adverse event is more likely to occur in larger dogs (more than 20 kg), and is also more likely to occur with cisternal vs. lumbar contrast injections. In addition, the likelihood of postmyelographic seizure activity increases with increasing total volume (not dose on a ml/kg basis) of contrast injected. This is the main factor explaining a significant difference in the prevalence of seizures in two main studies. In a study with 503 dogs, the authors found a 3% prevalence of seizures. The mean volume of iohexol was 11.7 ml and 4.5 ml in dogs that did have and did not have seizures, respectively. In another study where the authors found a prevalence of 21.4% of seizures in 182 dogs, the mean volume was 16.8 ml and 9.1 ml for dogs that did and did not have seizures. Since the total volume of contrast medium is the main factor causing postmyelographic seizures, it is recommended to limit the initial volume of contrast to 8 ml and only use larger volumes if necessary. Larger dogs, primarily those with cervical lesions, also have a higher risk of seizures. Most patients that seizure will do so only once or twice in the 24 hrs following the procedure, and the seizures usually cease with intravenous diazepam injection (0.2–0.4 mg/kg). Maintaining slight elevation of the patient's head during and after the procedure (until the patient is awake) and assuring hydration with intravenous fluids during and 24 hrs after myelography are recommendations to limit the occurrence and severity of postmyelographic seizure activity.

   All dogs receiving a myelogram should be under close hospital observation (e.g. in an ICU) for the first 24 hrs following the procedure. Parenchymal damage from insertion of the needle is rare in myelography, but may occur, especially in the cervical region. Worsened neurologic status post myelogram is usually caused by transient chemical myelitis secondary to contrast injection. The risk for this may be higher in patients with existing inflammatory disease or chronic spinal cord compression (e.g. chronic type II disc disease). In the authors' experience, the risk of transient neurologic worsening appears to be highest in dogs with cervical spondylomyelopathy (CSM). These dogs may be markedly worse the day after the myelogram, but typically regain premyelogram neurologic status within 72 hrs. Inadvertent contrast injection into the parenchyma or the central canal of the spinal cord may cause worsened neurologic status. In most cases, patients recover from this iatrogenic trauma, but permanent deficits may occur in a small proportion of animals. Myelography is contraindicated for patients with known or highly suspected inflammatory disease of the CNS, as it may cause worsening of neurologic status.

   Myelography is also contraindicated in patients that may have elevated ICP. Since cervical hyperesthesia occasionally is associated with forebrain lesions, any historical or clinical indication of an underlying encephalopathy should prompt consideration of an alternative imaging modality (e.g. CT or MRI).
5. There are four basic myelographic patterns: normal, extradural, intradural/extramedullary, and intramedullary (Fig. 5.7). Normally, the contrast columns parallel each other and conform to the vertebral canal, except at the cauda equina region, where the subarachnoid space tapers. The spinal cord ends at about the L6 vertebral region in most dogs and at the first sacral vertebral region in most cats, although there may be quite a bit of variation between breeds.

   The spinal cord is normally larger at the cervical and lumbosacral intumescences. The ventral subarachnoid space is often less prominent than the dorsal subarachnoid space in the thoracolumbar region in dogs. The dorsal subarachnoid space in the atlantoaxial region is often wider than the remainder of the spinal cord. The cervical spinal cord region in cats often appears wider on myelography, in comparison to dogs. A normal myelographic pattern is often associated with degenerative myelopathy and FCEM. A normal myelogram may also occur with inflammatory myelopathies.

   Intervertebral disc extrusion/protrusion is the most common cause of an extradural myelographic pattern. Other causes of extradural patterns include vertebral fracture/luxation, congenital vertebral anomalies, hypertrophied soft tissue structures (e.g. interarcuate ligament, synovial membranes), extradural hemorrhage, vertebral neoplasia, and soft tissue neoplasia (e.g. feline lymphosarcoma). It is important to realize that the nature of an extradural compression is best appreciated when viewed tangential to the direction of the cord deviation. For example, if a disc extrusion is compressing the cord

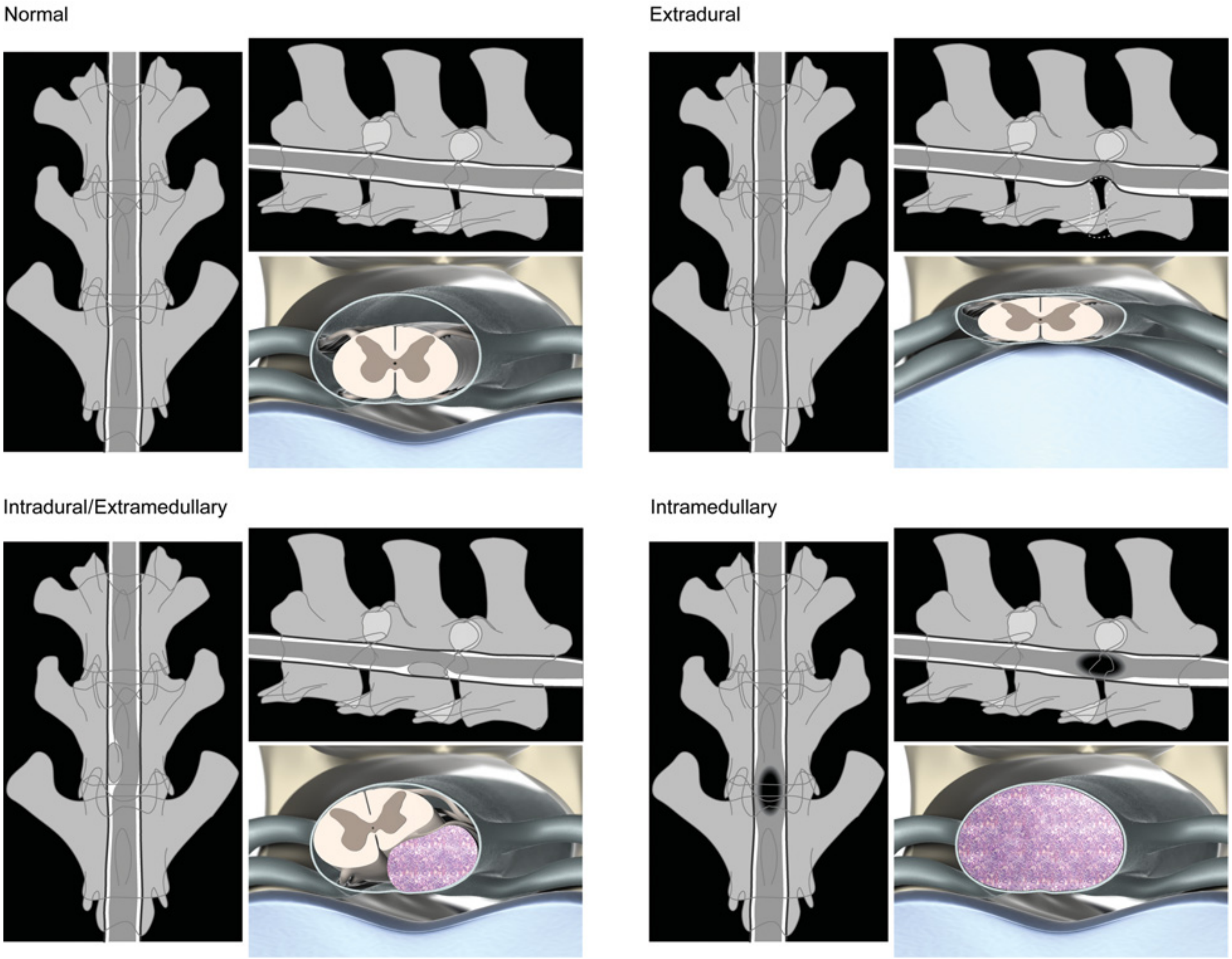


Figure 5.7 Four basic myelographic patterns: Normal, Extradural, Intradural/extramedullary, Intramedullary. (The Ohio State University. Reproduced with permission.)

from ventral to dorsal, with no lateralizing component, the myelographic pattern as viewed from a ventrodorsal view (parallel with direction of compression) could be misinterpreted as intramedullary. With intervertebral disc extrusions, which are often ventrolateral (i.e. ventral but somewhat lateralized), it is usually helpful to obtain oblique views in addition to standard dorsal and ventral views, in order to ascertain the correct side of disc extrusion for purposes of surgical planning. In one study, the accuracy of correctly identifying the side of disc extrusion was significantly higher for oblique vs. ventral views, but the accuracy was higher still when information from these views was combined.

An intradural/extramedullary pattern is produced when there is a lesion within the subarachnoid space (intradural), but not invading the parenchyma of the cord (extramedullary). As the contrast flows around the obstructive lesion, it may be outlined, appearing as a "filling defect." Sometimes, the filling defect is incompletely outlined, and resembles a golf tee, hence the term "golf tee sign" (Fig. 5.8). Intradural/extramedullary patterns are most often associated with neoplasia, primarily meningiomas and nerve sheath tumors. Much less commonly, intradural hemorrhage may lead to this myelographic pattern. Intradural/extramedullary lesions may produce enough spinal cord swelling that contrast is excluded from the region of the mass. In such cases, the myelographic pattern may appear to be intramedullary. In such cases, a CT is often performed through the abnormal region, as contrast is better visualized on CT images.

An intramedullary pattern is typically associated with spinal cord edema, expansile parenchymal masses, or intraparenchymal hemorrhage. Differential diagnoses include FCEM, neoplasia (e.g. astrocytoma, lymphosarcoma), inflammatory disorders (e.g. GME in dogs, FIP in cats), and trauma (e.g. hemorrhage and edema). In addition to apparent spinal cord swelling on myelographic images, contrast leakage into the spinal cord parenchyma may be appreciated in cases of spinal cord myelomalacia (Fig. 5.9).

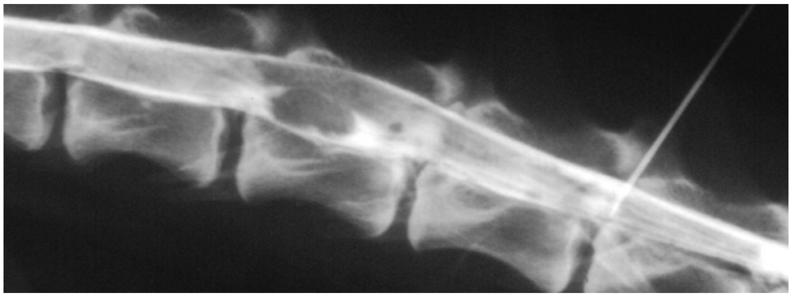


Figure 5.8 Myelographic appearance of a "golf tee sign" (lateral view), indicative of an intradural/extramedullary lesion.

C. Epidurography[12, 19, 42, 72, 79, 83, 89, 92, 95]

1. Myelography is often inadequate for the evaluation of cauda equina lesions in dogs because the subarachnoid space ends at the conus medullaris, which is in the L6 region in most canine patients. Epidural contrast injection may help delineate compressive cauda equina lesions, particularly those at the L7/S1 intervertebral disc space (e.g. degenerative lumbosacral stenosis). Epidurography is associated with a low level of morbidity. Due to the irregular contour of the epidural versus subarachnoid space, the contrast columns of an epidurogram appear comparatively rough and uneven in comparison with the contrast columns of a myelogram.

   Iohexol or iopamidol is used. The volume of contrast to inject is 0.1–0.2 ml/kg body weight. After aseptic preparation of the chosen site, injection of contrast material may be performed at L7/S1, at the sacrocaudal junction, or between one of the caudal intervertebral spaces. The disadvantage to L7/S1 contrast injection is that injection artifact may produce an unsatisfactory epidurogram in some cases.

   Multiple radiographic views are helpful. These include lateral films taken with the coxofemoral joints in neutral, flexed, and hyperextended positions. In a normal epidurogram, contrast fills the epidural space evenly with the pelvis in any position.

   Potential abnormalities that may be appreciated on an epidurogram include complete obstruction of cranial flow of contrast media past the L7/S1 space, or dorsal deviation of the ventral contrast column over this space (Fig. 5.10). This deviation may be exacerbated on extended views, and alleviated on flexed views. Occasionally, ventral deviation of the dorsal contrast column may be appreciated.

D. Discography[12, 72, 79, 83, 95]

1. Discography is used less often than epidurography for evaluation of L7/S1 disc lesions. Similar to epidurography, this procedure is associated with a low level of morbidity. Discography involves injecting iohexol or iopamidol (0.1–0.3 ml/kg body weight) directly into the nucleus pulposus of the disc, after which radiographs are procured.
2. After aseptic site preparation, the spinal needle is placed directly into the L7/S1 disc, preferably under fluoroscopic guidance. In a normal disc, it is very difficult to inject contrast. In a degenerative disc, 2–3 ml of contrast is often readily injected in a large-breed dog. Compression of the cauda equina region by the contrast-delineated L7/S1 disc is often readily evident (Fig. 5.11).
3. The authors prefer to perform a combination discography/epidurography procedure using a single needle puncture. After the discogram is performed, the needle is withdrawn from the disc into the epidural space, and additional contrast is injected. Additional radiographs are then obtained after the epidural contrast is administered (Fig. 5.12).

E. Computed tomography (CT)[4, 7, 19, 29, 38, 43, 44, 47, 52–59, 66, 75, 77, 79, 81, 83, 100, 105]

1. In computed tomography, X-rays and computers are used to provide cross-sectional images of the patient. The final images comprise many small image squares called pixels. The thickness of these image squares (voxels) is determined by the chosen image thickness. The patient is placed in the opening of the CT gantry (Fig. 5.13). The gantry contains the X-ray tube, X-ray collimators, and X-ray detectors. The X-ray tube and detectors are on opposite sides, and the patient is between them. Slice thickness is controlled by the collimators. The X-ray tube rotates around an object of interest as X-rays are

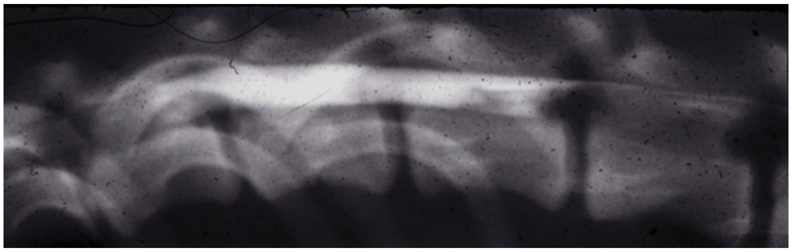


Figure 5.9 Lateral myelographic view of a dog with myelomalacia. Note the mixing of the contrast agent with the spinal cord parenchyma.

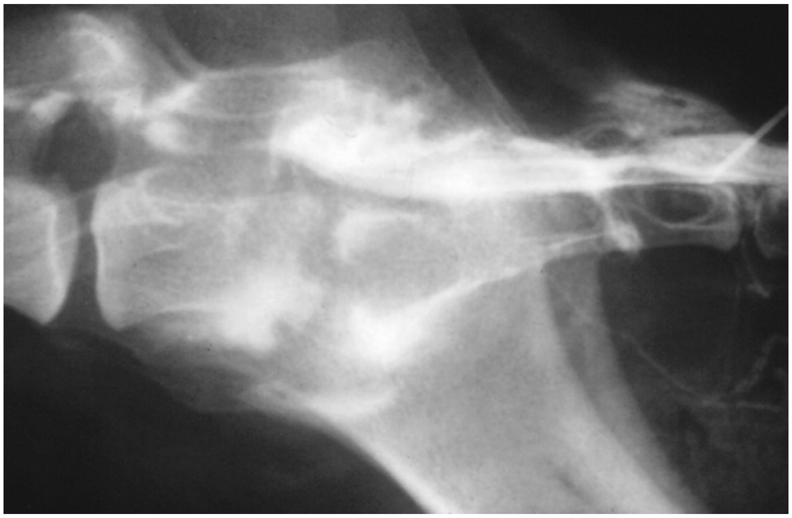


Figure 5.10 Lateral view of an epidurogram in a dog with degenerative lumbosacral stenosis. There is a ventral extradural compressive lesion at the L7/S1 intervertebral disc space. There is also evidence of discospondylitis at this site.

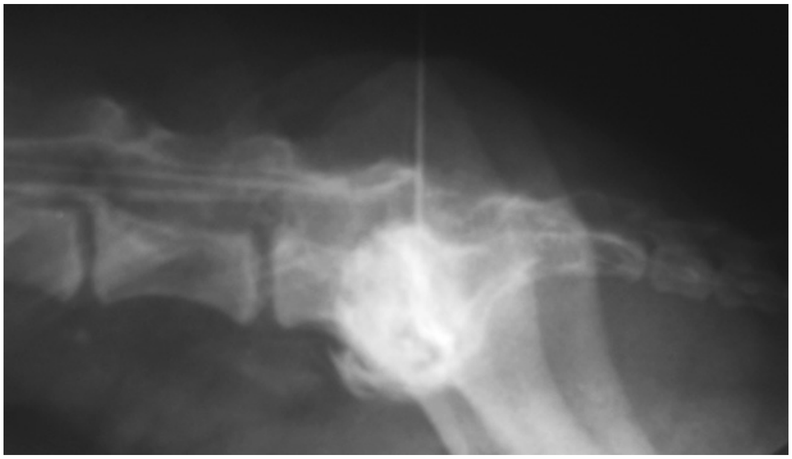


Figure 5.11 Discogram (lateral view) from a dog with a compressive disc lesion at L7/S1.

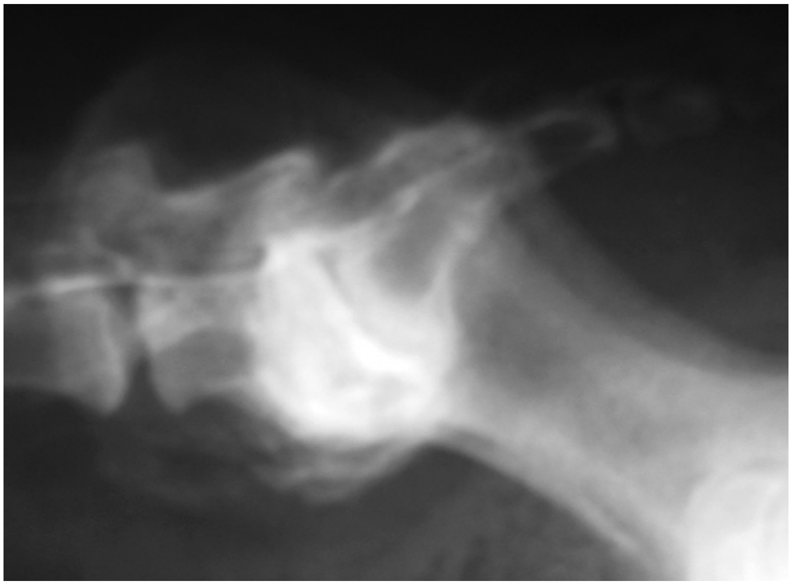


Figure 5.12 Combined discogram/epidurogram (lateral view) from a dog with degenerative lumbosacral stenosis.

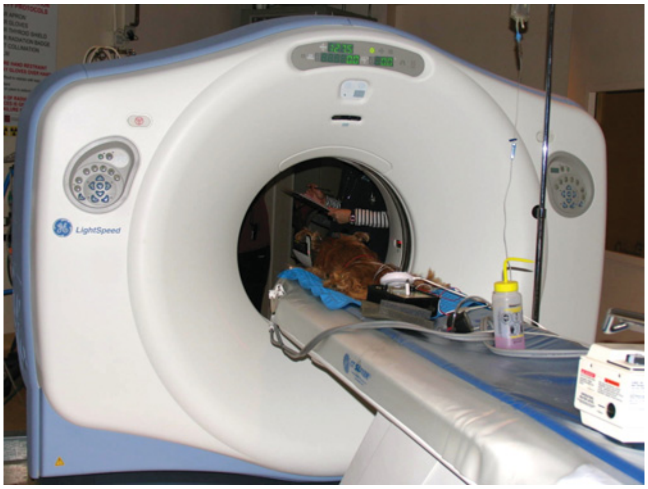


Figure 5.13 Patient in the gantry of the CT machine.

emitted. As the X-ray beam passes through an object, it is attenuated by tissues in its path. Each tissue attenuates the beam to a different degree. The different attenuating abilities of different tissues, or linear attenuation coefficients, provide the basis of tissue contrast. The attenuated beam of X-ray photons is received by the detector and the information is fed into the computer. The computer assigns grayscale numbers (Hounsfield units) to the tissues that the X-ray beam passed through, based upon their linear attenuation coefficients.

2. The resultant image reflects the different grayscale numbers of different tissue types, and therefore their respective abilities to attenuate X-rays. As one would expect from conventional X-ray procedures, bone appears white, air appears black, and fluid is somewhere in between (gray). The corresponding Hounsfield numbers for these tissues are +1000, –1000, and 0, respectively.
3. The human eye can discern approximately 20 shades of gray. The number of shades of gray in the image, as well as the central gray color (above which tissues are brighter, below which they are darker) can be manipulated once the image information is received by the computer. Choosing the central gray color, above which tissues appear brighter, and below which darker, is referred to as setting the window level (WL). The Hounsfield unit of the tissue of interest is typically chosen as the center of the window level. The number of shades of gray assigned to a particular image represents the window width (WW). A narrow window width is chosen for soft tissue (e.g. brain parenchyma) in order to improve contrast resolution (the ability to discern differences in composition of tissues in close proximity). A wide window width is chosen for tissues in which good inherent contrast already exists (e.g. air in the frontal sinus region), or when imaging a region where a wide range of tissue densities is displayed (e.g. bone/brain parenchyma interface). When imaging brain parenchyma, a WL of approximately 35 and a WW of 150 may be assigned (Fig. 5.14). In contrast, when imaging bony tissue, a WL of 420 and WW of 1500 may be used (e.g. a bone window; Fig. 5.15).

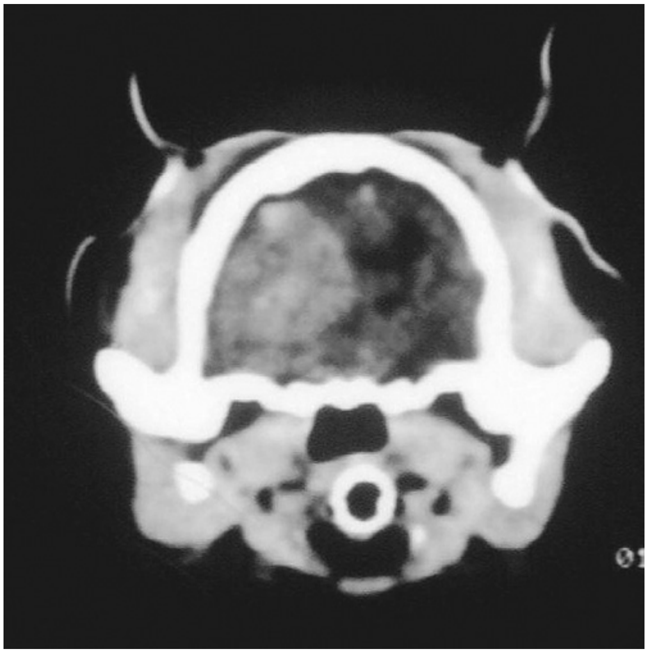


Figure 5.14 CT image of an intracranial meningioma in a cat (transverse view), using a soft tissue window.

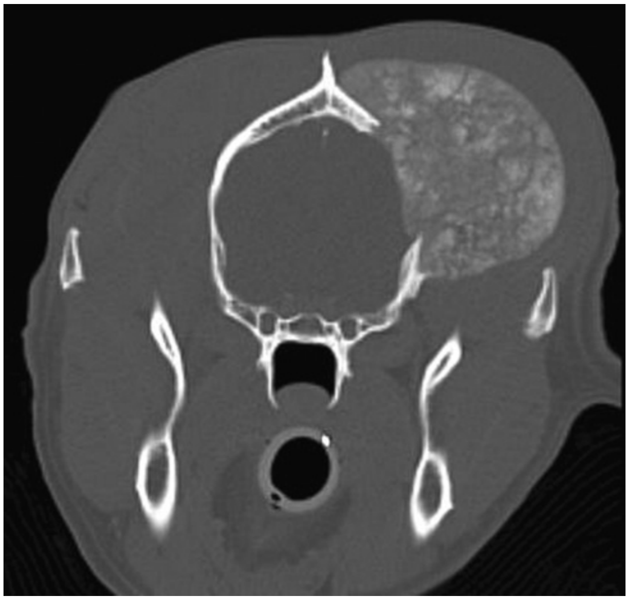


Figure 5.15 CT image of a multilobular osteochondrosarcoma of the skull in a dog (transverse view), using a bone window. (Dr. Dave Lipsitz, 2014. Reproduced with permission from Dr. Dave Lipsitz.)

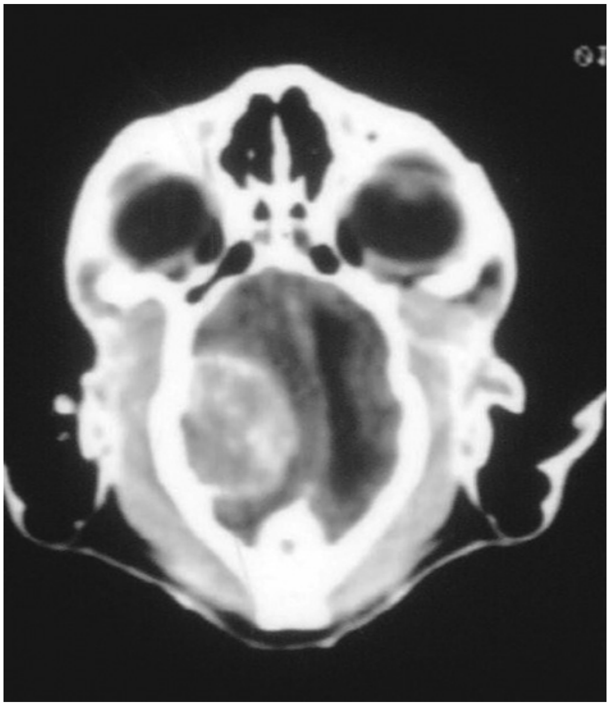


Figure 5.16 CT image of the cat's brain in Figure 5.14 (dorsal view) following intravenous administration of contrast.

4. After obtaining CT scans of the brain, nonionic iodinated contrast is often given intravenously and the patient is rescanned. The contrast agent will often demonstrate areas of blood–brain barrier disruption (Fig. 5.16).

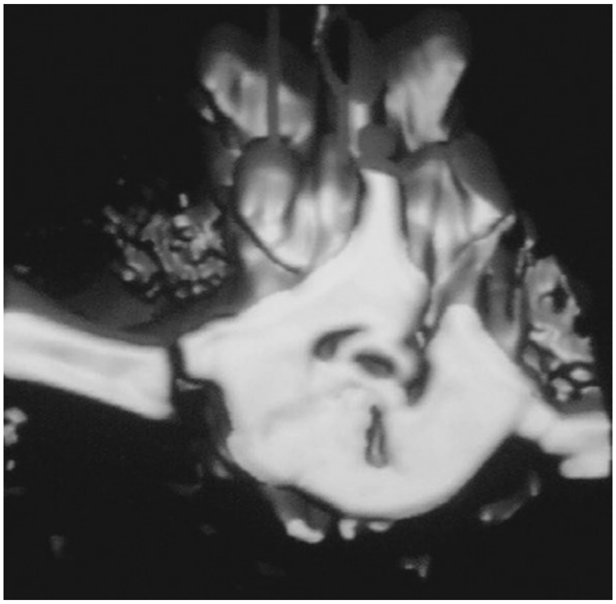


Figure 5.17 Three-dimensional reconstructed CT/myelographic image of a comminuted thoracic vertebral fracture in a dog.

5. With appropriate computer software, tissue voxels can be combined to produce a three-dimensional image (3-D reconstruction; Fig. 5.17 and 5.18) or to produce images in other planes.
6. CT can be used to help diagnose brain disorders. CT is also used in cases of spinal disorders, in many cases in conjunction with myelography (Fig. 5.19).

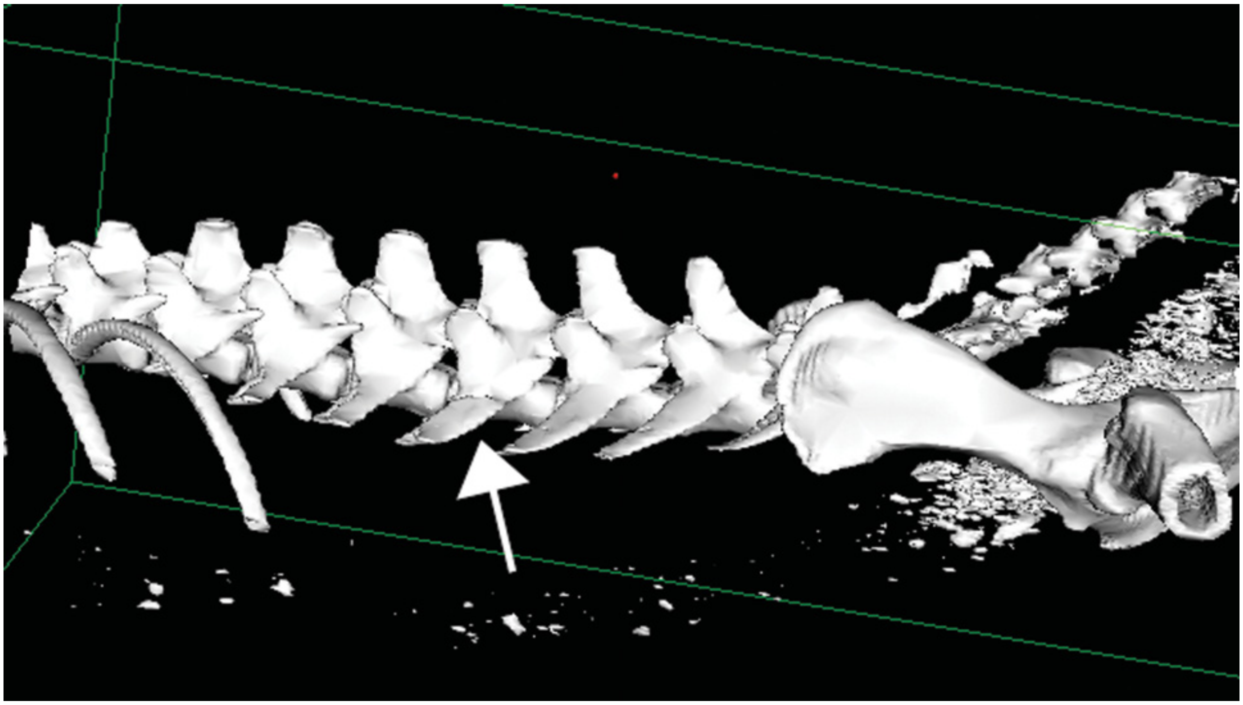


Figure 5.18 Three-dimensional reconstructed CT from a dog with spinal trauma. Observe linear fracture in the L4 transverse process (arrow).

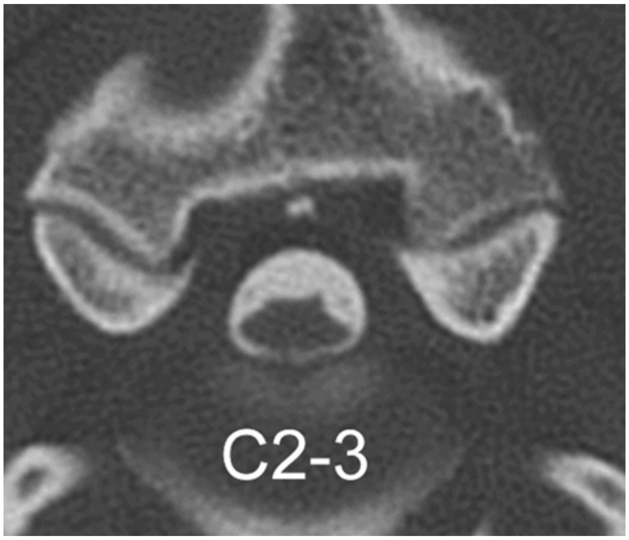


Figure 5.19 Combined CT/myelogram image (transaxial view) from a dog with a spinal arachnoid cyst. (Dr. P Scrivani, Cornell University, 2014. Reproduced with permission from Dr. P Scrivani.)

7. Noncontrast CT can be used in the diagnosis of acute intervertebral disc disease (IVDD). The normal spinal cord is surrounded by epidural fat and it can be seen on plain transverse CTs as an area of intermediate attenuation over the region of the intervertebral discs. Visualization of the spinal cord is more challenging over the vertebral bodies because of the lesser content of epidural fat. CT characteristics of acute intervertebral disc extrusion include hyperdense material within the vertebral canal, loss of epidural fat, and distortion of the spinal cord (Fig. 5.20). Chronic disc extrusions appear to be even more hyperattenuating possibly because of progressive mineralization. Acute intervertebral disc herniations are often associated with epidural hemorrhage. Acute and subacute epidural hemorrhage can be seen as irregular linear hyperdense areas cranial and caudal to the herniated disc material. It is often difficult to distinguish between hemorrhage and extruded disc material because blood is often admixed with disc. If the extruded nucleus pulposus is not mineralized, identification of disc material is more difficult and has to be based on loss of epidural fat and displacement of the spinal cord. If surgery is planned, myelography should then be performed to precisely localize the site of extrusion (Fig. 5.21).

   It is important to reformat the transverse CT images for assessing the cranial and caudal extent of disc herniation and to compare multiple sites of disc herniation. Recently, multiplanar reformatting was proposed as a useful technique to increase diagnostic certainty.

   Recent studies have compared myelography and CT in the diagnosis of acute IVDD in dogs. In one study with 182 dogs, noncontrast CT had a sensitivity of 81.8%, while myelography had a sensitivity of 83.6%. Another study found a sensitivity of 90% for CT, and 88% for myelography. A study with 19 chondrodystrophic dogs found agreement with surgical findings in 94.7% of dogs using myelography, 100% using conventional CT, and 94.7% using helical CT. It is possible that the differences in results among studies are related to different patient populations, i.e. chondrodystrophic only versus other breeds. The reported sensitivities are for acute intervertebral disc herniations. The diagnostic sensitivity of plain CT in nonmineralized chronic, type II disc protrusions is currently unknown, but it is likely significantly less than the reported values for acute disc herniation. In chronic cases, CT myelography would likely be necessary. Importantly, a normal noncontrast CT does not rule out IVDD.

8. Computed tomographic findings in dogs with lumbosacral disease include loss of epidural fat, increased soft tissue opacity within the intervertebral foramen, bulging of the intervertebral disc, vertebral canal stenosis and

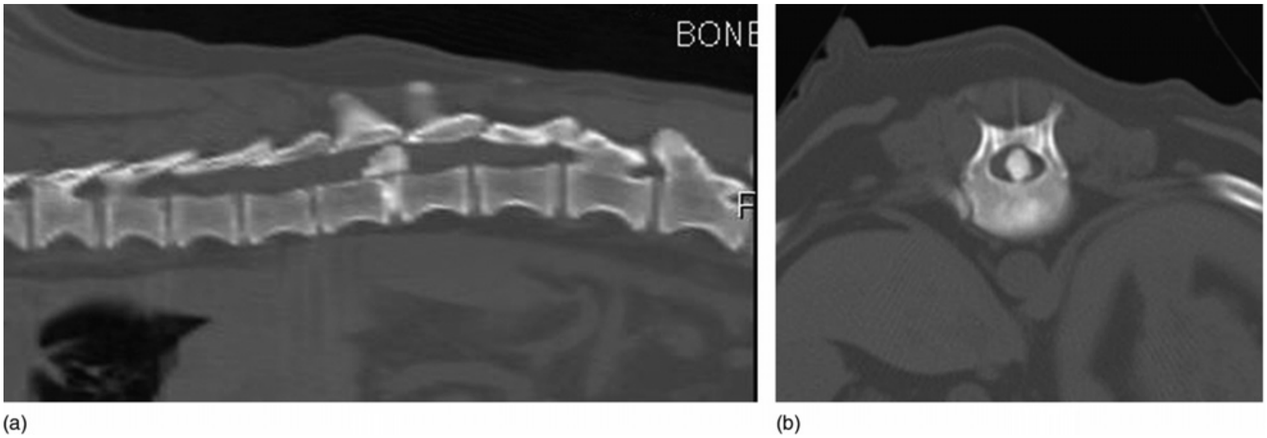


Figure 5.20 Noncontrast (plain) CT with a dog with acute intervertebral disc extrusion. (A) Reconstructed sagittal CT, and (B) transverse CT. Observe hyperdense mineralized material within the vertebral canal.

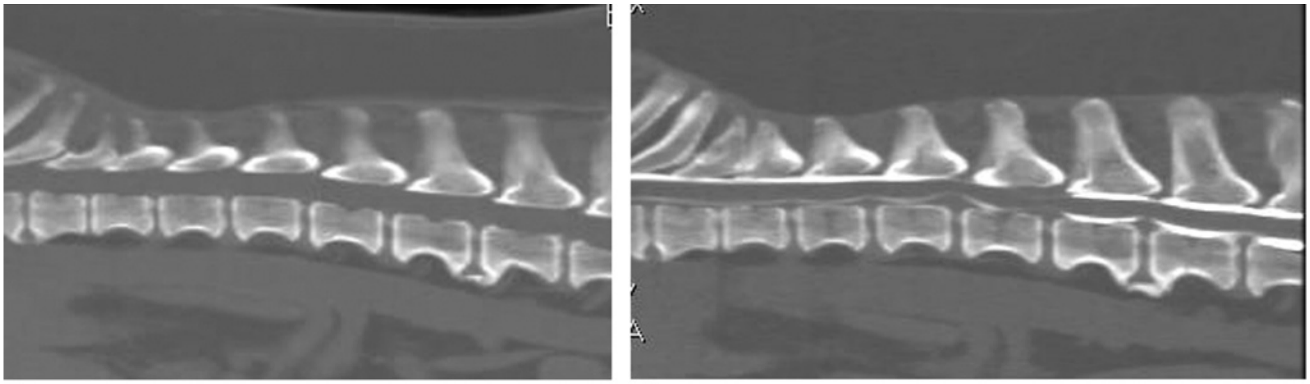
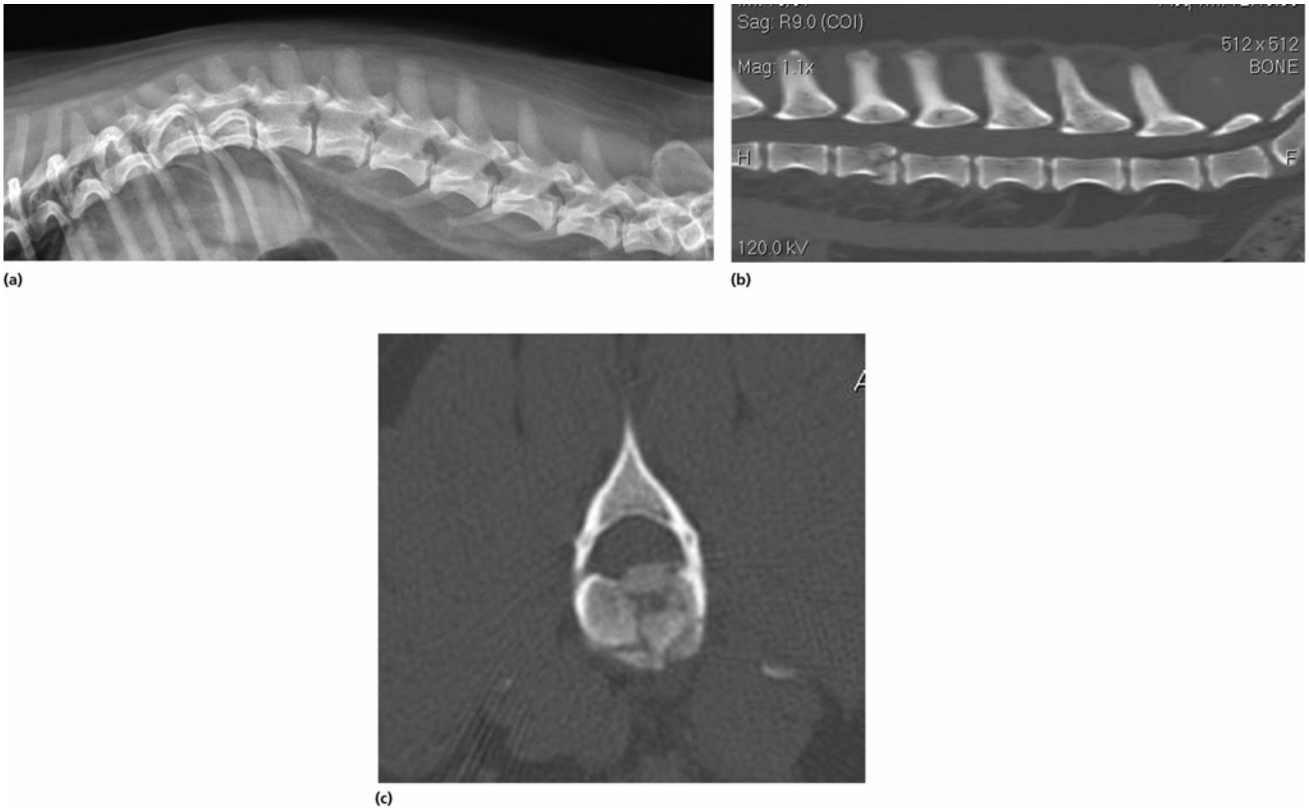

(a) (b)

Figure 5.21 CT images of a dog with intervertebral disc disease before (A) and after (B) administration of intratechal contrast (myelogram).

thickened articular processes. In noncontrast CT, the epidural fat surrounds the nerve roots and dural sac, however, with stenosis and compression, the epidural fat is lost and the compressive soft tissue becomes indistinguishable from adjacent nerves. The use of intravenous contrast for CT evaluation of the LS area increased the sensitivity for detection of ventral and lateral compressions. The use of subarachnoid contrast (myelography) associated with CT is not recommended for evaluation of the lumosacral area, because the contrast medium causes blooming and beam hardening artifacts making interpretation difficult.

9. CT is primarily important for patients suspected of having spinal trauma A study compared the diagnostic sensitivity of survey radiographs and CT in dogs with confirmed spinal fractures and luxations. Radiographs missed approximately 25% of the lesions detected on CT (Fig. 5.22). CT is the gold standard test for the evaluation



(a) (b) (c)

Figure 5.22 Images of a dog with spinal trauma with a fracture in the vertebral body of L2. (A) Lateral radiograph, (B) sagittal CT, and (C) transverse image. Note that fracture identification is facilitated with the use of CT.

of spinal trauma in humans, and should be used whenever possible in the evaluation of dogs and cats with spinal trauma.

10. Advantages of CT over other imaging modalities are numerous. CT provides superior soft-tissue contrast in comparison with conventional radiography. Noncontrast CT can also be performed with sedation only, whereas this is not possible with magnetic resonance imaging (MRI). The cost of CT is typically less than MRI. CT is a more rapid imaging modality than MRI, and bone and acute hemorrhage are better visualized with CT versus MRI; these attributes make CT preferable to MRI in acute head trauma patients. Other advantages of CT imaging are the ability to alter window settings after data acquisition and the ability to form 3-D reconstructed images.
11. There are several disadvantages of CT compared to MRI. CT involves exposure to ionizing radiation (X-rays), whereas MRI does not. MRI provides superior soft-tissue detail in comparison with CT. CT is usually adequate for visualizing mass lesions in the brain and spinal cord. However, subtle parenchymal lesions (e.g. inflammatory foci in GME) as well as brain (especially brainstem) and spinal-cord lesions in very small dogs and cats may be more appreciable on MRI than CT. Image artifacts are typically more of a problem with CT versus MRI. In particular, beam hardening, which appears as black streaks, is a common CT artifact when imaging the caudal fossa (Fig. 5.23). This artifact is due to the dense bone in the petrous temporal region. The average energy of the X-ray beam that traverses this thick bone and reaches the detectors is very high, because photons of lower energy are absorbed by the bone. The computer interprets the high average energy beam as X-rays that have passed through a low-density structure, incorrectly assigning the tissue a low Hounsfield unit number (black streaks). Beam hardening does not occur in MRI.

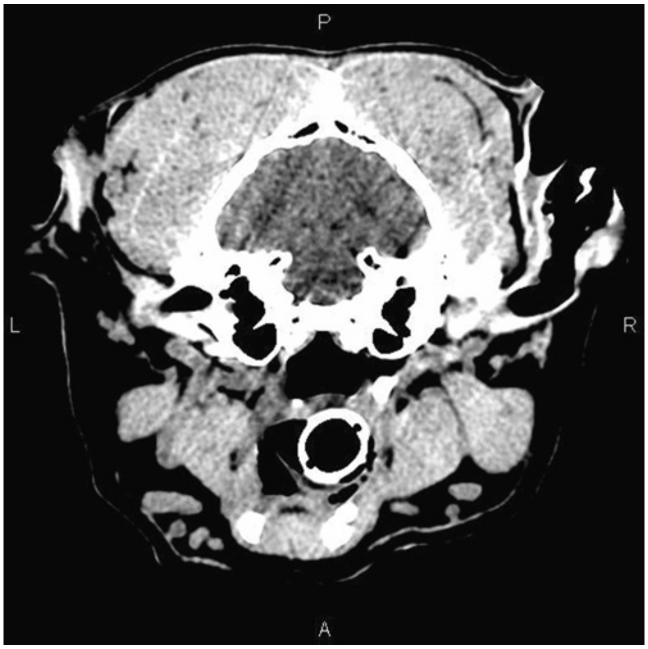


Figure 5.23 Transverse CT image of the caudal fossa of a dog, demonstrating beam-hardening artifact in the brain-stem region.

Electrodiagnostics

Electrodiagnostic examinations take advantage of the body's electrical properties to help characterize neurologic disorders. These tests require both specialized instrumentation and individuals trained in performing the tests. There are numerous electrodiagnostic machines available, the majority of which are capable of performing most or all of the procedures discussed below (Fig. 5.24). There are two main categories of electrical activity measured in clinical neurology: spontaneous and evoked. Spontaneous potentials are electrical signals produced by the body in the absence of an externally applied stimulus.

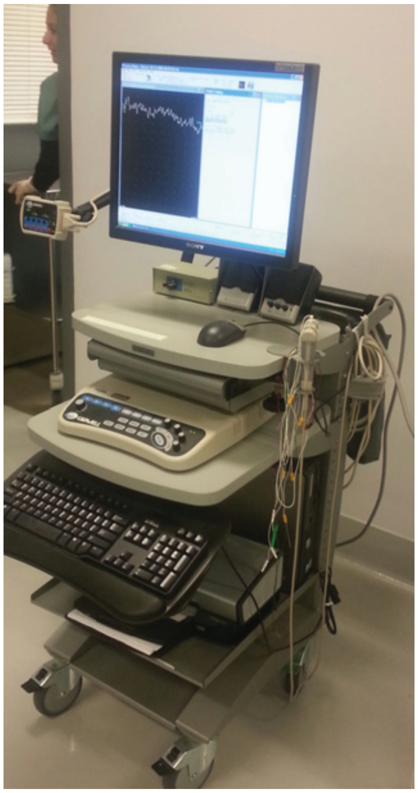


Figure 5.24 Cadwell Sierra Wave model.

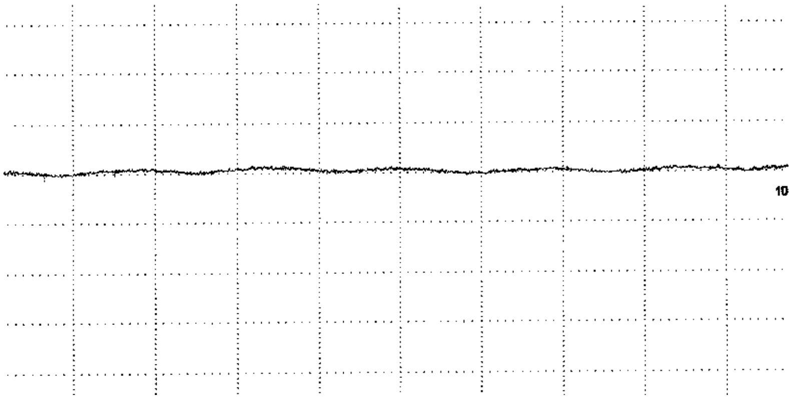


Figure 5.25 Normal silent EMG tracing from a dog.

Evoked potentials are electrical impulses caused by an externally applied stimulus.

A. Spontaneous activity

  1. Electromyography (EMG)[1, 21, 33, 45, 74]

    a. Electromyography is the recording of spontaneous electrical activity from muscle. This testing is performed with the patient under general anesthesia. The authors prefer the use of a concentric needle electrode for EMG studies. The needle electrode is inserted into muscle tissue and muscle activity is recorded. The needle is repositioned several times to sample different areas of the muscle, and multiple muscles are evaluated. Both the sound and the appearance of spontaneous muscle activity are evaluated during EMG studies. Abnormal muscle activity from EMG evaluation is sensitive, but not very specific. Muscle fibers often become hyperexcitable with both denervation (due to neuropathies) and more direct damage (myopathies). Therefore, abnormal EMG activity confirms the presence of either a neuropathic or a myopathic process, but not specifically one or the other. Electomyographic abnormalities may not be detectable for five to seven days following denervation. It should also be kept in mind that not all myopathies or neuropathies are characterized by abnormal EMG activity.

    b. In general, muscle tissue is silent on EMG evaluation (Fig. 5.25) of the anesthetized patient. Small deviations from baseline (monophasic potentials) are occasionally recorded from muscles, especially near motor points (sites where major nerve trunks connect with muscle bellies). This normal activity is called endplate noise or endplate potentials and reflects small depolarizations (miniature endplate potentials) at neuromuscular junctions (Fig. 5.26). Endplate noise sounds similar to small waves breaking at the seashore or the sound heard when one listens to a seashell. Immediately after insertion of the needle electrode into a muscle belly, there is typically a short burst of electrical activity, called insertional activity. This is due to mechanical irritation and damage to muscle fibers by the needle, and is normal unless it lasts more than one to two seconds after the needle stops moving. Replacement of muscle tissue by fat or connective tissue in chronic denervation or myopathies may lead to the absence of insertional activity.

    c. In addition to prolonged insertional activity, abnormal EMG activity includes fibrillation potentials, positive sharp waves, and complex repetitive discharges. In general, all of these abnormal potentials indicate either neuropathy or myopathy, but are not specific for either.

    Fibrillation potentials are biphasic or triphasic spikes of short duration that are thought to arise from individual muscle fibers (Fig. 5.27). They sound like popping noises. When occurring as a train or

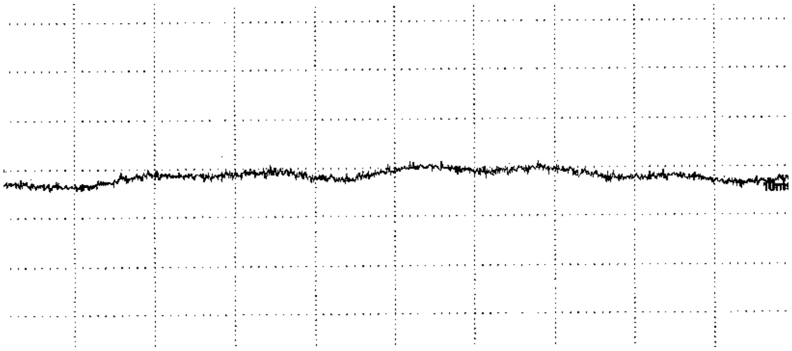


Figure 5.26 Endplate potentials recorded from a normal dog.

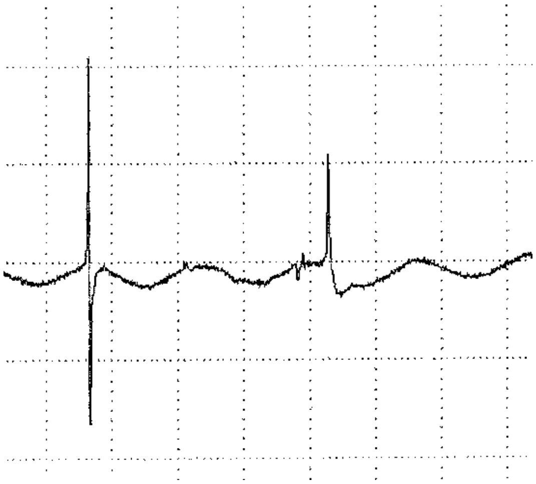


Figure 5.27 Fibrillation potentials.

continuous run, the sound is like eggs or bacon frying, or a heavy rain falling on a tin roof. Fibrillation potentials are believed to represent severe or chronic disease, compared with positive sharp waves.

Positive sharp waves often occur concurrently with fibrillation potentials. These potentials are of longer duration than fibrillation potentials and appear to be monophasic (Fig. 5.28). Positive sharp waves are believed to originate from individual muscle fibers, but a conduction block in the sarcolemma leads to the more prolonged potential. When positive sharp waves occur in a train or burst, it sounds like a racecar driving past.

Complex repetitive discharges or bizarre high-frequency potentials are synonymous catchall terms applied to polyphasic potentials that do not appear to be fibrillation potentials or positive sharp waves. These potentials are thought to arise from bared muscle spindles and are often associated with chronicity. They tend to have constant amplitude and frequency (i.e. they do not wax and wane). The sounds of these potentials are varied and have been described as revving motorcycle engines and airplanes flying.

Myotonic discharges are often described as a distinct entity, rather than a subcategory of complex repetitive discharges (Fig. 5.29). These are high-frequency, biphasic or triphasic repetitive discharges that wax and wane, producing a "dive-bomber" sound. They are typically recorded following needle electrode insertion or repositioning. Although not specific for any disorder, these discharges are most often associated with myotonia (either congenital or due to hyperadrenocorticism).

2. Electroencephalography (EEG)[21,46,86,99]
   a. Electroencephalography refers to the recording of spontaneous electrical activity of the cerebral cortex, and the interpretation of these recordings. Historically, EEG had many practical applications, including its use in localizing seizure foci. In modern veterinary neurology, the clinical utility of EEG examination is limited. The likelihood of EEG examination contributing substantially to the management of a patient with an established generalized seizure disorder is low. As a localizer of focal brain abnormalities, EEG is fairly inaccurate and provides no structural information. The increased availability and use of CT and MRI technology has been associated with a decrease in the use of EEG examinations. However, EEG remains an important diagnostic tool.

   Electroencephalography is often helpful in cases of focal seizure disorders, in which the diagnosis of the condition as a seizure disorder is sometimes equivocal. The authors have also found EEG examination useful as a determinant of brain death in comatose patients who have been resuscitated following cardiac arrest. When EEG examination is performed in this latter context, it is usually done so in conjunction with a BAER examination (see the next section).

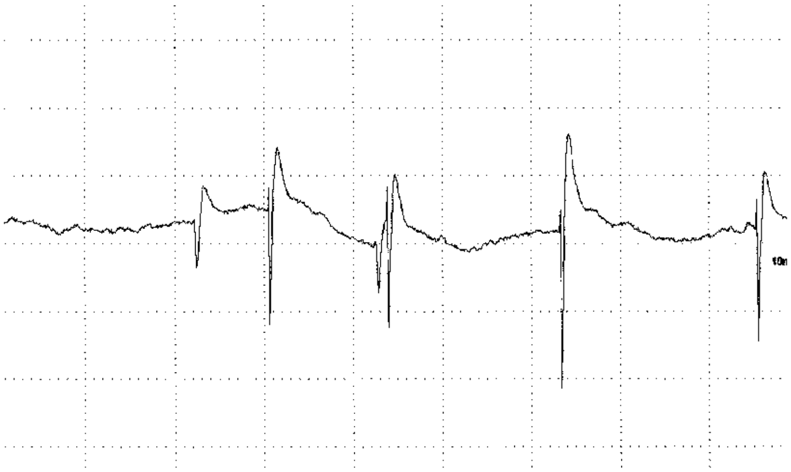


Figure 5.28 Positive sharp waves.

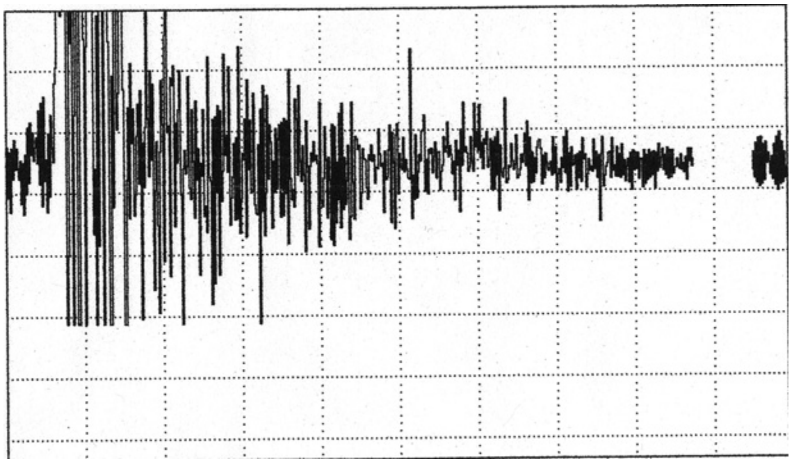


Figure 5.29 Myotonic discharges from a dog with congenital myotonia.

b. Electroencephalography is performed using small scalp recording electrodes. These electrodes are placed in specific areas so that electrical activity in multiple regions of the cerebral cortex can be simultaneously recorded (Fig. 5.30). Each channel (derivation) represented on the EEG recording represents electrical potentials occurring between two scalp electrodes, the first of the named pair being the exploring electrode and the second being the reference electrode. The arrangement of multiple derivations of electrode pairs is referred to as a montage.

There are multiple ways to perform an EEG examination. Since abnormal EEG activity is likely to occur during physiologic sleep, and since general anesthesia may induce spike activity (associated with seizure disorders) in normal patients, it is not recommended to perform EEGs in anesthetized patients. The authors prefer to perform EEGs in a quiet darkened room with the patient lightly sedated (e.g. meperidine, 5 mg/kg intramuscularly). The patient typically will become drowsy and fall asleep, allowing the measurement of both awake and sleeping EEG activity. A full EEG recording takes approximately 20–40 min to perform.

c. Normal background electrical activity recorded on EEG examination primarily reflects the algebraic summation of oscillating resting membrane potentials and subthreshold postsynaptic potentials (PSPs) of cerebral cortical neurons (Fig. 5.31). Electrical activity of cerebral cortical neurons is influenced by the ascending reticular activating system (ARAS) of the brain stem, primarily the diencephalon. Fluctuations in membrane potentials of glial cells in the cerebrum probably also contribute to the EEG pattern. In general, the alert state is characterized by high-frequency, low-voltage activity. The frequency slows and the amplitude of measured potentials increases with drowsiness and non-REM (rapid eye movement) sleep. The EEG pattern of REM sleep is similar to the awake EEG pattern.

There is often a high degree of subjectivity in the interpretation of abnormal EEG recordings. In general, frequencies and amplitudes that appear either

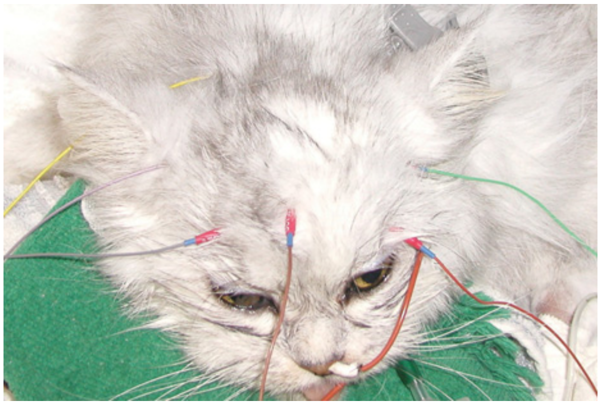


Figure 5.30 Typical scalp electrode arrangement for EEG recording.

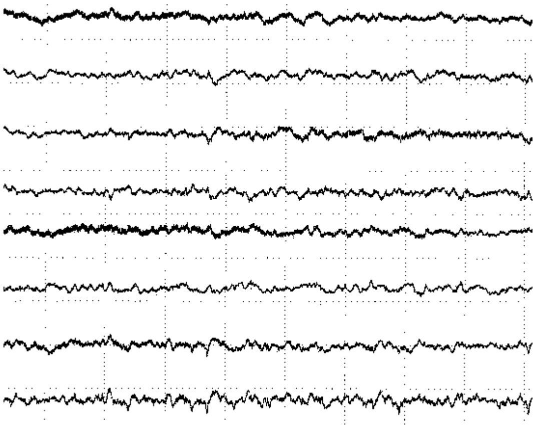


Figure 5.31 Normal EEG recording from a dog.

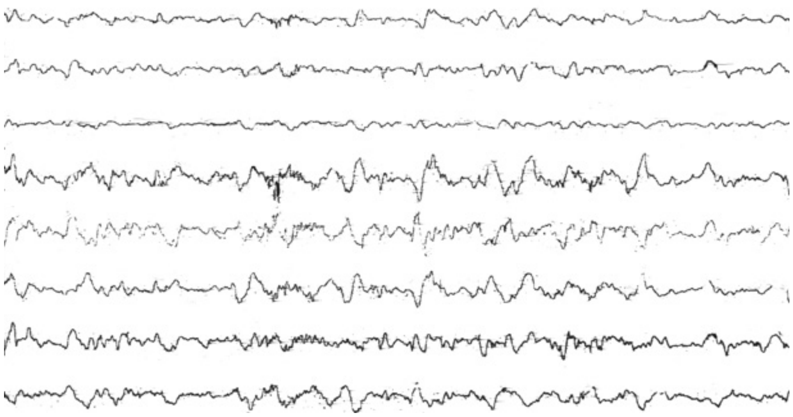


Figure 5.32 Spike activity from an EEG recording of a patient with seizure activity (Courtesy of Dr. Gregg Kortz.)

inadequate or excessive for the physiologic conditions under which they are measured (e.g. high-voltage, low-frequency activity in an awake patient) are indicative of brain dysfunction. Spike and spike-wave activity (Fig. 5.32) are indications of a seizure disorder.

B. Evoked activity

1. Brain-stem auditory evoked response (BAER)[21,39,57,67,71,74,94,98,111]

- **a.** Brain-stem auditory evoked response testing utilizes the auditory pathway for the evaluation of hearing and brain-stem disorders. The patient is administered auditory stimuli in the form of clicks delivered via specialized earplugs. The resultant evoked response is measured via subcutaneous scalp electrodes arranged in specific patterns. The normal BAER consists of four or five waves that are time-locked to the sound stimulus. These waves appear within 10 ms of the sound delivery (Fig. 5.33). The BAER is not appreciably affected by sedation or anesthesia, so it can be performed on awake, sedated, or anesthetized patients.
- **b.** The waves of the BAER correspond to sequentially activated neuronal groups and white-matter tracts associated with the auditory pathway. These waves represent a caudal to rostral chain of propagated depolarization. The appearance and latency (time between the sound stimulus and appearance of the wave) of each wave following the first wave is dependent upon the integrity of neural tissue caudal to the specific wave's site of generation, as well as upon the tissue comprising the generator site for that specific wave.
- **c.** There is general agreement that wave I is generated by the cochlear portion of the vestibulocochlear nerve. The generator sites of the remaining waves are not definitively known, and probably represent superimposition of action potentials from multiple brain-stem structures. Wave II is thought to arise from the cochlear nuclei in the medulla. Wave III is suspected to be generated by the rostral olivary nuclei and the dorsal nuclei of the trapezoid body, both located in the medulla. Wave IV likely represents action potentials from the lateral lemniscus and lemniscal nuclei of the pons. The caudal colliculi of the midbrain and medial geniculate nuclei of the diencephalon contribute to the generation of wave V.
- **d.** When performing the BAER, the patient is placed in ventral recumbency, the scalp electrodes are attached, and the earplugs are inserted. Each ear is stimulated separately, typically at 80 and 100 decibels (dB). The nonstimulated ear receives a masking or "white" noise 30–40 dB below that of the stimulated side. Similar to an electrocardiogram or an EEG, the BAER can be recorded with different arrangements of recording electrodes. The authors prefer a vertex to mastoid recording (VM), and occasionally record

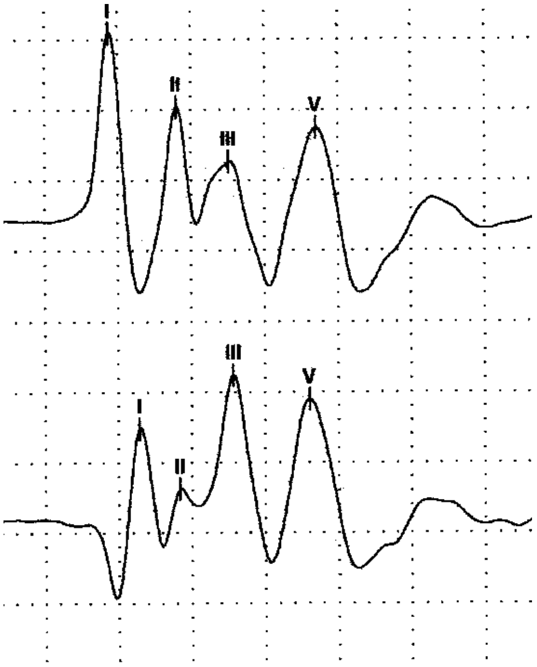


Figure 5.33 Normal BAER recording from a cat.

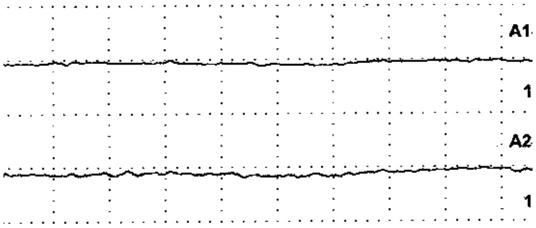


Figure 5.34 Flat line BAER recording from a puppy with congenital sensorineural deafness.

additionally with a vertex to first thoracic vertebra (VT1) lead arrangement. These two types of recording can be accomplished concurrently. Wave IV is often indistinguishable as a separate wave on the VM recording, and may be complexed with either wave III or V.

e. The appearance of four or five recognizable waves on a BAER recording confirms hearing ability on that side. A flat line is evidence of deafness (Fig. 5.34). Dogs with congenital sensorineural deafness (see Chapter 7) typically have flat BAER recordings at both 80 and 100 dB either unilaterally or bilaterally. A flat line, or relatively decreased amplitude of waves at 80 dB, and a detectable response at 100 dB suggest a conduction disturbance of hearing (e.g. fluid in the middle ear cavity due to otitis media). Similarly, a prolonged latency from sound stimulus to the appearance of wave I at 80 dB that improves at 100 dB suggests a conduction disturbance of hearing. For evaluation of brain-stem integrity, interwave intervals are calculated by the computer for peak-to-peak latencies between waves I and III, waves III and V, and waves I and V. These intervals should be within reference ranges and typically do not differ from right to left by more than about 0.1 ms. More specifically, in normal dogs, the mean difference in interwave intervals between left and right sides stimulated between 70 and 100 dB have been reported to range from 0.07 ms to 0.13 ms. Because of this range and the standard deviation on either side of the mean values, the authors feel that a left-to-right difference of 0.2 ms or greater be regarded as abnormal, with values between 0.1 ms and 0.2 ms being thought of as suspicious of a brain-stem abnormality. Brain-stem lesions (e.g. tumors) will cause a conduction delay, which will be measured as a prolonged latency that corresponds to the anatomic location of the lesion (Fig. 5.35). Although wave amplitudes are not often calculated for diagnostic purposes, a V/I amplitude of less than 0.5 is indicative of a brain-stem lesion. A patient that has experienced brain death will typically exhibit a flat BAER, or have only wave I present on the recording.

2. Motor nerve conduction velocity (MNCV)[21,23,28,33,74,80]
   a. Motor nerve conduction velocity studies are performed primarily in animals suspected of having neuropathies. For MNCV measurement, an electrical stimulus is applied to a nerve with subcutaneous electrodes, and the resultant depolarization of a muscle supplied by that nerve is recorded with a recording electrode. The depolarizing event is a large biphasic or triphasic muscle potential formed by action potentials of many muscle fibers from many motor units. It is usually referred to as a compound muscle action potential (CMAP) or an M wave. The latency, or time, from the stimulus to the onset of the M wave is measured by the computer. A minimum of two sites of a nerve must be stimulated in order to calculate a MNCV. The distance between the two stimulation sites (in meters) is divided by the difference in latency from stimulus artifact to M wave appearance for the two sites (in seconds) to arrive at MNCV in m/sec. The

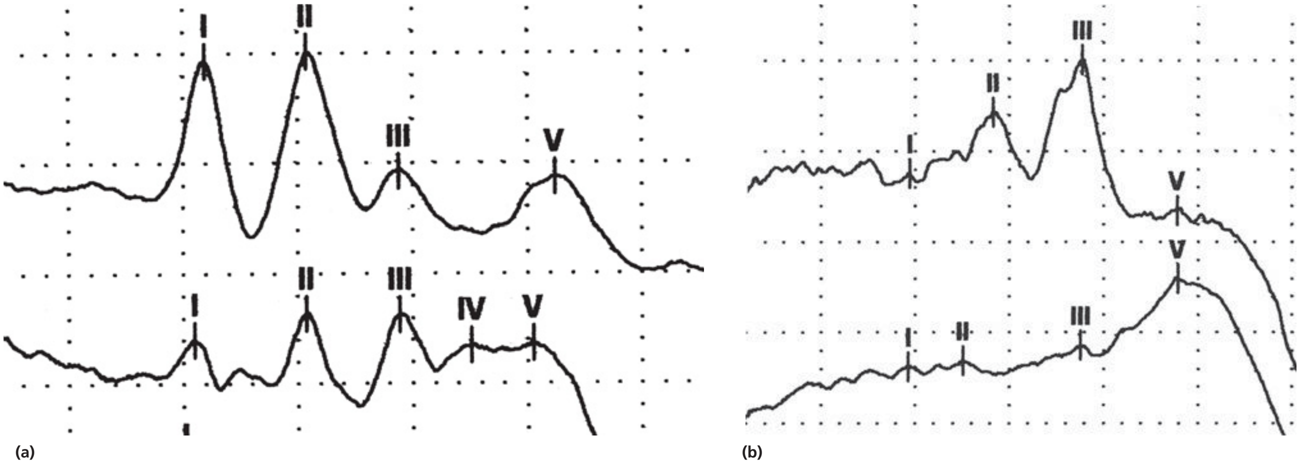


Figure 5.35 BAER recordings from a dog with a brain-stem lesion, after stimulating the left (A) and right (B) ears. Note the lack of symmetry between sides and the prolonged interwave latency on the second recording.

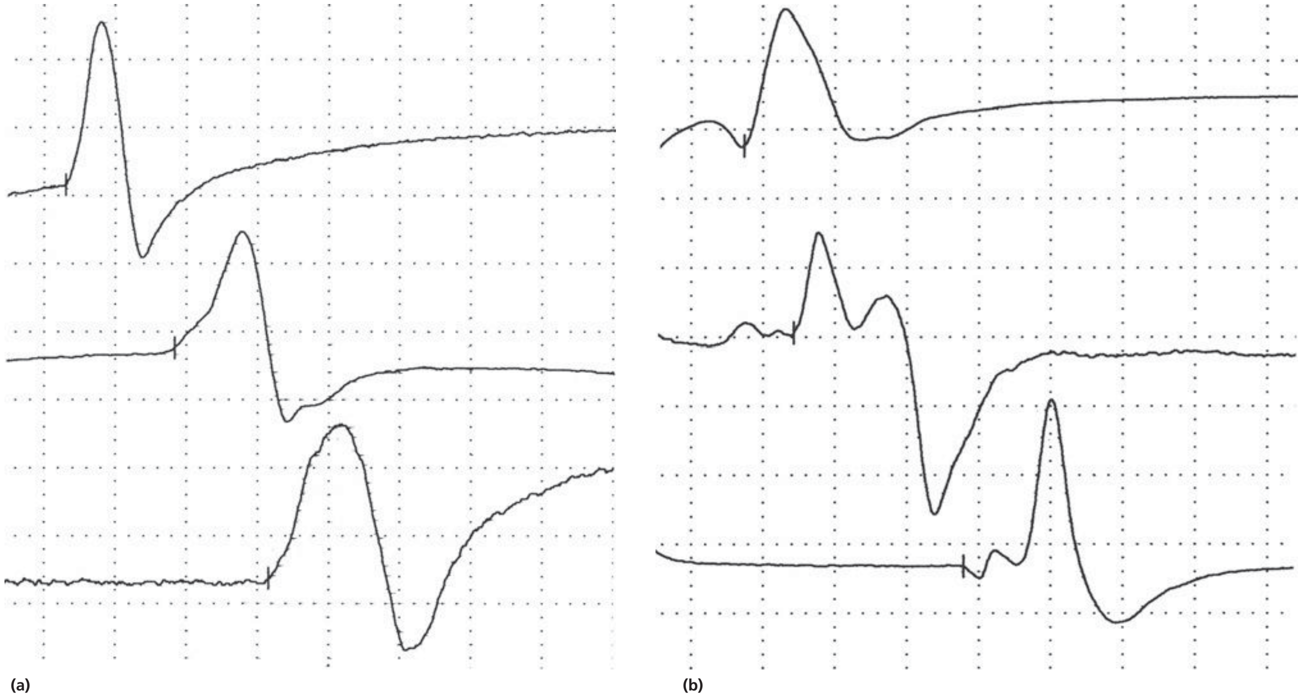


Figure 5.36 MNCV recordings (M waves) from the sciatic and peroneal nerves of a normal dog (A) and a dog with a progressive polyneuropathy (B). Polyphasic M waves are apparent on the second recording.

M wave is the result of orthodromic (proximal to distal) propagation of nerve depolarization.

b. When a nerve is artificially stimulated, as in MNCV testing, it also depolarizes antidromically (distal to proximal). Recording conditions can be set to measure one of two smaller waves: F waves or H waves. F waves result from antidromic motor nerve depolarization causing depolarization of lower motor neurons in the ventral horn of the spinal cord. This depolarization leads to a secondary orthodromic nerve depolarization back down the axon. The subsequent muscle response (F wave) is of much smaller amplitude and longer latency than the M wave. Similarly, the H wave is due to initial antidromic, then orthodromic propagation of depolarizing events. However, the H wave represents an electrically elicited stretch reflex. Rather than directly causing motor neuron depolarization from an antidromic volley up the motor axons, the H reflex involves antidromic depolarization that follows the sensory axons (e.g. Ia axons) into the spinal cord gray matter, leading to motor neuron depolarization. This motor neuron depolarization leads to a secondary muscle depolarization (H wave) of smaller amplitude and greater latency than the M wave. A smaller stimulus intensity than that used for F wave recording is necessary for H wave measurement. F and H waves are used primarily to evaluate diseases with nerve root pathology (e.g. polyradiculoneuritis).

c. General anesthesia is required for MNCV measurement. If the patient has clinical evidence of a generalized disorder (e.g. suspect polyneuropathy), the authors prefer using the sciatic nerve and its branches (i.e. peroneal or tibial nerves). After a nerve is severed, axons distal to the severed area will continue to conduct normally for up to four days. The nerve is stimulated at two or three sites and the MNCV is calculated after manually measuring the distance from stimulating to recording electrodes (Fig. 5.36). This measurement is performed using a tape measure and is the most likely source of error in this test. Normal MNCV is at least 50 m/sec in older patients, and is typically greater than 60 m/sec in young to middle-aged animals. Decreased body temperature may affect MNCV. The MNCV decreases by 1.8 m/sec for each drop in degrees Celsius from normal. Proximal nerve segments have faster MNCVs than distal nerve segments. In general, demyelination is more likely to cause slowed MNCV than is axonal loss. Small amplitude M waves or polyphasic M waves are often indicative of neuropathy but may result from myopathies also.

3. Sensory nerve conduction velocity (SNCV) and somatosensory evoked potentials (SSEP)[1,2,21,33,35,41,45,74,78,87]

a. Sensory nerve conduction velocity is typically measured in dogs and cats by stimulating a distal

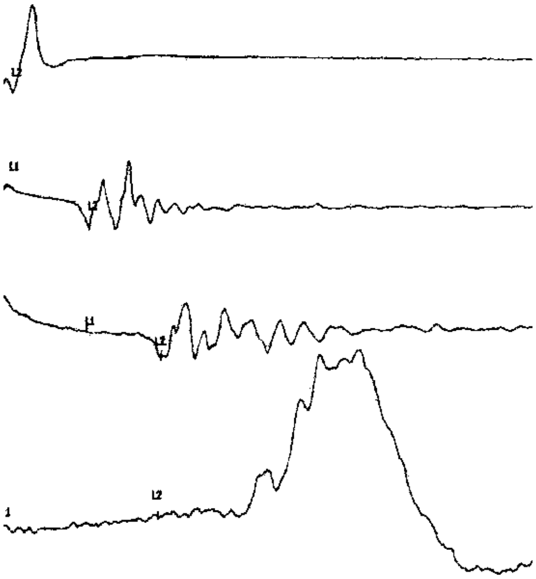


Figure 5.37 Simultaneous SNCV (top three waves represent peroneal/sciatic nerve at hock, stifle, and hip regions) and SSEP (bottom recording represents the lumbosacral intumescence) recordings following distal peroneal nerve stimulation in a dog. (Dr. G Kort, 2014. Reproduced with permission from Dr. G Kortz.)

cutaneous nerve branch, and measuring compound action potentials (CAPs) over proximal sites on the parent nerve. The technique is similar to that used for MNCV, but the depolarization events of interest are antidromic, and CAPs from axonal depolarization are of much smaller magnitude than the CMAPs or M waves recorded in MNCV studies. Sensory nerve conduction velocity recording is primarily used to evaluate patients with suspected neuropathies, especially if MNCV evaluation is normal or equivocal. It is generally thought that SNCV is more sensitive an indicator of early neuropathic processes, compared to MNCV.

b. By placing needle recording electrodes near the interarcuate space over selected regions of the spinal cord, and/or over the scalp region, evoked activity of the CNS can be recorded following stimulation of a peripheral sensory nerve. This latter type of electrodiagnostic testing is referred to as somatosensory evoked potentials (SSEP). Depolarizing events recorded on an SSEP recording are due to axonal CAPs in the cauda equina region or spinal cord white matter (similar to the CAPs of peripheral nerves) as well as from gray matter field potentials. Field potentials refer to depolarization/repolarization events occurring in a group of neurons (e.g. interneuron pool) following excitation from an incoming volley of action potentials (i.e. from peripheral stimulation). Recording over the cervical and lumbosacral intumescence areas often results in a high-amplitude, long-duration potential, primarily due to these depolarization/repolarization events. These potentials are referred to as cord dorsum potentials. SSEP studies are used primarily to evaluate the functional integrity of the spinal cord ascending pathways.

c. The setups for SNCV and SSEP are similar. These studies are also performed under general anesthesia. The authors prefer to stimulate the distal branches of the peroneal nerve and record over proximal segments of the peroneal and sciatic. Recording is usually accomplished by leaving the stimulating electrodes from the MNCV in place, and converting these to recording electrodes. Additional recording electrodes can be placed along the spine or scalp, and SSEP recordings can be made simultaneously with SNCV recordings (Fig. 5.37).

4. Repetitive nerve stimulation (RNS)[30, 33, 73, 74, 90]

a. The repetitive nerve stimulation test measures successive CMAPs (M waves) induced by repetitively stimulating the nerve that supplies the muscle from which the potentials are recorded. With stimulation rates of five per second or less, the sequential M waves should be of equal amplitude and area as the first. A decremental response of 10% or greater indicates a problem with neuromuscular transmission. Though not specific for the disease, a decrementing RNS is usually indicative of myasthenia gravis (Fig. 5.38).

b. General anesthesia is required for RNS in dogs and cats. The authors prefer stimulating the peroneal nerve at the knee or hock level, and recording from a digital muscle. The setup is the same as for MNCV, but only one stimulation site is necessary for RNS. In cases of focal myasthenia gravis (MG), the limb RNS is sometimes normal. In suspect cases of focal MG with normal limb RNS, the authors have often demonstrated a decremental response in facial musculature

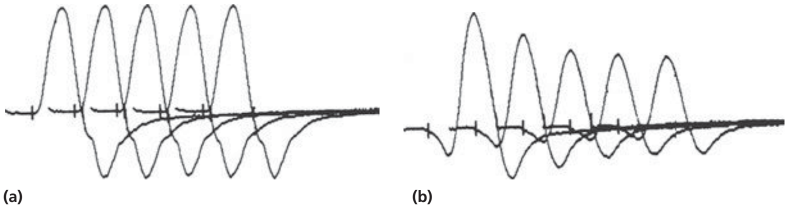


Figure 5.38 Normal RNS result (A) compared to a decrementing RNS recording (B). The latter recording is from a myasthenic dog. (Dewey, 1997[30].)

(e.g. orbicularis oculi muscle) following facial nerve stimulation.

5. Miscellaneous evoked response tests[3,48,65,69,74,82,90,101,106]
    a. The use of magnetic motor evoked potentials (MEPs) to evaluate descending motor pathways has been described in dogs. A magnetic field is applied to the cranium to stimulate regions of the cerebral motor cortex, and recordings of CMAPs (M waves) are made from limb muscles contralateral to the stimulated side. Recordings of depolarizing events can also be obtained from the spinal cord and peripheral nerves. Magnetic MEPs can be recorded under sedation.
    b. Single-fiber electromyography (SF-EMG) has also been described in dogs. This procedure makes use of a specialized needle electrode that records evoked action potentials from individual muscle fibers. The variability of neuromuscular transmission time for individual muscle fibers, referred to as “jitter,” is recorded. This test is both sensitive and specific for acquired MG in people (increased “jitter”), and may hold promise as a diagnostic test for that disease in dogs. Single-fiber EMG can also be performed under sedation, versus general anesthesia.

Biopsy/exploratory surgery[16,57,63]

A. Nerve and muscle biopsies are often performed in conjunction with electrodiagnostics. These should be used to help characterize and diagnose neuropathies and myopathies.

B. Exploratory spinal surgery is performed when imaging techniques do not adequately characterize a compressive spinal cord lesion, or when biopsy and debulking or resection of a neoplastic lesion is indicated.

C. Exploratory craniotomy is indicated for biopsy and debulking of neoplastic lesions seen on CT or MRI. Stereotactic brain biopsy is becoming more widely available for diagnosis of intracranial lesions without exploratory surgery.

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CHAPTER 6

Principles and Application of Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) of the brain

Silke Hecht

Basic MRI physics[135, 142, 235, 278, 351, 354, 385]

Magnetic resonance imaging (MRI) is the imaging modality of choice for the diagnosis of most neurologic diseases in human and veterinary patients. While an in-depth review of MR physics is beyond the scope of this chapter, an overview of basic principles and sequences will be provided to facilitate understanding of clinical applications and interpretation.

In general, any element with either an odd number of protons or an odd number of neutrons has a nuclear magnetic dipole moment and may therefore be suitable for MR imaging or spectroscopy. Hydrogen is the optimal element for MR imaging as (1) it is the most common element in the body, (2) its nucleus consists of a single proton and has the strongest magnetic dipole moment of any element suitable for MR imaging, and (3) most pathologic processes affecting the central nervous system (CNS) result in alteration of content, distribution, and ambient environment of hydrogen protons facilitating differentiation of diseased from normal tissue. This overview will focus on MR imaging of hydrogen protons.

Hydrogen protons in tissues are not static but spin around their axes, generating their own micromagnetic environments. In the absence of an external magnetic field the magnetic moments of the spinning protons are randomly oriented. However, when brought into a strong external magnetic field (i.e. an MR scanner), they rearrange under its influence. The magnetic field strength is denoted by the unit "tesla" (T). The strength of clinically used MR scanners ranges from approximately 0.2T (low-field) to 3T (high-field); higher-strength scanners (7–21T) are at this point limited to research institutions. The alignment of individual protons may be parallel or antiparallel with the external magnetic field. A slight majority of protons will align with the magnetic field, generating a magnetic vector ("net magnetization vector") which is utilized during MR imaging. The main magnetic field is denoted by B_0, the tissue magnetization vector by M_0. As long as M_0 is parallel with the much stronger B_0 it cannot be easily separated out and cannot be used for imaging. The goal of MR imaging is to manipulate tissue magnetization in a way that it can be distinguished from the external magnetic environment.

In addition to a spinning motion around their individual axes, hydrogen protons wobble (or precess) under the influence of B_0, similar to a spinning top wobbling under the influence of gravity. The precession frequency of the spinning protons is dependent on the strength of the external magnetic field and is described by the Larmor equation:

$$\omega_0 = \gamma B_0$$

where:

ω_0 = Larmor or resonant frequency

γ = gyromagnetic ratio specific for each MR active nucleus (42.56 MHz/T for hydrogen)

B_0 = external magnetic field strength.

In order to manipulate tissue magnetization so it can be separated from the main magnetic field, radiofrequency (RF) pulses are applied. Once the nuclei are exposed to an RF pulse exactly matching their precessional frequency they gain energy and start resonating. As a result of the energy gain some protons change their alignment with the magnetic field, causing the magnetic net vector to move away from B_0, or "flip." The most common flip angle of the tissue magnetization vector is 90° used in spin echo sequences (see below). Hydrogen protons flipped into this "transverse plane"—which is in perpendicular orientation to the main magnetic field (the "longitudinal plane")—continue to precess. According to Faraday's law, any change in the magnetic environment of a coil of wire will cause an electric signal. Strategic placement of receiver coils in the MR unit allows detection and measurement of magnetization in the transverse plane, which is the basis of image formation in MRI (Fig. 6.1).

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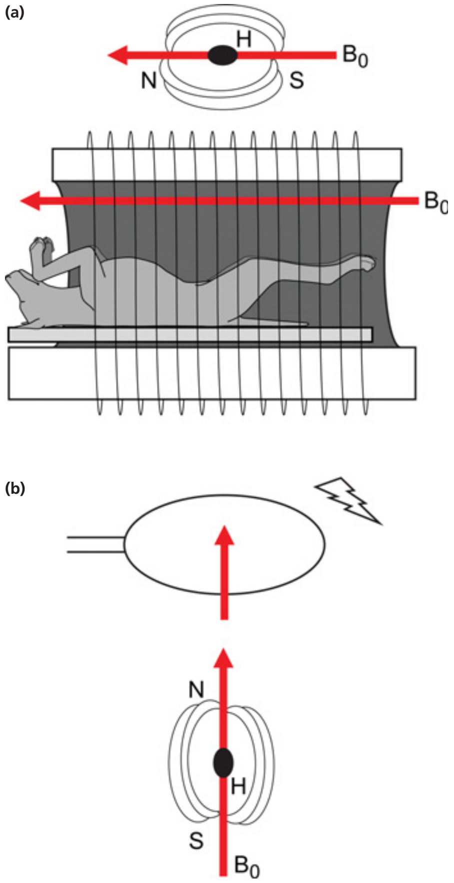

Figure 6.1 Schematic illustration of the alignment of the net vector (tissue magnetization) before (A) and after (B) application of a 90° RF pulse. (A) The net vector is aligned parallel to the main magnetic field (B_0) and cannot be measured. (B) After application of the 90° pulse the net vector is oriented perpendicular to the main magnetic field, and a current (signal) is induced in the receiver coil. (The Ohio State University. Reproduced with permission.)

After the RF pulse is switched off, the signal induced in the receiver drops off rapidly due to two concurrent processes:

T1-relaxation (spin-lattice relaxation): Excited hydrogen protons return to lower energy states, and the magnetic net vector realigns with the main magnetic field (Fig. 6.2).

T2-relaxation (spin-spin relaxation): The unified front of hydrogen protons quickly loses coherence, resulting in a signal drop-off. While true T2-relaxation is solely the result of micromagnetic inhomogeneities (spin–spin interactions, i.e. interference of one spinning proton's micromagnetic field with its neighbors), extrinsic magnetic field inhomogeneities (magnet imperfections, disruption of the magnetic field by paramagnetic or ferromagnetic substances, etc.) contribute to an even more rapid loss of phase coherence. This process is called T2*-relaxation (Fig. 6.3).

Three important tissue parameters for MR imaging include T1- and T2-relaxation times and proton density (PD), i.e. the actual amount of hydrogen protons in a certain tissue volume. The goal of MR imaging is to translate these inherent tissue differences into image contrast, which is accomplished by using different MR sequences.

MR sequences

Basic spin echo (SE) sequences[115, 179, 274, 279, 285–287, 293, 385]

These include T1-W, T2-W and proton density (PD) weighting, which are the most basic but also the most commonly used MRI sequences. Each SE sequence starts with a 90° RF pulse followed by a 180° pulse applied exactly halfway between the initial 90° pulse and the generation of the signal (echo) (Fig. 6.4). The 180° pulse is applied to cancel out external magnetic field inhomogeneities. It essentially reverses any effects an external disturbance (e.g. a nearby flowing vessel or paramagnetic methemoglobin in a hematoma) will have on proton alignment and resultant tissue signal. The small interactions occurring between individual protons and contributing to signal loss in the transverse plane cannot be reversed, resulting in true T2 relaxation contributing to image contrast. As the MR signal generated during a single episode of proton excitation is too small to create an image, the process is repeated many times until enough data have been collected. The time between the 90° pulse and the echo is called "time of echo" (TE) and the time between successive 90° pulses is called "time of repetition" (TR). The length of TR and TE determines weighting of an SE sequence (Table 6.1).

T1-weighting (T1-W): A short TR is chosen to maximize the differences in T1 relaxation between tissues (Fig. 6.5). This is combined with a short TE to minimize T2 effects.

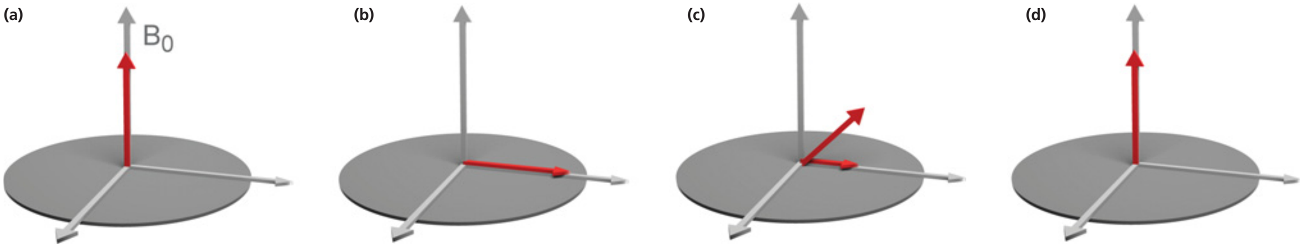

Figure 6.2 Schematic illustration of T1 relaxation. (A) Situation before the 90° pulse. The magnetic vector is aligned with the main magnetic field. (B) After the 90° pulse the vector is in the transverse plane. (C, D) The protons realign with the magnetic field. (The Ohio State University. Reproduced with permission.)

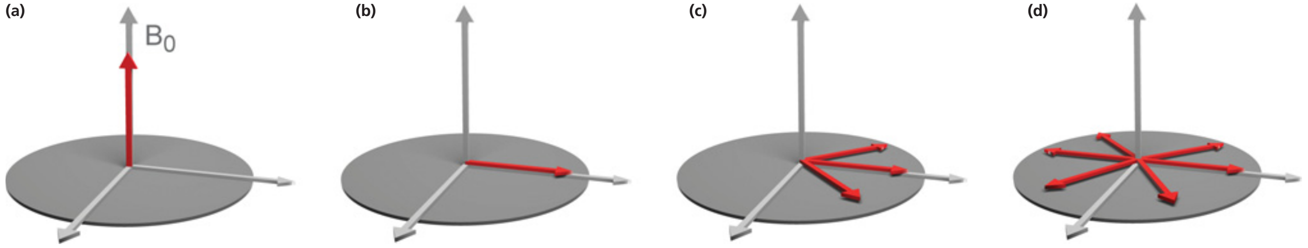

Figure 6.3 Schematic illustration of T2/T2* relaxation. (A) Situation before the 90° pulse. The magnetic vector is aligned with the main magnetic field. (B) After the 90° pulse the vector is in the transverse plane, the protons form a unified front, and the MR signal is strongest. (C, D) The precessing protons lose coherence, and the strength of the MR signal decreases. This occurs due to interference of individual protons with each other (T2 relaxation) as well as influence of external field inhomogeneities (T2* relaxation). (The Ohio State University. Reproduced with permission.)

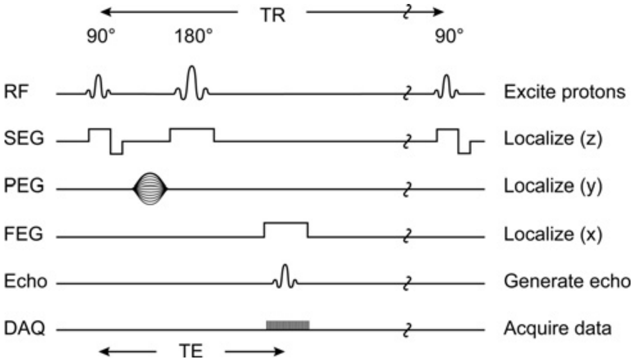

Figure 6.4 Schematic outline of a spin echo sequence. (The Ohio State University. Reproduced with permission.)
TR = time of repetition; TE = time of echo; RF = radiofrequency pulse; SEG/PEG/FEG = slice/phase/frequency encoding gradient (applied for spatial encoding of the MR signal); DAQ = Data acquisition.

Table 6.1 Influence of acquisition parameters on image contrast in a spin echo sequence.[36, 351, 385]

TR	TE	Weighting
Short (300–700ms)	Short (5–30ms)	T1-W
Long (2000–4000ms)	Long (60–150ms)	T2-W
Long (> 2000–4000ms)	Short (5–30ms)	PD-W

Fat has a short T1 relaxation time and is hyperintense, while fluid has a long T1 relaxation time and appears hypointense. Soft tissues have somewhat variable, intermediate T1 relaxation times and are medium in intensity. After uptake of administered paramagnetic contrast agents, physiologically contrast-enhancing tissues (e.g. pituitary gland) and contrast-enhancing pathologic lesions (e.g. certain brain tumors) are hyperintense (Fig. 6.6).

T2-weighting (T2-W): A long TE is chosen to maximize differences in T2 relaxation between tissues, combined with a long TR to minimize T1 relaxation effects. A long TE ensures that

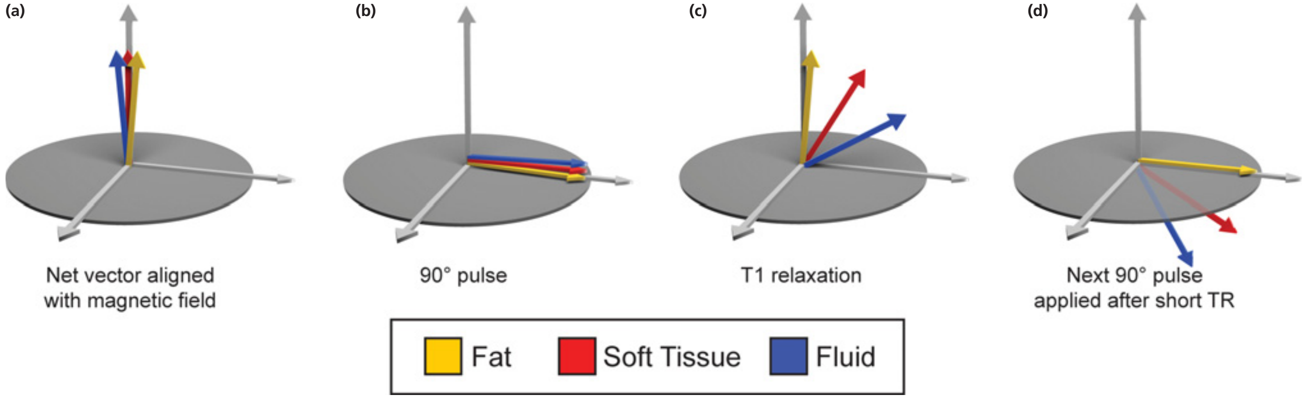
(a)
(b)
(c)
(d)
Net vector aligned with magnetic field
90° pulse
T1 relaxation
Next 90° pulse applied after short TR
Fat
Soft Tissue
Fluid

Figure 6.5 Schematic demonstration of a T1-W sequence. (A) Initially, the net vector of all hydrogen protons (fat, soft tissue, fluid) is aligned with the main magnetic field. (B) Immediately after application of a 90° RF pulse all tissues are in the transverse plane but are quickly separated due to differences in realignment with the main magnetic field (T1 relaxation). Fat has a very short T1 relaxation time, fluid has the longest relaxation time, and soft tissues are intermediate. (C) The second 90° RF pulse is applied when fat protons have realigned with the main magnetic field. (D) Fat is now alone in the transverse plane and gives the strongest MR signal, i.e. it appears bright on the resultant image. Fluid has the least transverse magnetization and appears dark; soft tissue is intermediate in its intensity. (The Ohio State University. Reproduced with permission.)

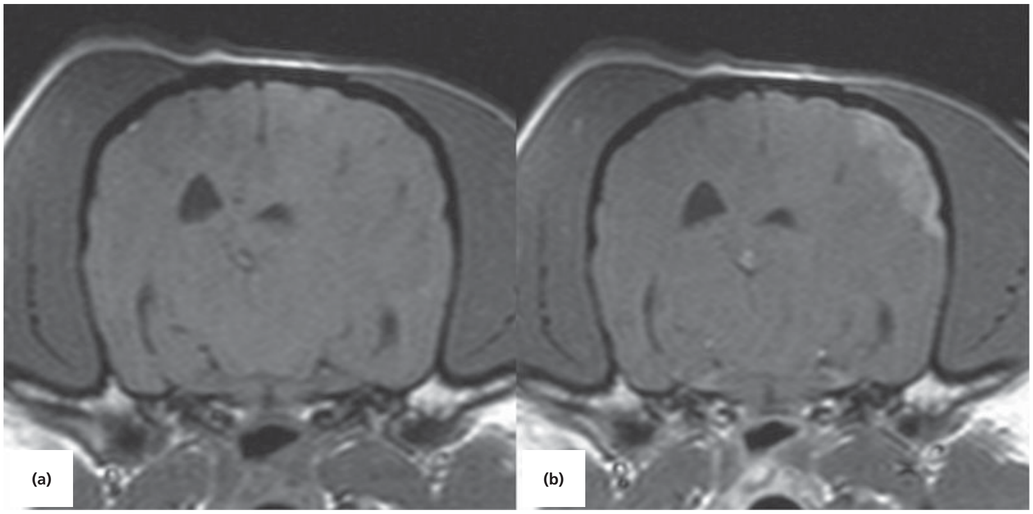

Figure 6.6 Transverse pre- (A) and post- (B) T1-W images of the brain of a dog with a large plaque-like meningioma of the left frontal, parietal, and temporal lobes. Fat associated with subcutaneous tissue and bone marrow and contrast-enhancing tissues appear hyperintense, fluid is hypointense, and soft tissues are intermediate. Additional mass effect beyond the margins of the contrast-enhancing lesion is indicated by midline shift and compression of the left lateral ventricle. The underlying reason (vasogenic edema) is not clearly identified using this sequence (see Fig. 6.8 and Fig. 6.10).

tissues with a short T2 relaxation time will have completely lost their transverse magnetization and have a low signal at the time of image acquisition, while tissues with longer T2 relaxation times still maintain their transverse magnetization and appear brighter (Fig. 6.7). Fluid has a long T2 relaxation time and therefore is hyperintense on T2-W images. Soft tissues have intermediate T2 relaxation times. Fat has a short T2 relaxation time and appears hypointense on conventional T2-W images. However, as conventional T2-W SE sequences have largely been replaced with shorter fast spin echo (FSE) or turbo spin echo (TSE) sequences in which additional pulses are applied (see below), fat typically appears hyperintense on today's T2-W MRI studies. A T2-W sequence can be considered a "pathology" scan, because abnormal fluid collections and tissues with abnormal increased fluid content ("juicy tissue," e.g. edema, inflammation, neoplasia) will appear hyperintense compared to normal tissues (Fig. 6.8).

Proton density weighting (PD-W): PD-W is achieved by choosing a long TR in combination with a short TE to minimize T1 and T2 effects on image contrast. PD-W images

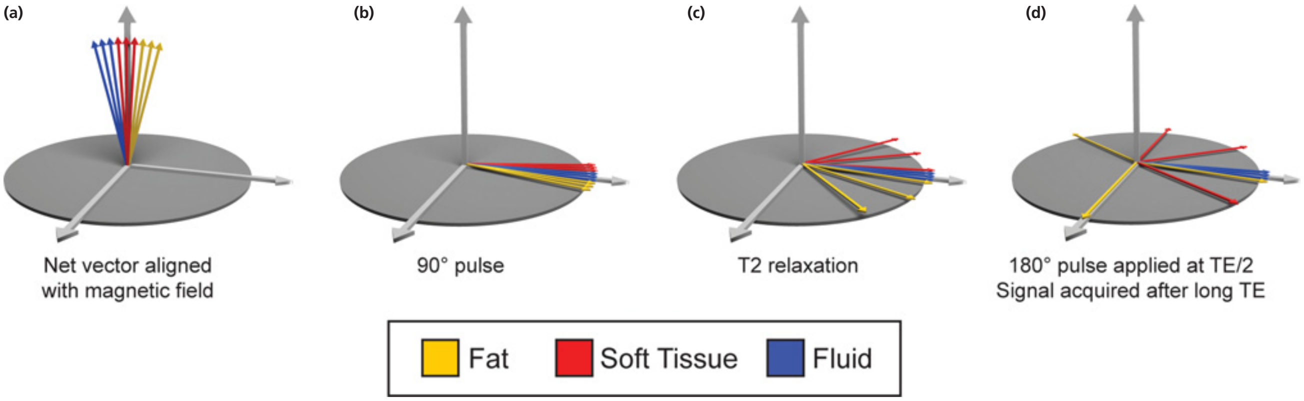
(a)
(b)
(c)
(d)
Net vector aligned with magnetic field
90° pulse
T2 relaxation
180° pulse applied at TE/2
Signal acquired after long TE
Fat
Soft Tissue
Fluid

Figure 6.7 Schematic demonstration of a T2-W sequence. (A) Initially, hydrogen protons in the same tissue are aligned with the main magnetic field and are in phase with each other. (B) Immediately after the 90° RF pulse hydrogen protons in the same substance (fat, soft tissue, fluid) precess in sync with each other in the transverse plane, and all tissues give a strong and uniform signal. (C) Spinning protons quickly lose their coherence due to interference with each other (T2 relaxation). Fluid has the longest T2 relaxation time; fat the shortest. (D) If waiting a long time until listening for the echo (long TE), protons in fat and soft tissues have lost most of their phase coherence. Fluid maintains the strongest transverse magnetization and appears bright on the resultant image. For SE sequences a 180° pulse is applied at TE/2 to cancel out external field inhomogeneities. (The Ohio State University. Reproduced with permission.)

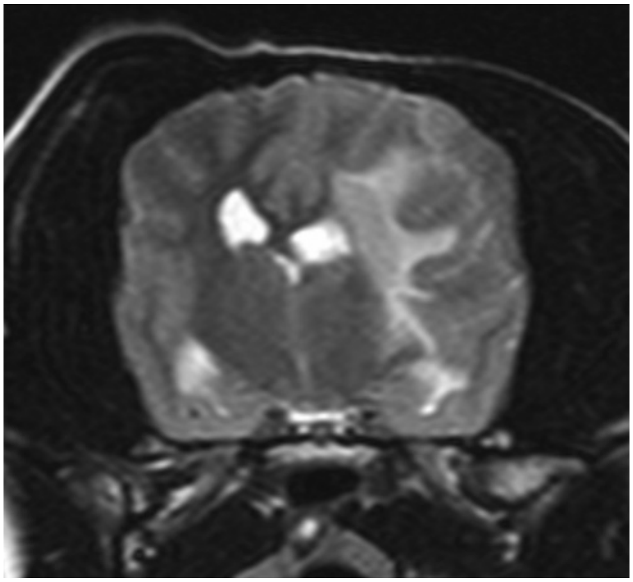

Figure 6.8 Transverse T2-W image of the brain of a dog with meningioma (same dog as Fig. 6.6 and Fig. 6.10). Fluid within the ventricular system is strongly hyperintense. The peripheral plaque-like mass is isointense to hyperintense to normal brain parenchyma. Extensive T2 hyperintensity to the white-matter tracts of the left cerebral hemisphere and associated mass effect are consistent with vasogenic brain edema.

are characterized by excellent anatomic detail (see Fig. 6.41A below) and are very useful in orthopedic imaging. They also provide a good contrast between gray and white matter, and although their value in the neuroimaging of small animals is limited, anecdotal evidence suggests they may be helpful in the evaluation of patients with degenerative brain disease.

Modified spin echo (SE) sequences[23, 50, 83, 94, 95, 131, 179, 217, 269, 293, 309]

These sequences are based on conventional SE principles, but additional pulses are applied to selectively suppress signal from certain tissues (inversion recovery sequences) or to accelerate data acquisition (FSE or TSE techniques and single-shot techniques).

Inversion recovery sequences: These are characterized by an initial 180° pulse (inversion pulse). Dependent on the time elapsed between this 180° pulse and initiation of the regular SE sequence (time of inversion; TI), they result in selective suppression of fluid (fluid attenuated inversion recovery; FLAIR) or fat (short tau inversion recovery; STIR).

FLAIR: A long TI prior to initiation of a SE sequence allows selective suppression of fluid (Fig. 6.9). Although FLAIR images are most commonly used for brain imaging, they may occasionally be helpful in the evaluation of spinal lesions. T2-W FLAIR images are useful in conjunction with regular T2-W images in characterizing T2 hyperintense lesions. Using FLAIR, pure fluid (cerebrospinal fluid and fluid in cystic lesions) is suppressed and becomes hypointense, while solid lesions remain hyperintense (Fig. 6.10). Additionally, this sequence increases conspicuity of small lesions bordering a fluid-filled ventricle or the subarachnoid space. Finally, FLAIR is helpful in differentiating true T2 hyperintense parenchymal lesions from pseudolesions created by inclusion of fluid-filled structures and brain parenchyma within the same slice thickness (volume averaging). Without modification of acquisition parameters, FLAIR is unable to suppress signal from fluids containing high-protein cell components or blood by-products, a potential pitfall when interpreting

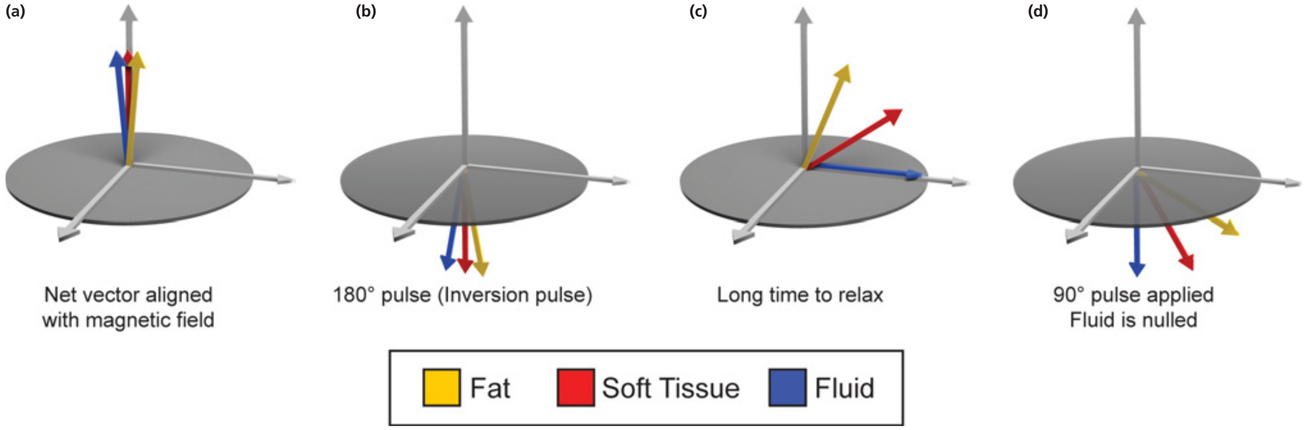

Figure 6.9 Schematic demonstration of a FLAIR sequence. (A) Initially, the net vector of all hydrogen protons (fat, soft tissue, fluid) is aligned with the main magnetic field. (B) Immediately after application of the initial 180° RF pulse (“inversion pulse”), the vectors of different tissues are flipped out of plane together but are quickly separated due to differences in T1 relaxation. Fat has a very short relaxation time, fluid has the longest relaxation time, and soft tissues are intermediate. (C) The 90° RF pulse is applied when fat has almost realigned with the main magnetic field and fluid has reached the transverse plane. (D) Fluid is now furthest away from the transverse plane and gives off no signal, i.e. it is effectively nulled. (The Ohio State University. Reproduced with permission.)

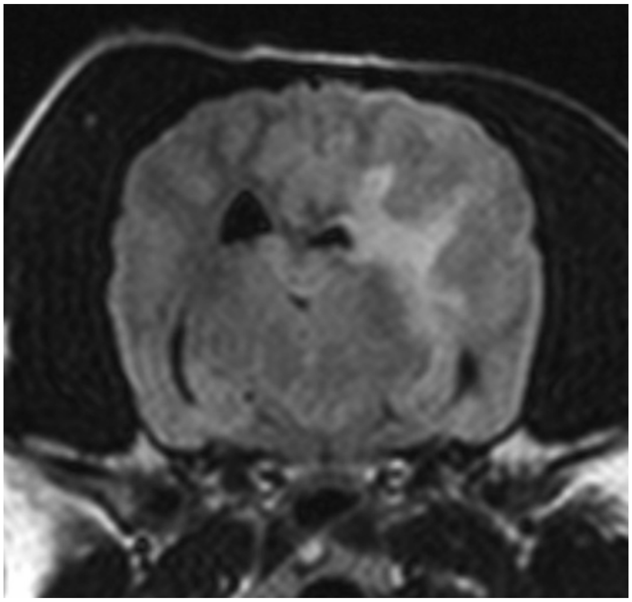

Figure 6.10 Transverse T2-W FLAIR image of the brain of a dog with meningioma (same dog as Fig. 6.6 and Fig. 6.8). Pure fluid within the ventricular system is attenuated, while hyperintensity to the white-matter tracts of the left cerebral hemisphere consistent with vasogenic edema persists. The plaque-like peripheral mass is isointense to adjacent tissues and not clearly seen.

images. Postcontrast T1-W FLAIR images are very sensitive in the detection of contrast-enhancing lesions and may be used as an alternative to conventional postcontrast T1-W SE images.

STIR: A short TI prior to initiation of an SE sequence allows selective suppression of fat (Fig. 6.11). This sequence is very valuable in orthopedic and spinal imaging as it allows differentiation of pathologic T2 hyperintense lesions within the vertebral canal, vertebrae, and surrounding paraspinal tissues from fat (Fig. 6.12).

Fast (FSE) or turbo (TSE) spin echo techniques: In conventional SE imaging one 180° pulse is applied during each TR, and one echo (signal) is generated. In FSE and TSE, multiple 180° pulses are applied during each TR and multiple echoes are received, resulting in a decrease in scan time without compromising image quality. FSE/TSE techniques have essentially replaced conventional SE sequences in T2-W imaging. One potential disadvantage is strong hyperintensity of fat on T2-W FSE/TSE images as hyperintense epidural fat in the vertebral canal may obscure T2-hyperintense lesions within adjacent spinal cord, and hyperintense fat in bone marrow may obscure or mimic skull or vertebral lesions. This disadvantage can easily be compensated for by adding a fat-saturation technique or comparing T2-W images to other sequences (see Fig. 6.12).

Single-shot techniques: These ultrafast techniques employ a single RF pulse, further decreasing scan time. The resultant images are characterized by very strong T2 contrast and are most beneficial in imaging of fluid-filled spaces. "Quick-brain" MR imaging was initially introduced as an alternative technique to CT scanning for assessing children with hydrocephalus. Other indications in humans include macrocephaly, Chiari malformation, intracranial cysts, screening prior to lumbar puncture, screening for congenital anomalies, and trauma. These sequences have gained popularity in veterinary medicine for spinal imaging due to their myelographic effect, which can be used to classify spinal lesions, identify sites of significant intervertebral disc herniation and diagnose spinal subarachnoid cysts (Fig. 6.13).

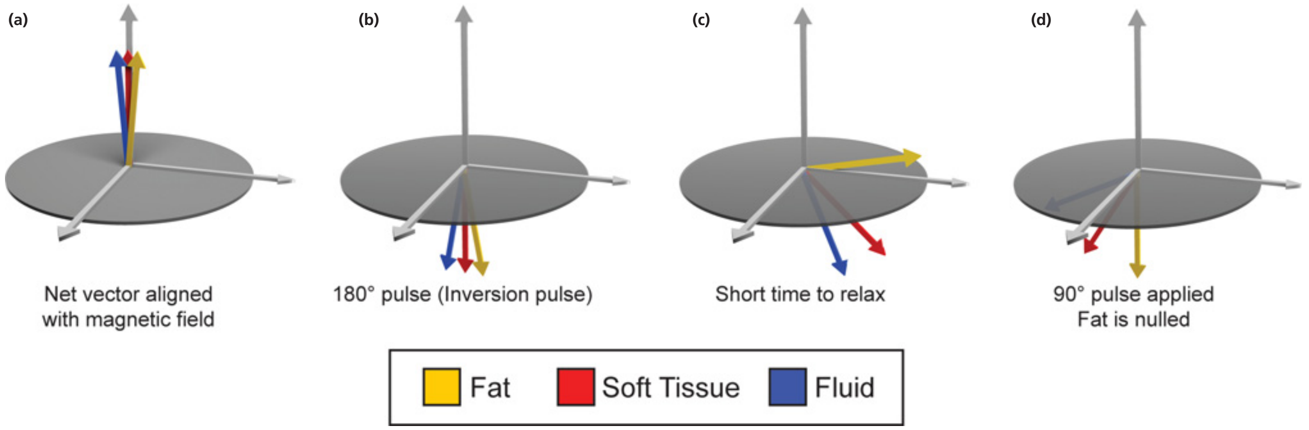

Figure 6.11 Schematic demonstration of a STIR sequence. (A) Initially, the net vector of all hydrogen protons (fat, soft tissue, fluid) is aligned with the main magnetic field. (B) Immediately after application of the initial 180° RF pulse ("inversion pulse"), the vectors of different tissues are flipped out of plane together but are quickly separated due to differences in T1 relaxation. Fat has a very short relaxation time, fluid has the longest relaxation time, and soft tissues are intermediate. (C) The 90° RF pulse is applied when fat has reached the transverse plane while fluid and soft tissue lag behind. (D) Fat is now furthest away from the transverse plane and gives off no signal, i.e. it is effectively nulled. (The Ohio State University. Reproduced with permission.)

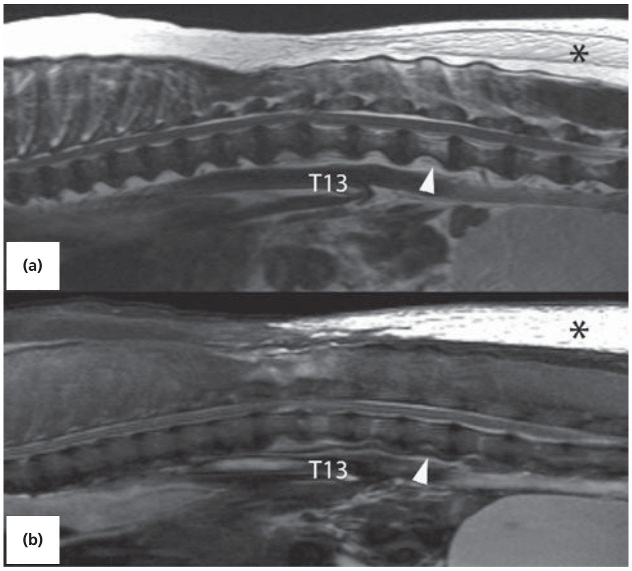

Figure 6.12 Sagittal T2-W FSE (A) and STIR (B) images of the thoracolumbar spine in a dog following trauma. Traumatic intervertebral disc herniation and mild subluxation at T12/13 along with multifocal disc degenerative changes are evident on both sequences. (A) Multifocal T2 hyperintensities within the vertebral bodies (most obvious in the caudal half of L2; arrowhead) are seen. (B) Most vertebral hyperintensities are attenuated (arrowhead), indicating that they are consistent with fatty degeneration of bone marrow. The cranial half of T13 remains hyperintense, consistent with bone contusion. Additionally, extensive subcutaneous edema dorsal to the lumbar spine (*) and patchy hyperintensities in the epaxial muscles dorsal to T12/13 are accentuated due to suppression of adjacent fat.

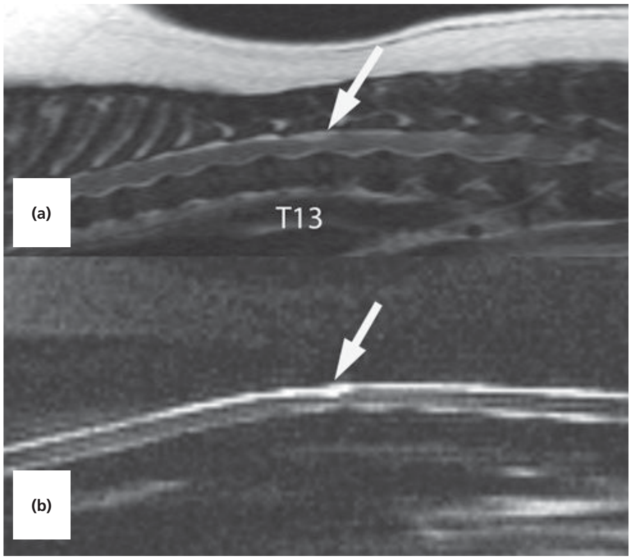

Figure 6.13 Sagittal T2-W FSE (A) and half-Fourier-acquisition single-shot turbo spin echo HASTE (B) images of a dorsal subarachnoid cyst/diverticulum at T13/L1. The lesion is accentuated on the heavily T2-W (myelographic) single-shot sequence.

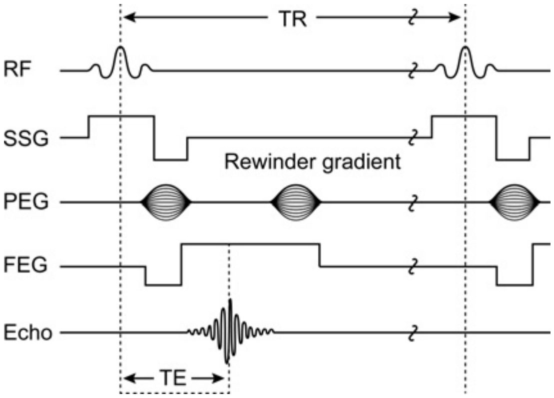

Figure 6.14 Schematic outline of a gradient-echo sequence. In contrast to SE techniques only a single RF pulse is applied which is used in conjunction with gradient reversals. (The Ohio State University. Reproduced with permission.)
TR = time of repetition; TE = time of echo; SSG/PEG/FEG = slice/phase/frequency encoding gradient (applied for spatial encoding of the MR signal).

Gradient recalled echo (GRE)[36, 81, 94, 104, 110, 131, 179, 208, 224, 259, 265, 279, 286, 289, 294, 319, 350, 352, 366, 383–385, 387]

While the generation of SE images relies on the application of pairs of RF pulses, GRE sequences utilize only one initial RF pulse in conjunction with gradient field reversals (Fig. 6.14). GRE sequences use smaller flip angles and shorter TRs than SE sequences (Table 6.2), resulting in shorter scan times. The lack of a 180° pulse has important implications for image weighting and quality: (1) conventional GRE sequences can be used to acquire T1-W, PD-W and T2*-W images—acquisition of truly T2-W images is not possible—and (2) GRE sequences are prone to susceptibility artifacts as there is no compensation for external field inhomogeneities. A plethora of GRE applications have been developed in recent years, including conventional, steady-state, coherent, incoherent (spoiled), steady-state-free precession, balanced, fast, single-shot and echoplanar imaging (EPI) sequences. A comparison between sequences developed by different vendors is difficult as a uniform nomenclature system does not exist. For example, vendor-specific names/acronyms used for a similar coherent gradient echo sequence are “FISP” (Siemens), “GRASS” (GE), “FFE” (Philips), “Rephased SARGE” (Hitachi) and “SSFP” (Toshiba). Rapid development in the field of GRE sequences led to numerous new and advanced applications of MR imaging,

Table 6.2 Influence of acquisition parameters on image contrast in a gradient echo sequence.[37, 385]

TR	TE	Flip angle	Weighting
Short (< 50ms)	Short (< 5ms)	Large (70–90°)	T1-W
Long (> 100ms)	Long (15–25ms)	Small (5–20°)	T2*-W
Long (> 100ms)	Short (< 5ms)	Small (5–30°)	PD-W

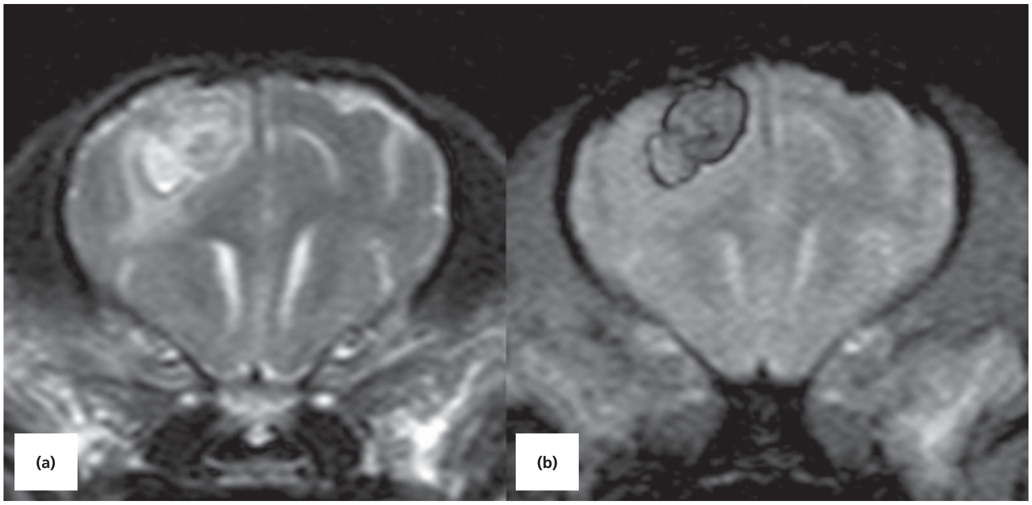

Figure 6.15 Transverse T2-W FSE (A) and T2*-W GRE (B) images of the brain in a dog with a hemorrhagic infarct. (A) An irregular heterogeneous T2 hyperintense mass is associated with the right frontal lobe. Diffuse T2 hyperintensity extending along the adjacent white-matter tracts is consistent with vasogenic edema. (B) The mass is strongly hypointense on T2*-W image, consistent with susceptibility artifact and indicative of hemorrhage.

such as motion-free (breath hold) abdominal imaging, 3D volumetric imaging, and 3D MR angiography (MRA). Some GRE sequences more or less routinely used for the imaging of the CNS in small animals at this point include T2*-W GRE, T1-W 3D GRE, 2D/3D volumetric acquisition, and magnetic resonance angiography (MRA).

T2-W GRE sequence:* Gas interfaces, soft-tissue mineralization, fibrous tissue, and certain blood degradation products (e.g. methemoglobin) cause magnetic field inhomogeneities which appear as a signal void (susceptibility artifact, see below) on T2*-W images. T2*-W is most commonly utilized to identify intracranial or spinal hemorrhage and to differentiate it from other lesions (Fig. 6.15; see also Figs 6.38, 6.41B and 6.50). Additional indications may include identification of intracranial mineralization (e.g. in meningiomas) or abnormal gas pockets (e.g. in brain abscesses).

T1-W 3D GRE: These sequences may be beneficial to evaluate small structures (e.g. pituitary gland or cranial nerves; Fig. 6.16) after intravenous administration of contrast medium, as they allow acquisition of thin slices (< 1 mm) without interslice gap and permit multiplanar reconstruction of the 3D dataset in additional planes.

2D/3D volumetric acquisition (steady-state-free precession): These sequences are characterized by high contrast between fluid-filled structures and surrounding tissues and may be beneficial in evaluating small structures, such as the inner ear.

Magnetic resonance angiography (MRA): MRA techniques maximize vascular contrast by enhancing the signal from spins in flowing blood and/or suppressing the signal from surrounding stationary tissues. Although this can be accomplished without contrast medium administration (digital subtraction MRA, phase contrast MRA, time-of-flight MRA) contrast-enhanced MRA (CE-MRA) is considered a superior technique due to improved image quality. In humans, evaluation of the intracranial circulation provides valuable information in the diagnosis and prognosis of various abnormalities such as aneurysms, arterial and venous steno-occlusive diseases, inflammatory arterial diseases, and congenital vascular abnormalities. Although intracranial vascular abnormalities are infrequently reported in the veterinary literature, MRA might be considered a quick and low-risk procedure to evaluate intracranial vessels in select cases.

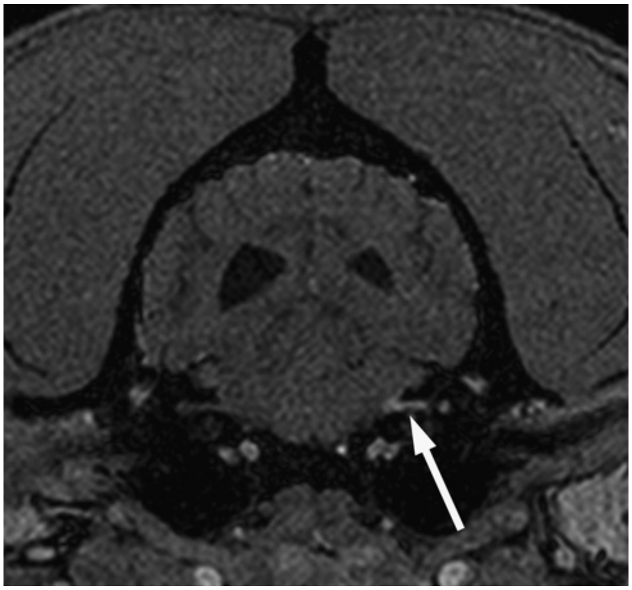

Figure 6.16 Postcontrast transverse T1-W GRE (volume interpolated breath hold examination; VIBE) image of the brain in a dog with left-sided facial paralysis (slice thickness 0.9 mm). Contrast enhancement of the left facial nerve is noted (arrow), consistent with facial neuritis.

Functional imaging[18, 25, 37, 45, 48, 62, 126, 142, 143, 154, 194, 223, 238, 253, 268, 284, 297, 334, 352, 370, 381, 385, 399]

Diffusion-weighted imaging (DWI): Diffusion describes the motion of molecules in tissues. This process is not truly random due to the presence of physiologic boundaries (cell membranes etc.) and is referred to as "apparent diffusion." DWI utilizes opposing gradients to produce signal differences based on mobility and direction of water diffusion. Normal tissues have more water mobility, resulting in greater signal loss, while tissues with less water mobility experience restricted diffusion. In human as well as veterinary medicine DWI is most commonly used in the diagnosis of ischemic stroke. In acute cerebral ischemia, restricted diffusion occurs secondary to failure of the cell membrane ion pump and subsequent cytotoxic edema. An acute stroke is characterized by marked hyperintensity on a DWI and hypointensity on a synthesized apparent diffusion coefficient (ADC) map derived from two or more DWIs (Fig. 6.17). In humans DWI is also used to differentiate benign from malignant lesions and distinguish neoplasia from edema or infarction. While some initial studies in animals have yielded promising results, the value of DWI in the diagnosis of neurologic disorders other than acute stroke remains to be determined. Diffusion tensor imaging (DTI) is a specialized DWI technique which utilizes strong multidirectional gradients to map white matter tracts (Fig. 6.18). Initial studies proved feasibility of this technique in dogs, which may ultimately aid in the diagnosis of white matter disease and facilitate surgical planning.

Perfusion-weighting imaging (PWI): PWI allows an estimate of blood volume passing through the capillary bed per unit of time. This is most commonly accomplished by tracing the passage of a bolus of contrast agent through the cerebral vasculature. Perfusion imaging is often used in combination with DWI in patients with acute ischemic stroke, where the difference between diffusion and perfusion abnormalities provides a measure of the ischemic penumbra (area of reversible ischemia that can be salvaged if blood flow is re-established promptly). Other potential applications include assessment of tumor malignancy based on metabolic activity and evaluation of tissue viability of vascular organs.

Functional MR imaging (fMRI): This is a rapidly evolving area in human medicine which allows evaluation of brain activity during certain activities or following stimulation. Any activity/stimulus (e.g. viewing a picture or smelling food) results in activation of a specific area in the brain, which necessitates an increase in blood flow. The resultant focal increase in oxyhemoglobin and decrease in deoxyhemoglobin can be detected by means of MRI due to their inherent difference in magnetic susceptibility (blood oxygen level dependent, or BOLD, imaging). The result is a map of functional brain areas during a specific activity or after a specific stimulus (Fig. 6.19). Unfortunately, application of this technique in veterinary patients is thus far limited due to the need for immobilization or general anesthesia. However, initial attempts in conditioned awake dogs yielded promising results, and fMRI in animals is likely to gain importance with development of faster sequences and experience.

Magnetic resonance spectroscopy (MRS): MRS is a method to measure tissue chemistry by recording signals from specific metabolites. *In vivo* MRS is most commonly performed using hydrogen protons (^{1}H [proton] spectroscopy). Although other metabolites can be recorded using this technique, proton spectroscopy has the advantages of a high signal-to-noise ratio and a relatively short examination time as it can be added to conventional MR imaging protocols. Applications in neuroimaging include monitoring of biochemical changes occurring in tumors, metabolic

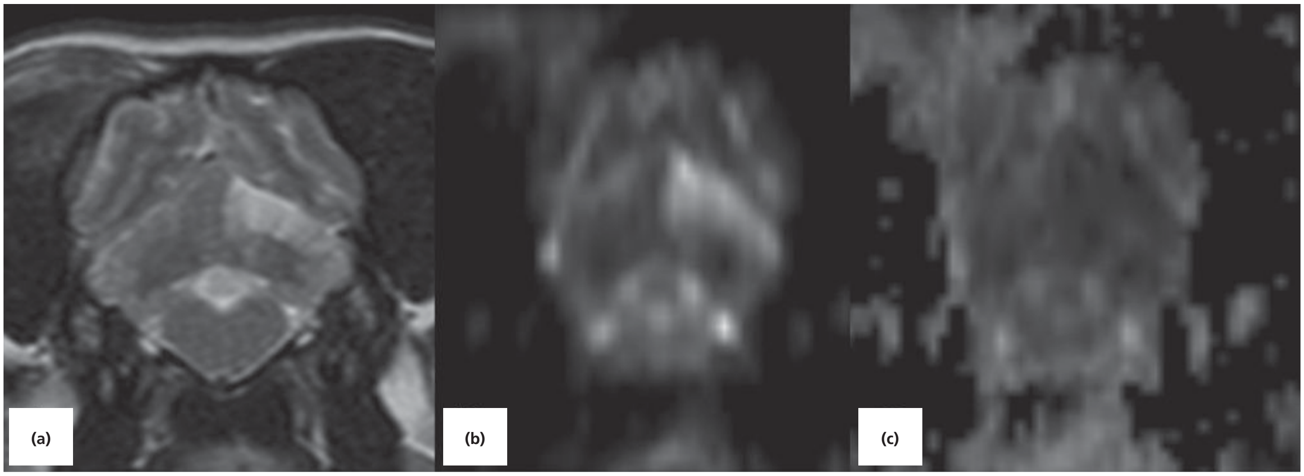

Figure 6.17 Ischemic cerebellar infarct in a dog. (A) The transverse T2-W image demonstrates a sharply marginated wedge-shaped hyperintense lesion associated with the left cerebellar hemisphere. (B, C) The lesion remains hyperintense on the diffusion-weighted image (B) and is hypointense on the ADC map (C), consistent with restricted diffusion and ischemic stroke.

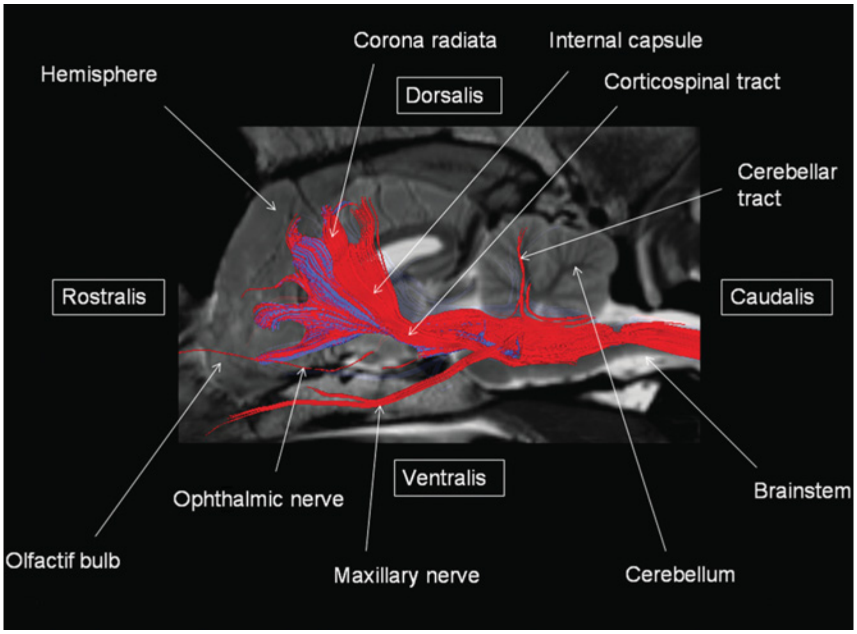

Figure 6.18 Diffusion tensor imaging of the corticospinal tract in a dog (sagittal view). (Jacqmot *et al.*, 2013. Reproduced with permission from Wiley.)[143]

disorders, inflammatory, and neurodegenerative diseases. With increasing availability of higher-strength magnets, MRS is gaining popularity in clinical veterinary medicine.

Technical modifications[34, 56, 64, 65, 70, 99, 370, 373]

Spatial presaturation: Spatial presaturation pulses are used to suppress undesired signals from anatomic areas within the imaging field of view. These pulses are not commonly applied in brain imaging but may be helpful in spinal imaging where they can be used to suppress signal from neighboring vessels or peristaltic bowel, thus minimizing motion artifacts.

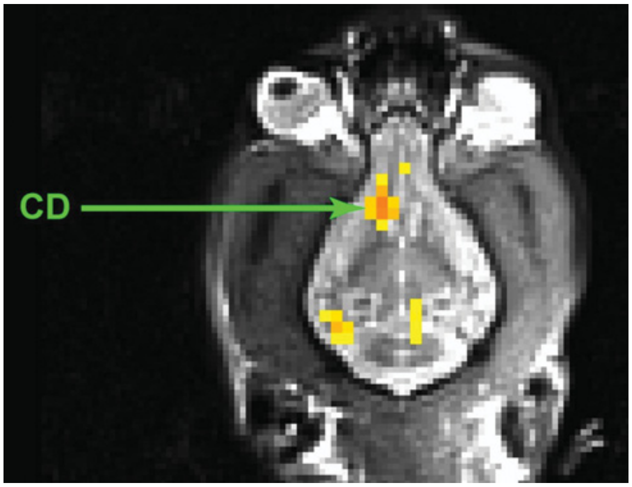

Figure 6.19 Functional MRI (fMRI) demonstrating increased activity in the area of the right caudate nucleus (CD) in response to a hand signal (image summed from data acquisition in two awake dogs). (From Berns *et al.*, 2012. Reprinted with permission.)[25]

Fat saturation: Unlike STIR, which is an entirely separate MR sequence, selective fat saturation pulses can be applied to any sequence to suppress signal from fat without affecting signal intensity of other tissues. Fat saturation has proven especially beneficial when applied to postcontrast T1-W images of the brain and spine as it facilitates differentiation of contrast-enhancing lesions from adjacent fat and aids in the identification of meningeal enhancement (Fig. 6.20).

Magnetization transfer imaging: Magnetization transfer pulses can be applied in SE or GRE sequences to produce additional signal suppression of tissue water. The technique may be used qualitatively to increase the visibility of lesions seen during MRA and following contrast administration or quantitatively to aid in the diagnosis of white matter disease.

Artifacts[37, 57, 100, 101, 132, 307, 406]

A detailed discussion of MR artifacts is beyond the scope of this chapter. However, some important artifacts frequently encountered when imaging the CNS in small animals will briefly be discussed.

Motion: Motion artifacts are probably less common in veterinary than in human medicine as most patients are scanned under general anesthesia. However, even if the animal does not move during the scan, physiologically moving structures (e.g. the heart) will still result in artifacts. Motion artifacts always occur in the direction in which the phase encoding gradient was applied, regardless of the direction of motion. They manifest as “ghosts” of the moving structure at various locations along the phase axis, blurring and/or parallel bands. Remedies include better restraint of the patient, breath-hold techniques (limited in most systems due to duration of scan),

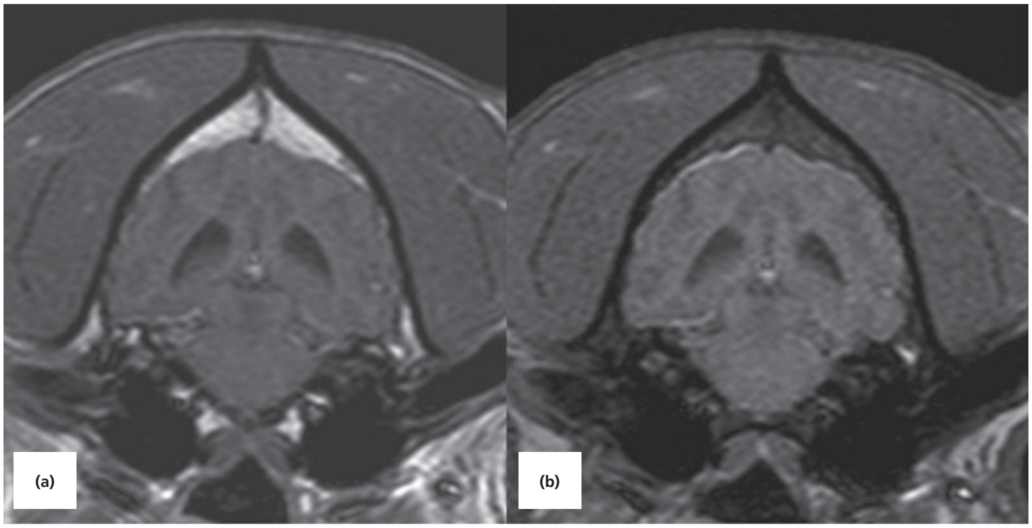

Figure 6.20 Transverse postcontrast T1-W SE images of the canine brain without (A) and with (B) fat saturation. (A) No abnormalities are detected. (B) Suppression of adjacent bone marrow fat allows identification of meningeal enhancement, most obvious along the right occipital lobe.

cardiac/respiratory gating, presaturation pulses, flow compensation techniques, motion correction techniques, and flipping phase and frequency encoding gradients (if motion artifact interferes with evaluation of area of interest).

Cerebrospinal fluid (CSF) flow artifacts: A CSF flow void artifact appears as artificial loss of signal from CSF, which is most commonly encountered on T2-W images. It is attributed to a rapid or turbulent flow of CSF, where flowing protons move so quickly that they are not exposed to both the initial 90° and the 180° refocusing RF pulse. It may occasionally be seen in normal dogs, but it seems more common in small-breed dogs with increased ventricular size and syringomyelia. As this artifact is more likely to occur with a smaller slice thickness and a longer TE, modification of imaging parameters will decrease severity. However, a decrease in TE will also result in an undesirable change in weighting and may not be feasible. A similar artifact known as "entry slice phenomenon" appears as an artificially high signal at a site of CSF flow when nonsaturated spins enter the imaging plane and generate a strong signal after application of the 90° pulse (Fig. 6.21). CSF flow associated artifacts can easily be identified by comparison with other sequences and image planes as they will not be consistent findings.

Chemical shift artifact of the first kind: This is a misregistration artifact resulting from a minimal difference in precession frequency between fat and water protons. The MR unit is tuned to "listen" for hydrogen protons and expects them to precess at a certain frequency at a certain location. Hydrogen protons in fat precess ever so slightly slower than hydrogen protons in water. This minimal difference is enough to misplace the signal from fat on the resultant image. This artifact occurs in the direction of the frequency encoding (or "readout") gradient and manifests at a strongly hypointense and an opposite strongly hyperintense crescent at any fluid-fat interface. This artifact is important to recognize as it occurs at the interface of subarachnoid space and epidural fat when imaging the spine and may mimic a lateralized lesion if the frequency encoding gradient is applied in a laterolateral (rather than dorsoventral or ventrodorsal) direction (Fig. 6.22). The effect of this artifact on diagnostic image quality can be minimized by swapping the phase and frequency encoding gradient, increasing the receiver bandwidth, and using fat-suppression techniques (see above).

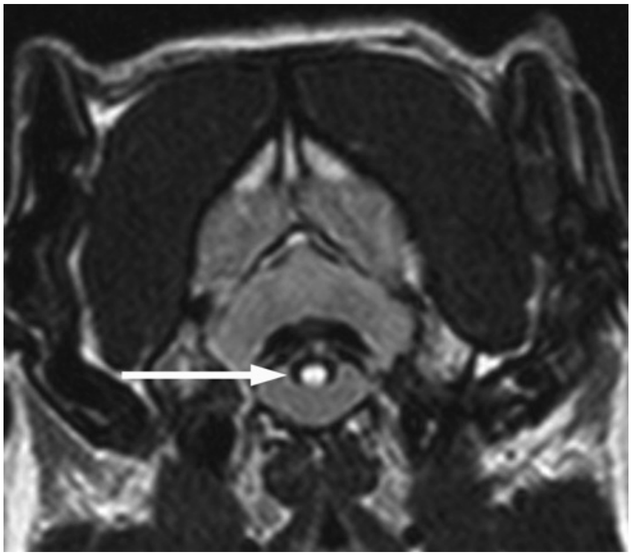

Figure 6.21 CSF flow artifact. A strongly hyperintense area is observed within the mildly dilated fourth ventricle on transverse T2-W FLAIR image (arrow). This was not identified on other sequences, ruling out a true intraventricular lesion.

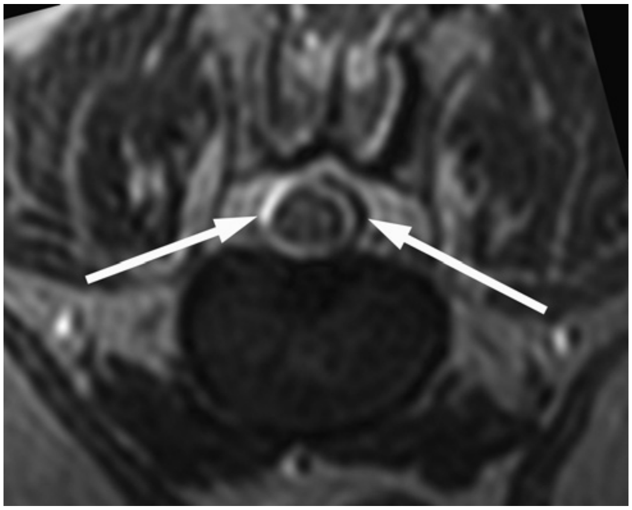

Figure 6.22 Chemical shift artifact observed at the border of subarachnoid space and epidural fat in the lumbar spine of a dog. The frequency encoding gradient has been applied in a laterolateral direction. The chemical shift artifact results in a black crescent to the left and a white crescent to the right of the spinal cord (arrows) due to misregistration of the signal from fat bordering fluid. This may be confused with a lateralized lesion and is best avoided by applying the frequency encoding gradient in a dorsoventral or ventrodorsal direction.

Susceptibility: Magnetic susceptibility is a term used to describe the magnetic properties of a material. Diamagnetic materials (e.g. soft tissues) have very low susceptibility and weaken a magnetic field. Paramagnetic materials (e.g. gadolinium and certain hemoglobin degradation products) have a slightly stronger susceptibility and focally enhance a magnetic field. Ferromagnetic materials (e.g. iron) become strongly magnetized and experience a large force when placed in an external magnetic field. Presence of materials with differing susceptibility in the field of view results in susceptibility artifacts. These range in severity from focal signal voids in case of hemorrhage (see Figs 6.15, 6.38, 6.41B, 6.50) to geometric image distortion, progressive or abrupt signal void in the area of the object, and areas of sharply defined high signal intensity adjacent to the object in case of ferromagnetic materials. Susceptibility artifacts may be beneficial (e.g. improved detection of small hemorrhagic infarcts) or detrimental (e.g. identification microchip immediately adjacent to area of interest). Possible remedies include the use of (F)SE rather than GRE sequences, decreasing TE, use of STIR rather than fat saturation pulses, swapping phase and frequency encoding gradients, and increasing receiver bandwidth.

Partial volume averaging: This artifact occurs when materials of different intensity are included in the same slice thickness (or even the same voxel) and their intensities are averaged. This artifact is significant as hyperintensities adjacent to fluid-filled structures (subarachnoid space, ventricles) on T2-W images resulting from averaging of brain and CSF signal may be misinterpreted as parenchymal lesions. Remedies include decreasing slice thickness, verification of lesions on additional planes, and verification of any T2 abnormality on FLAIR.

Contrast media in MRI[62, 64, 116, 119, 150, 186, 271, 275, 276, 310, 405]

MRI contrast agents most commonly used in veterinary medicine are gadolinium-based. Contrast medium is administered at a dose of 0.1 mmol/kg, which may be increased to improve detection of poorly enhancing lesions. Enhancement is seen if a lesion is vascularized and is located outside the blood–brain barrier. Gadolinium-based contrast media predominantly affect T1 relaxation, and enhancing lesions appear hyperintense on T1-W images (see Figs 6.6, 6.16, 6.20). Certain normal intracranial structures outside of the blood–brain barrier—such as pituitary gland, choroid plexus, trigeminal nerve, and blood vessels—show physiologic contrast uptake. Some disagreement exists as to the optimal timing of MR image acquisition following contrast medium administration (immediate vs. delayed). However, at least for the brain, postcontrast images are usually acquired in more than one plane, and immediate and delayed images are therefore acquired inadvertently. Dynamic studies monitoring contrast enhancement (wash-in and wash-out) over time are not commonly used in veterinary medicine at this point but may be useful for the evaluation of the pituitary gland, cerebral perfusion, and brain tumors. MR contrast agents are considered very safe for use in veterinary patients, and reports of adverse effects are limited to one publication describing suspected anaphylactoid reactions in three dogs.

MRI guided tissue sampling[49, 91, 123]

MRI guided tissue sampling is rapidly gaining popularity in human medicine due to continued improvements in the field of MRI-compatible instruments and technologies. While it is not commonplace in veterinary neuroradiology at this point, initial studies have shown promising results.

MRI of the brain

MR imaging techniques[94, 115, 131, 238, 286, 287]

Positioning: An MR examination of the brain in small animals is typically performed in sternal recumbency. Under certain circumstances (e.g. if a subsequent examination of the cervical spine is to be performed), dorsal recumbency may be preferable.

Recommended standard planes and sequences:

- sagittal T2-W images
- transverse T2-W, T1-W, T2*-W and FLAIR

- sagittal, dorsal, and transverse T1-W images after intravenous gadolinium injection (+/– fat saturation)
- additional sequences as described above may be necessary depending on lesion characteristics.

Approach to the MR examination of the brain[15, 45, 50, 57, 121, 131, 140, 178, 182, 195, 280, 287, 288, 301, 344, 367, 394]

Many disorders of the brain can result in similar MR findings, and some intracranial abnormalities can be detected as incidental findings unrelated to a patient's clinical presentation. Therefore, familiarity with signalment (species, breed, sex, and age), normal anatomy and variants, and pertinent history (clinical signs, time of onset of clinical signs, course of disease, concurrent or previous diseases) are crucial when evaluating brain MRI scans. Intracranial lesions may be extra-axial (i.e. originating outside actual brain parenchyma) or intra-axial (originating from brain parenchyma). Differential diagnoses for extra-axial lesions include certain inflammatory (e.g. meningitis), neoplastic (e.g. meningioma, nasal tumor), and traumatic lesions (e.g. epidural/subdural hematoma). Differential diagnoses for solitary intra-axial lesions include neoplasia, hematoma, cyst, abscess/granuloma, and infarct. Although inflammatory brain diseases usually manifest as multifocal lesions, solitary masses may be encountered on occasion. Masses in specific locations may allow a presumptive diagnosis of certain tumor types (e.g. pituitary tumor, nerve sheath tumor, medulloblastoma). Differential diagnoses for multifocal brain lesions include metabolic/toxic brain disease, inflammatory brain disease, infarcts, and some intracranial neoplasms (lymphoma, disseminated histiocytic sarcoma, metastases, occasionally meningiomas and other primary brain tumors).

Associated findings in intracranial disease[12, 14, 15, 46, 68, 71, 72, 75, 82, 86, 129, 162, 163, 165, 180, 219, 229, 236, 304, 323, 333, 348, 351, 353, 371, 376, 380, 400]

A variety of pathologic changes can be associated with various brain diseases, including hydrocephalus, vasogenic edema, mass effect, brain herniation, and hemorrhage. Hemorrhage will be covered under "Acquired brain disorders" later in the chapter.

Hydrocephalus: Hydrocephalus is defined as the abnormal accumulation of CSF within the cranium. It is a multifactorial disorder which can be classified in various ways:

1. Location
    a. Ventricular system (internal hydrocephalus) vs. subarachnoid space (external hydrocephalus)
2. Etiology
    a. Congenital vs. acquired
    b. Obstructive vs. nonobstructive
        1. Obstructive hydrocephalus = blockage of CSF flow, e.g. secondary to an intracranial space occupying lesion or congenital stenosis of mesencephalic aqueduct or lateral apertures
        2. Compensatory hydrocephalus = decreased volume of brain parenchyma, e.g. following trauma, infarction, or necrotizing encephalitis (hydrocephalus ex-vacuo)
        3. Decreased resorption (secondary to inflammatory processes or due to underdevelopment of arachnoid villi) or increased production (seen in choroid plexus tumors) of CSF (very rare)
3. Morphology
    a. Communicating (communication between ventricular system and subarachnoid space) vs. noncommunicating (no communication between ventricular system and subarachnoid space)
4. Pressure
    a. Hypertensive (increased pressure within dilated CSF-filled space, e.g. secondary to obstruction) vs. normotensive (e.g. hydrocephalus ex-vacuo).

MRI findings in hydrocephalus include dilation of one or more ventricles and/or dilation of the subarachnoid space. In most cases, abnormal CSF accumulation appears hyperintense on T2-W images, hypointense on T1-W images, and attenuates on FLAIR (Fig. 6.23). If CSF contains abnormal cells and/or protein (e.g. in cases of inflammation or intraventricular hemorrhage), altered signal intensity may be observed. Hydrocephalus may be associated with periventricular edema characterized by periventricular T2 hyperintensity, which is most obvious on FLAIR images. In extreme cases CSF may dissect along periventricular white matter, creating diverticula and clefts. Dependent on the etiology of hydrocephalus, potential concurrent findings include other congenital anomalies, an intracranial mass, or signs of trauma. Imaging diagnosis of pathologic hydrocephalus

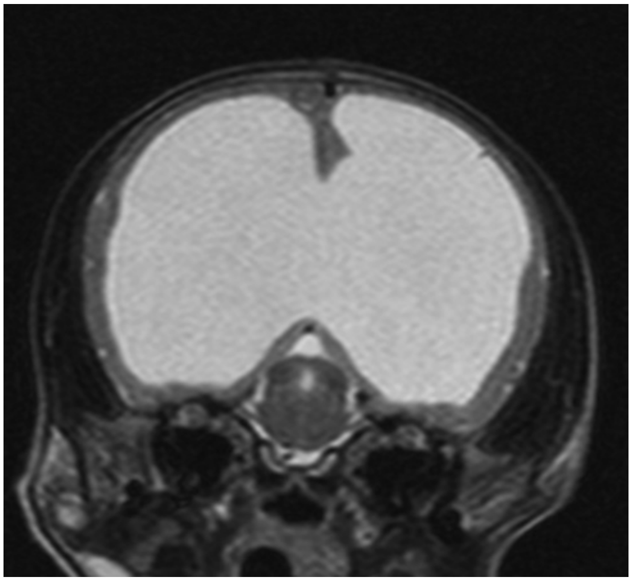

Figure 6.23 Congenital hydrocephalus in a 2-mo-old Golden Retriever. T2-W transverse image shows severe dilation of the lateral and third ventricles.

can be challenging. In one study describing ultrasound evaluation of canine ventricles, normal lateral ventricular height was reported to be 0–14% of dorsoventral height of the cerebral hemisphere, moderate ventricular enlargement was defined as 15–25%, and > 25% was considered indicative of severe ventricular enlargement. However, ventriculomegaly and ventricular asymmetry are common findings in asymptomatic animals, and this finding may or may not be clinically significant. Progressive dilation of ventricles and subarachnoid space are also anticipated findings with increasing age and may not be pathologic. Therefore, imaging diagnosis especially of mild ventricular and/or subarachnoid space dilation should be judged in the light of clinical presentation.

Vasogenic edema: Vasogenic brain edema may be seen concurrently with a number of intracranial diseases. Under normal circumstances, exchange of substances between the blood and the brain is limited by the blood–brain barrier. Damage to brain capillaries results in leakage of fluid into the extracellular space (vasogenic edema). The edema migrates along the white matter fiber tracts and may create a mass effect. Vasogenic edema appears hyperintense on T2-W MR images and hypointense on T1-W images and often has the same signal intensity as the lesion causing the edema (see Figs 6.8, 6.10, 6.15, 6.34, 6.42, 6.46, 6.49). After contrast medium administration, gadolinium leaks out of damaged capillaries and may result in increased signal intensity of the underlying lesion, while edema remains isointense to hypointense (see Fig. 6.6).

Mass effect: Space-occupying lesions within the cranial vault (e.g. tumor, abscess/granuloma, edema, hydrocephalus) are commonly associated with a mass effect, which is indicated by displacement of the falx cerebri or compression of the ventricular system (see Figs 6.6, 6.8, 6.10, 6.15, 6.24, 6.31, 6.32, 6.34, 6.41, 6.42, 6.46, 6.49).

Brain herniation: Increase in intracranial pressure (e.g. due to an intracranial mass) can lead to compression and displacement of brain parenchyma. Foramen magnum herniation (herniation of the caudal portion of the cerebellum into and through the foramen magnum), subfalcine (herniation of part of the cerebral cortex across midline into the opposite half of the cranial vault), and caudal transtentorial herniation (displacement of portions of the cerebral cortex ventral to the tentorium cerebelli) may be encountered (see Fig 6.24, Fig. 6.42, Fig. 6.49).

Seizures and cerebral necrosis: The relationship between seizures and evidence of structural brain damage seen on MRI remains diagnostically challenging. In humans, severe seizure activity causes reversible changes in certain areas of the brain, such as the neocortex, hippocampus, and amygdala. Brain parenchymal changes including edema, neovascularization, reactive astrocytosis, and acute neuronal necrosis have been reported in dogs with seizures and manifest as unilateral or bilateral T2 hyperintense and T1 hypointense foci with variable contrast enhancement associated with piriform and/or temporal lobes (Fig. 6.25). Resolution of these changes on recheck examination indicates that they most likely represent sequelae to rather than underlying cause of seizures. On the other hand, cerebral cortical necrosis (polioencephalomalacia) appearing as increased T1 and T2 signal intensity of the gray matter of temporal and parietal lobes with mild contrast enhancement reported in a dog with seizures and necrosis of the hippocampus and the piriform lobes in cats with seizures appearing as bilaterally symmetric T2 hyperintense lesions with variable contrast enhancement are thought to be the underlying cause rather than result of

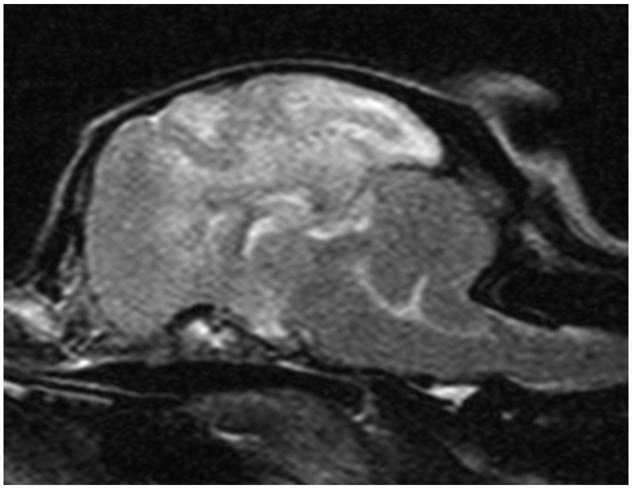

Figure 6.24 T2-W sagittal image of the brain of a dog with severe diffuse brain disease and swelling. There is subtentorial herniation of the occipital lobes and herniation of the cerebellum through the foramen magnum.

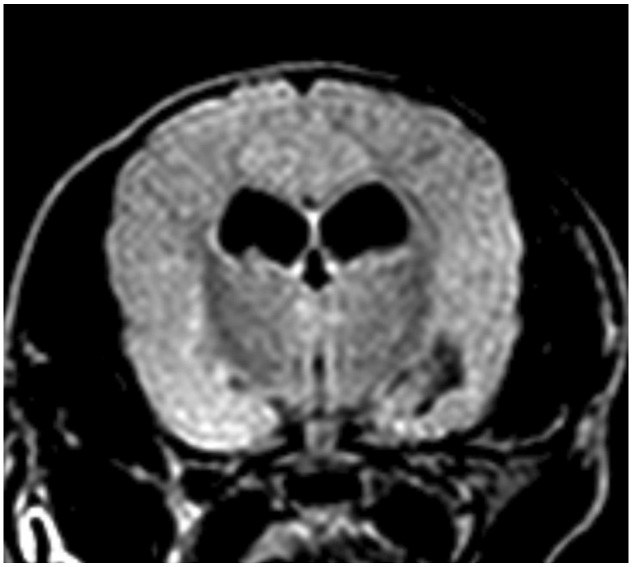

Figure 6.25 Transverse T2-W FLAIR image of the brain in a young dog with seizures and presumptive seizure-induced brain changes. There is hyperintensity to the piriform lobes, more severe on the right.

seizures. In some cases it may not be possible to differentiate whether brain changes found on MRI and/or histopathology represent the underlying cause or are the result of seizures.

Congenital brain disorders

Forebrain (telencephalon and diencephalon)[66, 127, 145, 146, 158, 193, 212, 226, 229, 295, 303, 313, 314, 332, 333, 343]

Congenital hydrocephalus is most commonly seen in toy and brachycephalic breed dogs and appears as dilation of the ventricular system of variable severity as described above (see Fig. 6.23).

Hydranencephaly manifests as a near complete destruction and/or lack of development of the neocortex and has been described in two kittens following intrauterine parvovirus infection. Affected animals show a reduction of size of one or both cerebral cortices to a thin mantle surrounding a large, centrally located cavity.

Porencephaly appears as cystic cavities in the cerebrum due to cell destruction or failure of development. These cavities show signal typical of CSF on MRI and may communicate with ventricles or subarachnoid space (Fig. 6.26).

Lissencephaly is a disorder of cortical neuronal migration characterized by paucity, absence, and/or hypoplasia of cerebral gyri and thickening of the cerebral cortex. The disease has been reported in dogs and cats and appears to be hereditary in Lhasa Apsos. MRI findings include a smooth cerebral surface and a thick neocortex with absence of the corona radiata.

Holoprosencephaly (HPE) is a failure of the forebrain to bifurcate normally and is characterized by an absence or reduction in the size of midline prosencephalic structures (corpus callosum, septum pellucidum, septal nuclei, fornix, and optic nerves), incomplete separation of normally paired forebrain structures (lateral ventricles, cingulate gyri, and caudate nuclei), and hydrocephalus. Dependent on severity, HPE can be subdivided into alobar, semilobar, and lobar HPE.

Agenesis or dysgenesis of the corpus callosum is a feature of HPE but may also occur as an isolated abnormality. Miniature Schnauzers appear to be predisposed both for this condition as well as for lobar HPE. Agenesis or dysgenesis of the corpus callosum is best seen in midsagittal MR images. On transverse images, unusually upturned, pointed corners of the lateral ventricles are evident (Fig. 6.27).

Protrusion of meninges alone or meninges along with brain tissue through a calvarial defect are termed *meningocele* and *meningoencephalocele*, respectively. Superficial meningoencephaloceles may be diagnosed clinically; however, diagnosis of basal or ethmoidal meningoencephaloceles requires advanced imaging. Ethmoidal encephaloceles are characterized by a defect in the cribriform plate with rostral herniation of the olfactory bulb(s) (Fig. 6.28).

Rathke cleft cysts are pituitary cysts containing mucoid or, less commonly, serous fluid and cellular debris and appear as cystic lesions in the middle cranial fossa. They are hypointense on T1-W images, hyperintense on T2-W images, may show mild ring enhancement, and may not suppress on FLAIR due to composition of fluid.

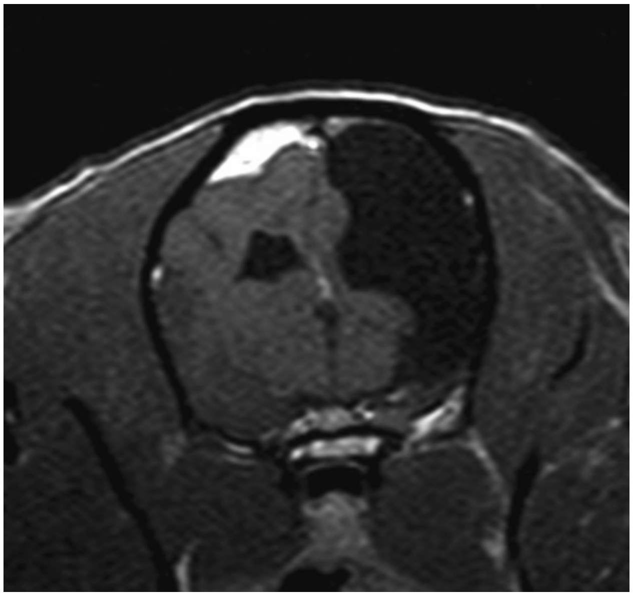

Figure 6.26 Porencephaly in an 8-yr-old pug. There is a large CSF isointense lesion associated with the left cerebral hemisphere which is confluent with the left lateral ventricle and the subarachnoid space. This was an incidental finding when an MR examination of the cervical spine was performed.

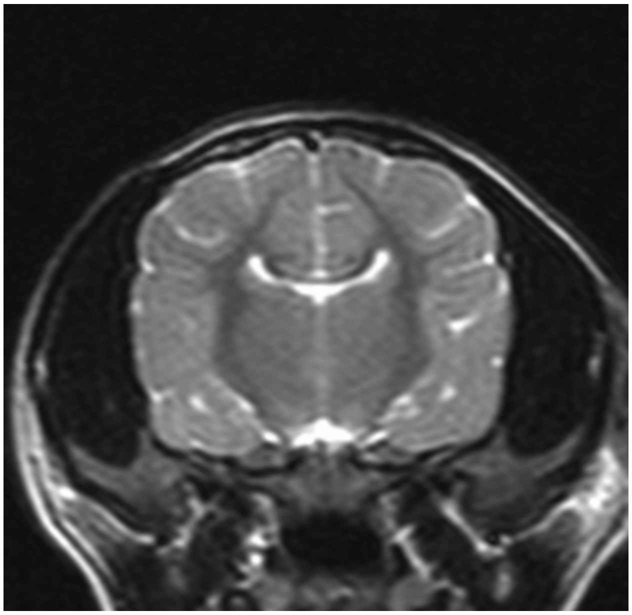

Figure 6.27 Dysgenesis of the corpus callosum in a 4-mo-old Miniature Schnauzer presented with hypodipsic hypernatremia. The corpus callosum is small, and the lateral ventricles have unusually upturned and pointed corners.

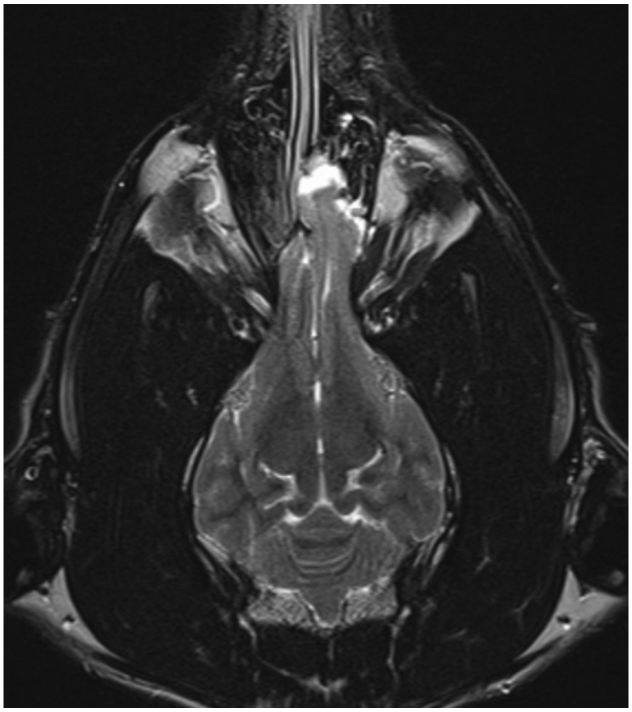

Figure 6.28 Ethmoidal encephalocele in a 10-mo-old dog. The dorsal T2-W image demonstrates absence of the left portion of the cribriform plate and herniation of the left and part of the right olfactory bulb into the caudal nasal cavity.

Midbrain and hindbrain (mesencephalon, metencephalon, myelencephalon)[33, 41, 43, 44, 53, 55, 60, 63, 67, 73, 76, 78, 105, 152, 164, 166, 167, 198, 209, 210, 212, 213, 220, 229, 230, 240, 264, 267, 272, 282, 291, 292, 299, 302, 313, 327, 333, 339, 361, 363, 368, 369, 401]

Chiari malformations are a group of structural defects involving brain stem, cerebellum, upper spinal cord, and surrounding bony structures in humans. Secondary formation of a cystic cavity within the cervical spinal cord parenchyma and/or dilation of the central canal (syringomyelia) are common. A disorder similar to Chiari type I malformation in humans termed “Chiari-like malformation and syringomyelia” has been reported in dogs. Cavalier King Charles Spaniels are most commonly affected, but the disease is seen in a variety of breeds and can be found in symptomatic and asymptomatic animals. The condition is characterized by crowding of the caudal fossa resulting in attenuation of the subarachnoid space surrounding the cerebellum, compression and, in severe cases, herniation of the cerebellum into or through the foramen magnum, which is best demonstrated on T2-W median-sagittal images. Additional findings include a focal bending of the cranial aspect of the spinal cord, hydrocephalus, and syringomyelia (Fig. 6.29).

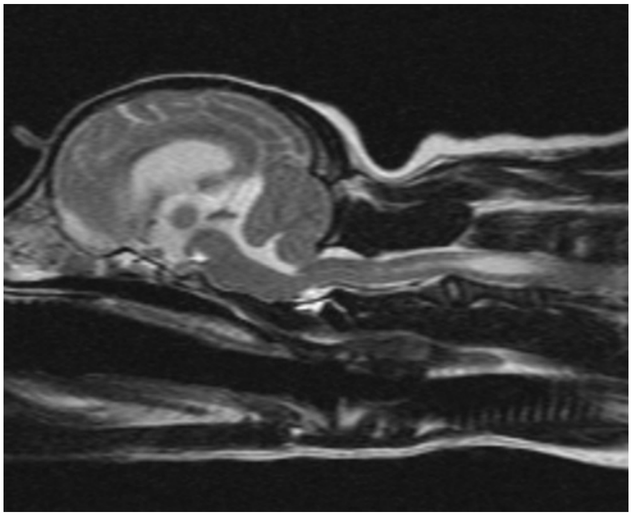

Figure 6.29 Chiari-like malformation in a 3-yr-old Cavalier King Charles Spaniel. Sagittal T2-W image of brain and cranial cervical spine shows crowding of the caudal fossa with compression of the cerebellum, mild generalized ventriculomegaly, and linear to tubular T2 hyperintensity associated with the central and dorsal aspect of the cervical spinal cord, consistent with syringomyelia.

Atlanto-occipital overlapping without prior trauma is a recently recognized anomaly in small- and toy-breed dogs, which is usually associated with other abnormalities such as Chiari-like malformation, syringomyelia, occipital dysplasia, or atlantoaxial instability. The abnormality is best identified on midsagittal images, which reveal craniodorsal displacement of the atlas and overlap of its lamina with the occipital bone (Fig. 6.30).

Cerebellar hypoplasia can occur as a primary developmental defect or secondary to viral infection in utero, most commonly parvovirus. The cerebellum may appear small, with increased CSF signal noted around and extending into the folia. Congenital cerebellar abnormalities may not always be apparent on MRI examination; and no abnormalities were detected in Coton de Tuléar dogs with neonatal cerebellar ataxia. Differentiation of

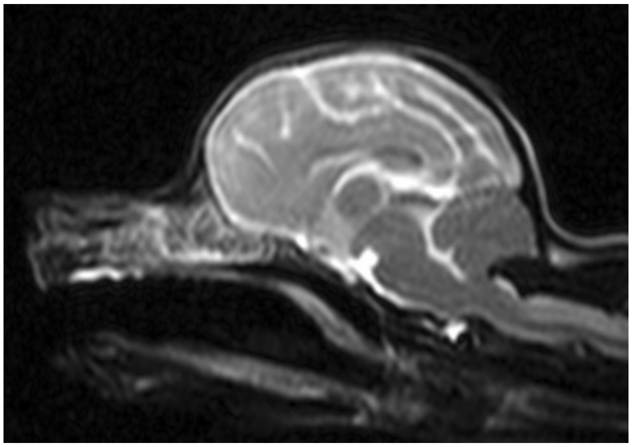

Figure 6.30 Atlanto-occipital overlapping in a 1-yr-old Yorkshire Terrier. There is abnormal angulation and cranial displacement of the atlas into the cranial vault with marked cerebellar compression. Mild syringomyelia of the cranial cervical spinal cord is also noted.

true cerebellar hypoplasia from degenerative disease (cerebellar atrophy, abiotrophy, degeneration; see below) may not be possible solely based on imaging findings.

The *Dandy–Walker malformation complex* in human patients refers to a group of congenital CNS anomalies that primarily involve the cerebellum and adjacent tissues. The primary abnormality is partial or complete absence of the cerebellar vermis and cystic dilation of the fourth ventricle. Comparable cases of cerebellar vermian aplasia or hypoplasia and associated cystic dilation of the fourth ventricle have been reported in dogs. Possible concurrent findings include generalized ventricular enlargement, extension of the cystic fourth ventricle into the supratentorial space with displacement of the occipital lobes, reduced size of the cerebellar hemispheres, widening and irregular gyrification of cerebral sulci, and absence of the corpus callosum.

Polymicrogyria is a disorder of cerebrocortical development resulting in an increased number of small, disorganized gyri in the dorsal and lateral cerebral cortex. It has been reported in Standard Poodles in which a hereditary basis is suspected. On MRI abnormal gyri are best seen on dorsal T2-W images. Concurrent ventriculomegaly is common.

Intracranial epidermoid and dermoid cysts are benign space-occupying lesions that originate from remnants of ectodermal tissue due to defects of neural tube closure. They are often located in the cerebellopontine angle or the fourth ventricle. Signal intensity is variable and dependent on cyst content: cysts with a high lipid content appear hyperintense on T1-W and T2-W images, while cysts with lower lipid content appear hypointense on T1-W images and hyperintense on T2-W images. Dermoid cysts containing adnexa (e.g. hair) may show suspended low-intensity foci in all sequences. Cysts often contain protein and keratin and therefore do not attenuate on FLAIR (Fig. 6.31). They usually do not show contrast enhancement, although ring enhancement may occasionally be noted.

Intracranial intra-arachnoid cysts (more appropriately termed *diverticula*) arise from splitting/duplication of the arachnoidea and occur in close association with an intracranial arachnoid cistern. They are usually considered a primary malformation, although they may develop secondary to inflammation or trauma. Quadrigeminal cistern cysts dorsal to the quadrigeminal plate are most common, but cerebellomedullary cistern cysts have also been reported. Intracranial intra-arachnoid cysts contain fluid isointense to CSF, with attenuation on FLAIR and no evidence of contrast enhancement (Fig. 6.32). Hemorrhage into intracranial intra-arachnoid cysts may change the signal intensity. Quadrigeminal cysts are of variable significance and are frequently incidental. One study found that compression of the occipital lobe by the cyst greater than 14% on median-sagittal image was always associated with clinical signs, while no association was found between the degree of cerebellar compression and clinical signs.

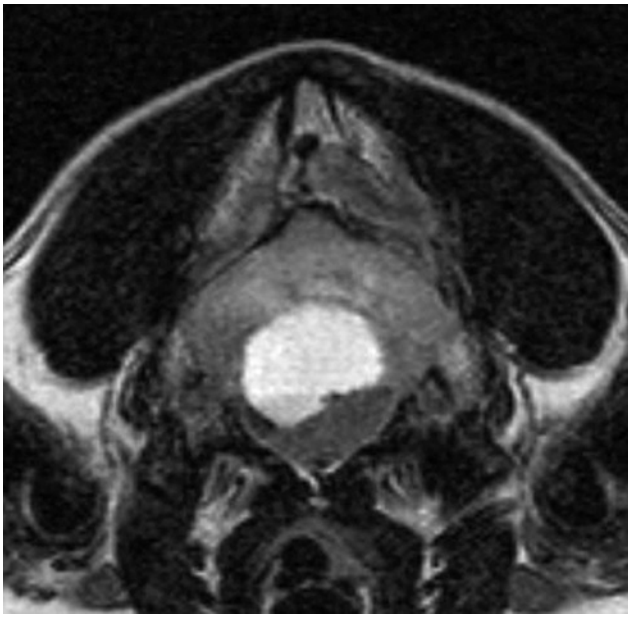

Figure 6.31 Epidermoid cyst in a dog. A large mostly cystic mass with a ventral solid component is associated with the fourth ventricle. Incomplete suppression of the cystic component on this FLAIR image is attributed to the protein content of the fluid.

Other *cystic lesions* documented in the caudal fossa in dogs include *cerebellar ependymal cysts* and *choroid plexus cysts*. On MRI these are well circumscribed, strongly hyperintense on T2-W, and of variable intensity on FLAIR images. After contrast medium administration they may be nonenhancing, ring-enhancing, or, surprisingly reported in a case of a choroid plexus cyst, strongly enhancing.

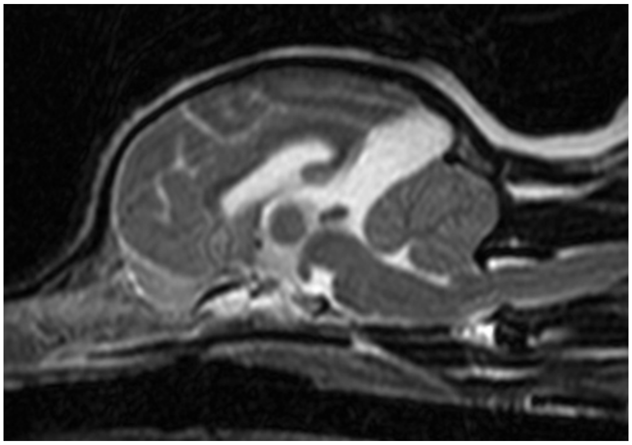

Figure 6.32 Incidental quadrigeminal cistern cyst in a 10-yr-old Chihuahua presented with cervical intervertebral disc disease. The sagittal T2-W image shows a strongly hyperintense smoothly marginated area extending caudodorsally from the mesencephalon which results in compression of the cerebellum and to a lesser degree the occipital lobes.

Acquired brain disorders

Inflammatory brain diseases[27, 52, 64, 190, 237, 250, 344]

Inflammatory brain diseases can affect brain parenchyma (encephalitis), meninges (meningitis), or both (meningoencephalitis). Dependent on underlying etiology, involvement of the spinal cord (myelitis/meningomyelitis) may occur. Encephalitis may cause no detectable abnormalities on MRI or may manifest as multifocal (rather than focal) lesions associated with brain parenchyma which typically appear hyperintense on T2-W images and hypointense on T1-W images. FLAIR has higher sensitivity than conventional SE sequences in detecting subtle brain lesions in dogs with clinical signs of multifocal brain disease, and its use is encouraged in all of these cases. Meningitis may not be detected with MRI or may appear as meningeal enhancement following administration of contrast medium (see Fig. 6.20).

Infectious inflammatory brain diseases[4, 13, 17, 19–21, 24, 29, 38, 59, 69, 71, 93, 97, 106, 114, 120, 133, 134, 148, 171, 174, 175, 191, 192, 199, 221, 228, 239, 249, 250, 255, 258, 308, 320, 328, 331, 335, 344, 384, 392, 404]

Canine distemper virus (CDV) and feline coronavirus (FCoV; previously called "feline infectious peritonitis virus," FIPV) are the most common causes of viral encephalitis in dogs and cats, respectively. In acute CDV infection, T2 hyperintense lesions and loss of contrast between gray and white matter on T2-W images may be found in the cerebellum and/or brain stem, corresponding to areas of demyelination. T2 hyperintense areas are occasionally seen in the temporal lobes, which may be related to infection or postictal edema. MRI findings in chronic distemper meningoencephalitis include essentially bilaterally symmetric T2 hyperintensity of the cortical gray/white matter junction of the parietal and frontal lobes, T2 hyperintensity of the arbor vitae of the cerebellum with partial loss of cerebellar cortical gray/white matter demarcation, subtle focal T2 hyperintensity of the pons, and meningeal contrast enhancement. In cats with feline infectious peritonitis (FIP) affecting the central nervous system MRI may show T2 hyperintensity and contrast enhancement of the ventricular lining, choroid plexus, and meninges compatible with ependymitis, choroiditis, and meningitis (Fig. 6.33). Concurrent findings may include hydrocephalus, syringomyelia, and herniation of the cerebellum secondary to increased intracranial pressure. A study investigating MRI findings in dogs experimentally infected with rabies found parenchymal abnormalities affecting the hippocampus, hypothalamus, basal ganglia, brain stem, and white matter which were more pronounced in the paralytic than the furious stage of the disease.

Mechanisms of *bacterial infection* of the CNS in cats and dogs include hematogenous spread, contiguous infection from adjacent structures (middle/inner ear, nasal cavity, sinuses, orbit, skull, vertebrae), direct inoculation (trauma, bite wound, surgery), and migration of foreign bodies or aberrant parasites.

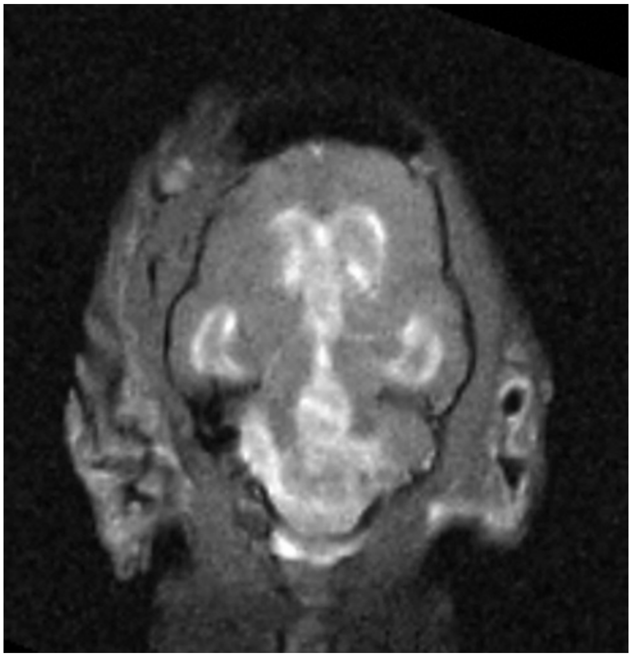

Figure 6.33 Dorsal postcontrast T1-W image with fat saturation of a 7-mo-old Siamese cat with presumptive diagnosis of FIP. There is mild hydrocephalus and contrast enhancement along the ventricular lining, the choroid plexus and to a lesser degree the meninges, consistent with ependymitis, choroiditis, and meningitis.

In addition to meningitis, diffuse cerebritis, and meningoencephalomyelitis, CNS infection may result in focal parenchymal abscesses or empyema in the subdural or epidural space. MRI features of intracranial infection secondary to plant foreign body migration, hematogenous spread from a mediastinal abscess, bacterial endocarditis, local extension from orbital disease and from osteomyelitis of the sphenoid bone, and as complication of otitis media or interna have been described in small animals. Intracranial abscesses are typically hypointense on T1-W and hyperintense on T2-W images, with strong peripheral contrast enhancement and associated brain edema (Fig. 6.34). Concurrent meningitis appearing as meningeal enhancement and/or thickening is common. Dependent on lesion location and extent, additional findings might include hydrocephalus and/or brain herniation. *Neurotuberculosis* (tuberculous meningitis, cerebral tuberculoma) results from hematogenous spread of organisms of the *Mycoplasma tuberculosis* complex and is infrequently reported in animals. MRI findings in one affected dog included a large heterogeneous T2 isointense to hypointense extra-axial mass with patchy peripheral contrast enhancement and hyperostosis and erosion of adjacent skull bones.

Fungal infections (Cryptococcosis, *Phaeohyphomycosis*, *Aspergillosis*, *Blastomycosis*, *Histoplasmosis)* have been reported to affect the CNS in dogs and cats. MRI findings are variable and may include intra-axial or extra-axial masses of variable contrast enhancement, gelatinous pseudocysts, meningeal enhancement, enhancement of the ventricular

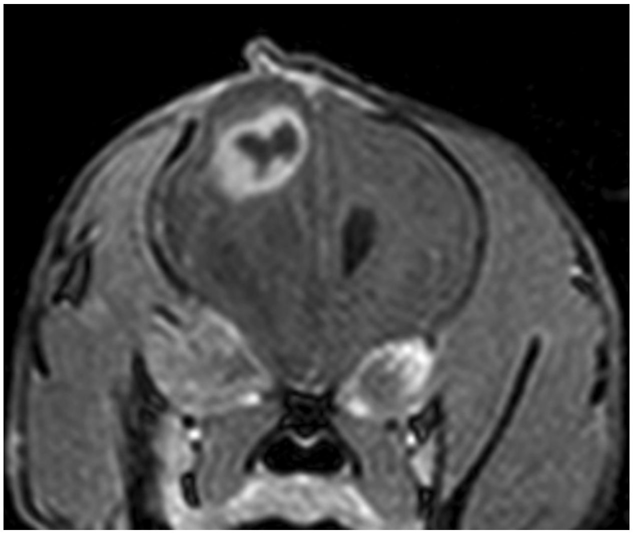

Figure 6.34 Brain abscess in a 2-yr-old dog several weeks after a bite wound to the head. The transverse postcontrast T1-W GRE image with fat suppression demonstrates a rounded strongly ring-enhancing mass with a nonenhancing center in the right frontal lobe. Additional finding include soft-tissue irregularities and a defect in the overlying skull, and hypointensity and mass effect to the entire right cerebral hemisphere consistent with edema.

lining, and intra-cranial extension of nasal or retro-orbital masses (Fig. 6.35). Associated findings may include edema, hydrocephalus, syringohydromyelia, and brain herniation.

Protothecosis is a rare infection with the achlorophyllic algae *Prototheca*, and only a few reports of CNS involvement are found in the veterinary literature. MRI findings in one dog included multifocal T2 hyperintense intra-axial lesions, ventriculomegaly, cerebellar herniation, syringomyelia, and meningeal enhancement.

Parasitic meningoencephalitis in dogs and cats is caused by aberrant migration of parasites such as *Dirofilaria*, *Baylisascaris*, *Cuterebra*, *Taenia*, *Ancylostoma*, *Toxascaris*, and *Angiostronglylus*. MRI features include focal or multifocal parenchymal lesions of variable signal intensity and peripheral parenchymal and/or meningeal contrast enhancement. Intraparenchymal hemorrhage is a common feature in parasite migration, and T2*-W images are especially useful in establishing a (presumptive) diagnosis.

Protozoal meningoencephalitis may be caused by a variety of organisms. MRI features in dogs infected with *Neospora* include cerebellar atrophy with T2 hyperintense material surrounding the cerebellum and extending into the sulci, loss of contrast between cerebellar gray and white matter, T2/FLAIR hyperintensities within the cerebellum, and meningeal contrast enhancement. In two dogs with systemic *Leishmaniasis* nonenhancing T2 and FLAIR hyperintense lesions in thalamus and brain stem found on MRI were attributed to ischemic infarcts secondary to systemic necrotizing vasculitis. *Toxoplasma* infection in cats may manifest as multifocal indistinct T2 hyperintense contrast-enhancing parenchymal lesions with associated brain edema.

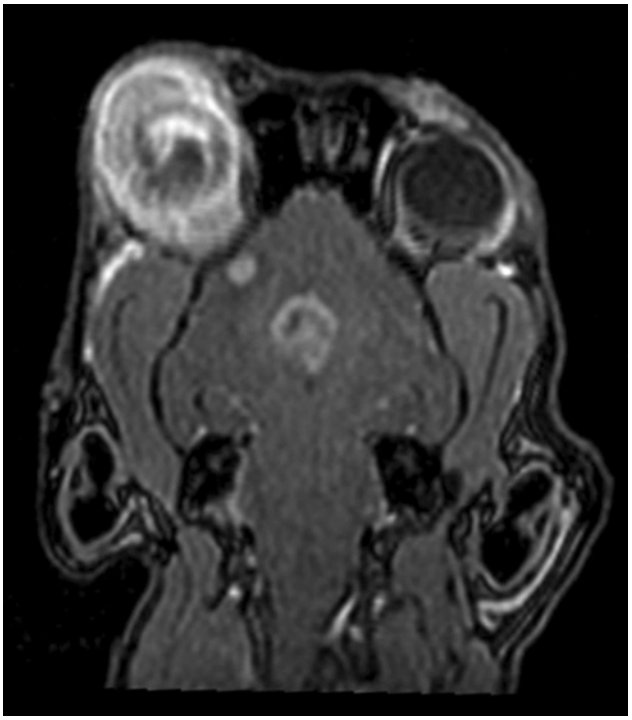

Figure 6.35 Blastomycosis in a cat. Dorsal T1-W postcontrast T1-W GRE image with fat suppression (reconstructed from transverse dataset) shows severe panophthalmitis of the right eye and two strongly contrast-enhancing intracranial masses.

Noninfectious inflammatory brain diseases/ meningoencephalomyelitis of undetermined etiology (MUE)[30, 40, 51, 58, 89, 137, 138, 151, 155, 157, 168, 172, 188, 189, 204, 206, 298, 326, 356, 375, 396, 402]

Several inflammatory conditions unrelated to infectious agents have been identified in dogs which generally respond to immunosuppressive treatment suggesting immune mediated etiology. Attempts have been made to separate these into specific diseases based on breed (e.g. "Pug dog encephalitis") and other criteria, however, due to overlap in clinical, diagnostic and pathologic findings a definitive premortem diagnosis is difficult. These disorders may be summarized under *Meningoencephalomyelitis of undetermined etiology (MUE)*.

Granulomatous meningoencephalitis (GME) can affect any breed of dog but most often occurs in young to middle-aged toy breeds. The disease can affect the brain and/or spinal cord. On MRI, GME lesions can be focal or multifocal and commonly affect the brain stem. Although the disease has a predilection for white matter, it is not associated with distinct topography. Lesions are typically hyperintense on T2-W and FLAIR images, iso- to hypointense on T1-W images and variably contrast enhancing (Fig. 6.36). Meningeal enhancement may or may

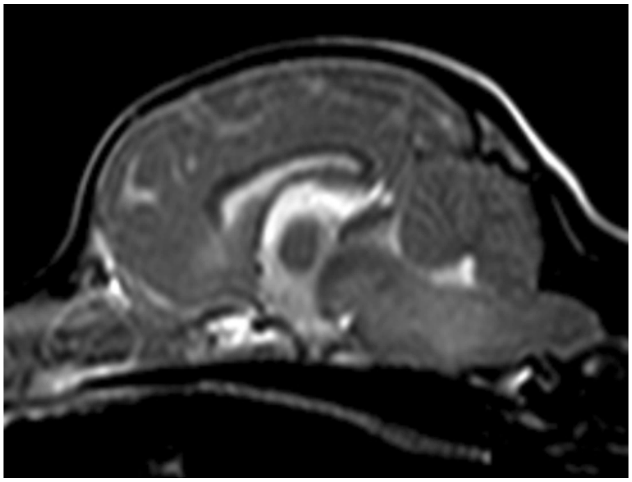

Figure 6.36 MUE (GME, presumptive) in a 4-yr-old Maltese. The T2-W sagittal image demonstrates an extensive diffuse hyperintense lesion associated with the brainstem.

not be observed. In ocular GME, MRI may show enlargement of the optic chiasm and fairly symmetric contrast enhancement of the optic nerves, optic chiasm, and visual pathways.

Necrotizing meningoencephalitis (NME) is characterized by cavitary necrosis in the neuroparenchyma. The disease was initially described in the pug breed ("pug dog encephalitis"), but similar disorders have since been reported in other small breeds including Maltese, Chihuahua, Pekingese, French Bulldog, Shi Tzu, and Lhasa Apso. A distinct form of NME described mainly in Yorkshire Terriers has been termed *necrotizing leukoencephalitis (NLE)*. Descriptions of imaging findings in this group of inflammatory brain disorders are not available for all breeds. NME in pugs is usually limited to the forebrain. MRI findings include diffuse asymmetric cerebral lesions which are nonuniformly hyperintense on T2-W images, isointense to hypointense on T1-W images, and affect gray and white matter resulting in loss of gray/white matter distinction. Additional findings include variable degrees of contrast enhancement of brain and leptomeninges, enlarged and asymmetric lateral ventricles, mass effect, brain herniation, and T2/FLAIR hyperintensity associated with the hippocampus and piriform lobes. MRI findings reported in Chihuahuas and French Bulldogs with NME are similar; however, brain stem involvement seems more common. In almost all cases of NLE reported in Yorkshire Terriers, lesions are located in the cerebrum and brain stem and appear iso- to hypointense on T1-W images, hyperintense on T2-W and FLAIR images, and show variable contrast enhancement. Concurrent hydrocephalus of variable severity is possible.

Other inflammatory intracranial diseases[250, 306, 341, 392, 398]

Greyhound nonsuppurative meningoencephalitis manifests as T2/FLAIR hyperintense lesions with minimal or absent contrast enhancement associated with olfactory lobes, frontal and frontotemporal gray matter, and caudate nuclei bilaterally. MRI in dogs with *idiopathic eosinophilic meningitis/meningoencephalitis* may be normal or show patchy regions of T2 hyperintensity and contrast enhancement in the cerebral cortex, solitary or multiple masses, meningeal enhancement, or enlargement and contrast enhancement of cranial nerves. In a boxer with *cerebral extension of steroid-responsive meningitis arteritis*, MRI findings included symmetrical multifocal to diffuse T2/FLAIR hyperintense changes of the cerebral gray matter and ependymal lining, increased periventricular signal, and a large amount of intraventricular sediment. A case of *lymphocytic meningoencephalitis* in a cat was characterized by multifocal T1 isointense and T2 hyperintense contrast-enhancing lesions. No intracranial abnormalities were detected on MRI in a cat diagnosed with *histiocytic encephalitis*. *Trigeminal neuritis* in dogs is characterized by diffuse enlargement of the nerves and is usually bilateral. Affected nerves are isointense to brain parenchyma on T1-W and PD-W images, isointense or hyperintense on T2-W images and show contrast enhancement.

Cerebrovascular disease

The term "cerebrovascular diseases" refers to all disorders in which there is an area of brain transiently or permanently affected by ischemia or bleeding and/or in which one or more blood vessels of the brain are primarily impaired by a pathological process.

Intracranial aneurysms and cerebrovascular malformations[234, 259, 340, 344, 346, 353]

An *aneurysm* is an abnormal focal enlargement of an artery of variable etiology. Patent aneurysms appear as signal void on both T1-W and T2-W images representing fast-flowing blood. Small aneurysms and aneurysms with turbulent flow are unreliably shown on conventional MRI and are better demonstrated by magnetic resonance angiography (MRA). While fairly common in humans, intracranial aneurysms are rarely diagnosed in veterinary patients. A case of a presumed aneurysm, most likely the result of traumatic arteriovenous fistulization, has been described in a dog. On CT images, an expansile enhancing mass was present along the intracranial cavernous sinus and extended through the orbital fissure into the retrobulbar space. With MRI, the structure appeared as a signal void due to the presence of rapidly flowing blood. The vascular origin of the lesion was confirmed with MRA.

Cerebrovascular malformations are congenital anomalies of brain vasculature. Different types include *arteriovenous malformations* (clusters of abnormal arteries and veins with direct arterial-to-venous shunts), *venous malformations* (anomalous veins separated by normal neural parenchyma), *cavernous malformations* (masses of contiguous sinusoidal vessels with no intervening parenchyma), and *telangiectasias* (masses of small capillary-type vessels separated by normal parenchyma). Animals with cerebrovascular malformations usually present with intracranial hemorrhage, and imaging findings are consistent with hemorrhagic stroke (see below). Identification of associated large vessels suggests vascular malformation as the underlying etiology of spontaneous intracranial hemorrhage. However, compression or obliteration of vessels by hematoma, extremely slow flow, and thrombosis may obscure the abnormal vessels, and specialized techniques (catheter angiography, repeat MRI, or MRA) may be needed to achieve a diagnosis.

Stroke (cerebrovascular accident)[3, 5, 7, 11, 26, 28, 35, 39, 45, 62, 79, 104, 107–109, 112, 114, 117, 126, 141, 148, 149, 153, 160, 181, 182, 196, 208, 216, 232, 263, 300, 329, 333, 345, 347, 352, 354, 383, 384, 389]

A stroke is a suddenly developing focal neurologic deficit resulting from an intracranial vascular event. In *ischemic stroke*, blood flow to an area of tissue is compromised due to intracranial arterial or venous obstruction. *Hemorrhagic stroke* results from the rupture of intracranial blood vessels.

Ischemic strokes can be categorized according to anatomic site, size, age, type (pallid or hemorrhagic), pathology (arterial vs. venous), mechanism (thrombotic, embolic, hemodynamic), and etiology. Causes of ischemic stroke in dogs include primary hypothyroidism, hypertension and diabetes, embolic metastatic tumor cells, necrotizing vasculitis due to systemic leishmaniasis, chronic renal disease, hyperadrenocorticism, intravascular lymphoma, septic thromboemboli, fibrocartilaginous embolism, migrating parasite or parasitic emboli (*Dirofilaria immitis*), and hypercoagulable state associated with hyperadrenocorticism, protein-losing nephropathy (PLN), or neoplasia. In approximately 50% of dogs with ischemic stroke, no underlying condition is identified. In cats, hypertrophic cardiomyopathy, neoplasia (lymphoma), and liver disease including hepatic lipidosis have been identified as potentially predisposing factors. *Territorial* infarcts occur when one of the main arteries supplying the brain is occluded. *Lacunar* infarcts are subcortical infarcts limited to the vascular territory of an intraparenchymal superficial or deep perforating artery. Small-breed dogs are more likely to have territorial cerebellar infarcts, and large-breed dogs are more likely to have lacunar thalamic or midbrain infarcts. Cavalier King Charles Spaniels and Greyhounds may be predisposed to infarcts. *Watershed* infarcts are infarcts in the boundary zone between large artery territories and are uncommon in veterinary patients. Diffusion weighted imaging (DWI) is sensitive to alterations in brain parenchyma following stroke and is capable of demonstrating abnormalities within minutes of an event (see above). Restricted diffusion (impairment of normal Brownian motion) occurs secondary to failure of the cell membrane ion pump and subsequent cytotoxic edema. This appears as marked hyperintensity on DWI and hypointensity on a synthesized ADC map derived from two or more DWI (see Fig. 6.17 above). On conventional MRI sequences, changes will be apparent within 12 to 24 hrs of onset. Although MRI findings in ischemic stroke may be similar to changes seen with other brain parenchymal diseases, there are certain distinguishing characteristics. An ischemic infarct appears as a homogeneous T2 hyperintense area with sharp demarcation between affected and nonaffected parenchyma and minimal to no mass effect. Lesions are typically confined to gray matter but may involve white matter in severe cases. Faint diffuse or peripheral contrast enhancement may be noted and has been reported in patients imaged between 1 and 45 days post onset of neurologic signs. Reperfusion injury of an ischemic infarct can occur, resulting in hemorrhagic infarction.

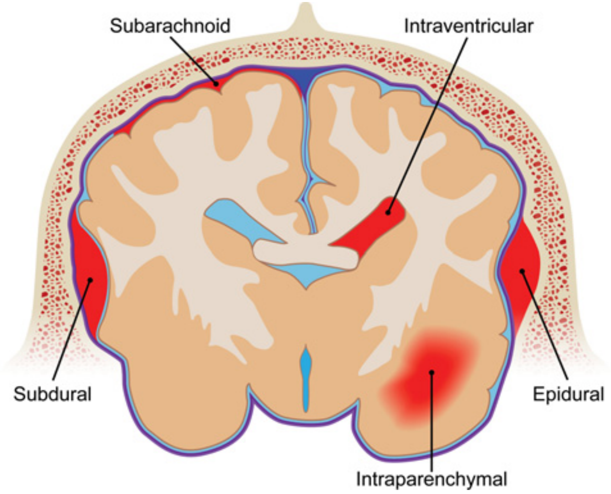

Figure 6.37 Schematic image illustrating appearance of different types of intracranial hemorrhage. (The Ohio State University. Reproduced with permission.)

Hemorrhagic stroke can be classified according to anatomic site (intraparenchymal, epidural, subdural, subarachnoid, intraventricular; Fig. 6.37), size, age, and etiology (e.g. intracranial neoplasia, von Willebrand factor deficiency and other coagulopathies, parasite migration, cerebral vascular malformation, idiopathic). The appearance of hemorrhage on MRI changes over time, allowing staging of a hematoma using conventional MRI sequences, although there is considerable variability (Table 6.3). Hemorrhage in areas with high ambient oxygen (ventricles; epidural, subdural, and subarachnoid space) "ages" more slowly than parenchymal or neoplastic hematomas, with a resultant change in time course of degradation. Deoxyhemoglobin, intracellular methemoglobin, hemosiderin, and ferritin have high magnetic susceptibility and are depicted with high sensitivity on T2*-W images (see Figs 6.15, 6.38, 6.41B, 6.50). Intraparenchymal hemorrhage appears as mass lesion(s) of variable size and intensity, and acute and subacute parenchymal hemorrhage is often associated with brain edema. In the acute stage, there is no contrast enhancement. With time, neovascularization in the surrounding brain tissue develops, resulting in ring-enhancement of the lesion. Special forms of intracranial hemorrhage are *cerebral microbleeds* which have been reported in humans and dogs. They appear as homogeneous, round hypointense foci on T2*-W GRE sequences, and are attributed hemosiderin deposits

Table 6.3 Change of appearance of intracranial hemorrhage over time.[28, 263]

Stage	Timeframe	Hemoglobin state	Intensity (T1-W)	Intensity (T2-W)
Hyperacute	< 12 hrs	Intracellular oxyhemoglobin	Similar to CSF	
Acute	Hours to days (longer in center)	Intracellular deoxyhemoglobin	Identical to brain or dark	Dark
Early subacute	Few days	Intracellular methemoglobin	Bright	Dark
Late subacute	Days to few weeks	Extracellular methemoglobin	Bright	Bright
Chronic	Weeks to years	Hemosiderin and ferritin	Dark	Dark

Source: Adapted from Bradley, 1993[28] and Parizel *et al.*, 2001[263].

stemming from past hemorrhages, presumably due to leakage from small vessels (Fig. 6.38). Identification of the underlying etiology of intraparenchymal hemorrhage can be challenging. The signal of hematomas secondary to neoplasms is more heterogeneous and complex than in spontaneous hematomas because of the presence of hemorrhagic components of varied age and, therefore, hemoglobin state, the presence of nonhemorrhagic areas, and, in some instances, the presence of necrotic and cystic components. Epidural hemorrhage assumes a focal biconvex configuration that may cross dural folds such as the falx and tentorium but not sutures, while subdural hemorrhage appears as a peripheral crescent-shaped collection of blood, which may cross suture lines but is limited by the falx cerebri and tentorium cerebelli. Subarachnoid and intraventricular hemorrhages result in an admixture of blood and CSF. With massive bleeding there may be a separation of intraventricular fluid into hemorrhagic and nonhemorrhagic strata. Subarachnoid or intraventricular thrombi may also develop.

Other vascular disorders[262, 281, 333, 355, 388, 390]

Feline ischemic encephalopathy (FIE) is a syndrome of cerebral infarction affecting adult cats which is attributed to aberrant *Cuterebra spp*. larval migration in the brain and toxin release by the parasites. MRI findings in chronic FIE include asymmetry of the cerebral hemispheres and bilateral symmetric enlargement of the subarachnoid space over the temporal lobes in areas supplied by the middle cerebral artery. Detectable lesions include parasitic tracks, superficial laminar cerebrocortical necrosis, cerebral infarction, subependymal rarefaction and astrogliosis, and subpial astrogliosis.

In *global brain ischemia (GBI)* the entire brain is affected by a transient period of complete ischemia followed by reperfusion. MRI findings include bilaterally symmetric increased T2/FLAIR signal intensity associated with gray matter and, to a lesser degree, with white matter of the occipital and parietal lobes and caudate nuclei/thalamus. There may be bilaterally symmetric contrast enhancement in these areas. In a report of a dog with GBI, repeat examination showed that lesions associated with gray matter decreased in extent and severity, and white matter changes resolved.

Metabolic, nutritional, toxic, and degenerative encephalopathies[1, 6–8, 31, 32, 55, 61, 80, 84, 85, 90, 102, 111, 113, 125, 128, 136, 159, 161, 177, 215, 218, 231, 242, 248, 251, 254, 256, 260, 270, 297, 316, 318, 333, 337, 338, 342, 357, 358, 364, 365, 372, 374, 378, 382]

Lysosomal storage diseases comprise a wide variety of inherited abnormalities which are characterized by the intracellular accumulation of one or more products of an interrupted metabolic

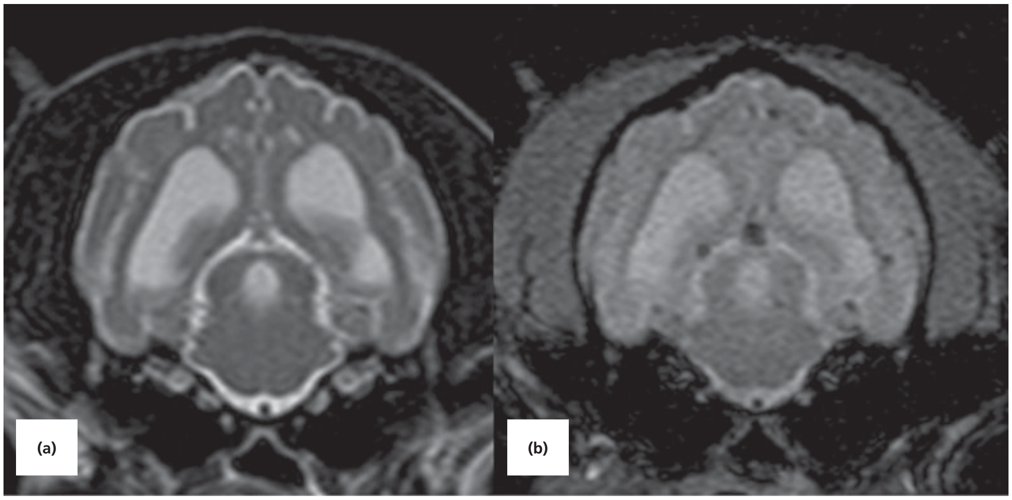

Figure 6.38 Multiple "microbleeds" in a 15-yr-old Yorkshire Terrier. (A) On the transverse T2-W image no definitive abnormalities are detected except mild generalized ventriculomegaly. (B) Multiple intraparenchymal small susceptibility artifacts are identified on the corresponding T2*-W image.

pathway. Several of these are used in animal models of human disease and therefore have been extensively studied. *Globoid cell leukodystrophy* (Krabbe's disease) is caused by mutations in the gene for galactocerebrosidase and has been described in a variety of dog breeds and cats. MRI findings include mild hydrocephalus, increased signal intensity in the corpus callosum on T1-W images, bilaterally symmetric increased signal intensity of the corpus callosum, centrum semiovale, internal capsule, corona radiata, and cerebellar white matter on T2-W images, and symmetric enhancement of the corpus callosum, internal capsule, and corona radiata after administration of gadolinium. *Gangliosidoses* are characterized by excessive neuronal accumulation of ganglioside. MRI findings in *gangliosidosis (GM2)* include cerebral and cerebellar atrophy of variable severity, bilaterally symmetric T2 hyperintensity and T1 hypointensity to the caudate nucleus, and diffuse T2 hyperintensity to cerebral white matter. MRI findings in *gangliosidosis* (*GM1)* include a relative increase in gray matter and an abnormal signal intensity of cerebral and cerebellar white matter on T2-W images, or diffuse T2 hyperintensity of the cerebral white matter and brain atrophy. *Ceroid lipofuscinosis* is characterized by the abnormal accumulation of lipoprotein pigment within cellular lysosomes. MRI findings include brain atrophy as indicated by the dilation of cerebral sulci and cerebellar fissures and ventriculomegaly. The enhancement and thickening of meninges have also been reported. In cats affected with *alpha-mannosidosis*, a decrease in ADC values of white and gray matter and an increase in T2 values of white matter have been reported, corresponding to neuronal swelling, abnormal myelin, and astrogliosis. Spectroscopy has proven useful in distinguishing cats with mannosidosis from normal animals. *Mucopolysaccharidoses (MPS)* are a group of diseases caused by different specific deficits of metabolism of glycosaminoglycan. No abnormalities were detected on MRI of the brain in Schipperkes with MPS III.

L-2-hydroxyglutaric aciduria is an inborn error of metabolism which has been described in a variety of dog breeds including Staffordshire Bull Terriers, West Highland White Terriers and Yorkshire Terriers. MRI findings include bilaterally symmetric and diffuse regions of gray matter hyperintensity on T2-W images with no evidence of contrast enhancement.

Mitochondrial encephalopathies resembling subacute necrotizing encephalomyelopathy (Leigh's syndrome) in human patients have been described in several dog breeds. MRI findings in *hereditary polioencephalomyelopathy* in an Australian Cattle dog and a Shi Tzu included bilaterally symmetric abnormalities in areas corresponding to vestibular and cerebellar nuclei, cervical spinal cord, and in areas corresponding to the dorsal nuclei of the trapezoid body, pontine nuclei, caudal colliculi, and the dorsolateral reticular formation. Lesions were isointense or hypointense on T1-W images, hyperintense on T2-W images, did not have a mass effect and did not show evidence of contrast enhancement. MRI examination in an Alaskan Husky with subacute *necrotizing encephalopathy* revealed bilateral cavitation extending from the thalamus to the medulla, with less pronounced degenerative lesions in the caudate nucleus, putamen, and claustrum.

Failure of the liver to remove toxic substances absorbed from the gastrointestinal tract may result in *hepatic encephalopathy*. MRI findings reported in dogs and cats with congenital portosystemic shunts include brain atrophy, bilaterally symmetric hyperintensity to the lentiform nuclei on T1-W images without contrast enhancement, and bilateral extensive T2 hyperintense lesions along the cerebral cortex.

Bilaterally symmetric lesions in the caudate nuclei were reported in a dog subsequently diagnosed with an *insulinoma* and were attributed to *hypoglycemia*. Lesions were strongly hyperintense on T2-W and FLAIR images, had a hyperintense rim with a hypointense center on T1-W images, and did not demonstrate evidence of contrast enhancement.

Thiamine deficiency results in insufficient ATP production in the brain with subsequent neuronal dysfunction. MRI findings in dogs include bilaterally symmetric multifocal T2, FLAIR, and postcontrast T1 hyperintensities in the red nuclei, caudal colliculi, vestibular nuclei of the brain stem, and the cerebellar nodulus, or bilaterally symmetric T2 hyperintensities in caudate nuclei and rostral colliculi. In cats bilaterally symmetric T2, FLAIR, and T2* hyperintense nonenhancing lesions are observed associated with the lateral geniculate nuclei, caudal colliculi, periaqueductal gray matter, medial vestibular nuclei, cerebellar nodulus, and facial nuclei (Fig. 6.39), with the caudal colliculi, medial vestibular nuclei, and facial nuclei also being hyperintense on T1-W images. Lesions improve or resolve with the implementation of thiamine treatment.

Hypocobalaminaemic encephalopathy in a cat resulted in bilaterally symmetric abnormalities mostly affecting gray matter; T2 hyperintense lesions were identified in thalamus,

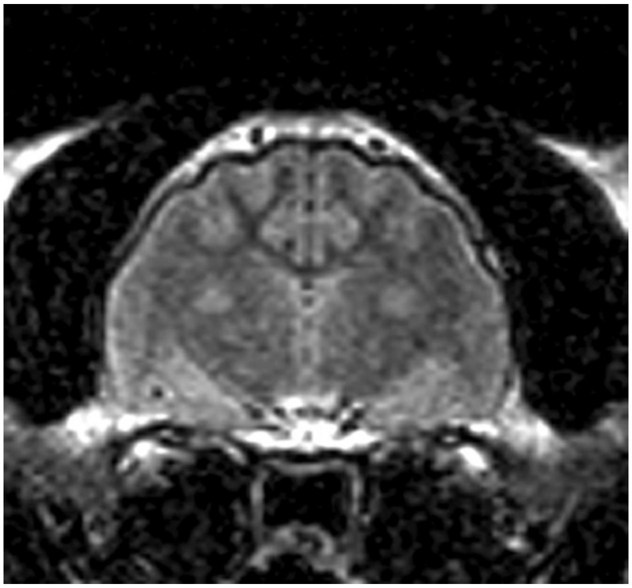

Figure 6.39 Thiamine deficiency in a cat. The transverse FLAIR image at the level of the thalamus shows bilaterally symmetric T2-hyperintense lesions at the level of the lateral geniculate nuclei.

mesencephalon, pons, caudal cerebellar peduncles, and interposital nuclei, which resolved after cobalamin treatment.

Myelinolysis is a brain disorder most commonly caused by the rapid correction of hyponatremia. Lesions were originally thought to be limited to the pons, but extrapontine locations including the thalamus, midbrain, cerebellum, basal nuclei, and cerebrocortical gray and white matter junctions have been reported in human patients. MRI findings in dogs include bilaterally symmetric T2/FLAIR hyperintense nonenhancing lesions within the thalamus, caudate nuclei, and along the cerebrocortical gray–white matter junction.

A series of progressive neurologic diseases have been summarized under the term *spongy degeneration*. These conditions are primarily, but not exclusively, diseases of white matter and may be hereditary. MRI findings in a Labrador Retriever included large, bilaterally symmetric T2 hyperintense and T1 hypointense nonenhancing lesions in the region of the deep cerebellar nuclei and smaller lesions within the thalamus ventromedial to the lateral ventricles.

Neuroaxonal dystrophy is a degenerative disease of the CNS characterized by the degeneration of neurons and axons. MRI features in Papillons and Papillon-related dogs included cerebral and cerebellar atrophy.

Cerebellar cortical abiotrophy refers to the degeneration of normal neuronal cell populations within the cerebellar cortex after birth. This disorder has been reported in a variety of dog breeds. Presumptive diagnosis is best made on sagittal T2-W images, where the small size of the cerebellum is indicated by marked increase in fluid separating the folia of the cerebellum (Fig. 6.40). Several attempts have been undertaken to quantify cerebellar size in normal dogs and dogs affected with cerebellar atrophy. Using a cut-off of 89%, the ratio between the brain stem and cerebellum midsagittal cross-sectional area could be used successfully to differentiate affected from unaffected dogs with a sensitivity and specificity of 100%. Differentiation of true abiotrophy from other causes of small cerebellar size (cerebellar atrophy, cerebellar hypoplasia) is not possible based on imaging findings.

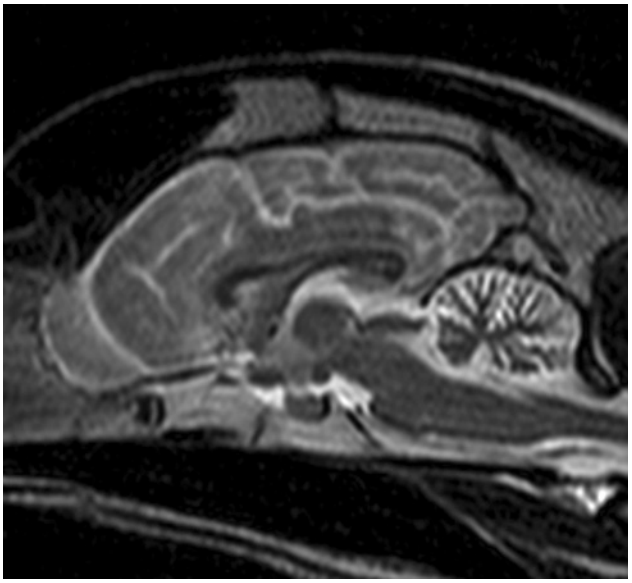

Figure 6.40 Cerebellar cortical abiotrophy in a 5-yr-old dog. Sagittal T2-W image demonstrates the small size of the cerebellum as indicated by an increase in fluid signal between the folia.

Trauma[2, 42, 170, 211, 257, 281]

MRI findings in dogs and cats with head trauma are infrequently reported. Possible findings include fractures, intracranial hemorrhage (Fig. 6.41), pneumocephalus, contusions, brain edema, intracranial abscess/meningitis (see Fig. 6.34 above), and parenchymal brain defects with compensatory CSF filling (hydrocephalus ex-vacuo). MRI appearance of traumatic intracranial hemorrhage corresponds to imaging features described above (see "hemorrhagic stroke").

Neoplastic and non-neoplastic mass lesions[182, 183, 321, 322, 348, 360, 393]

Numerous intracranial masses have been described in dogs and cats. They can be characterized by number, origin, location, size, margination, signal intensity, homogeneity, contrast enhancement, and concurrent imaging findings (ventriculomegaly, changes associated with cranium and/or meninges, hemorrhage, mineralization, mass effect, edema, cystic or necrotic component etc.). Mass lesions can be subdivided based on location into intra-axial (arising from within the brain axis) and extra-axial.

Malformations, hamartomas, cysts, and tumor-like lesions[79, 92, 197, 205, 207, 283, 305, 311, 325, 333, 391]

A variety of conditions are included in this group, and overlap exists with disorders described under congenital malformations and cerebrovascular disease. Cystic lesions of the brain (e.g. arachnoid cysts, ependymal cysts, dermoid and epidermoid cysts) are covered in the "Congenital brain disorders" section and congenital disorders of intracranial vessels are covered under the "Intracranial aneurysms and cerebrovascular malformations" section.

Hamartomas are masses formed by the disorderly overgrowth of tissue elements normally present at that site. MRI of a cat with cerebellar vascular hamartoma showed a heterogeneously T2 hyperintense mass lesion with heterogeneous contrast enhancement.

Hemangiomas appear as intra-axial masses of variable size and intensity, typically with heterogeneous contrast enhancement. They are often associated with hemorrhage, which is best detected using a T2*-W sequence. MRI findings in one case of cerebral *hemangioblastoma* have been reported in a dog. A large strongly contrast-enhancing mass lesion resulting in mass effect and subtentorial herniation was identified.

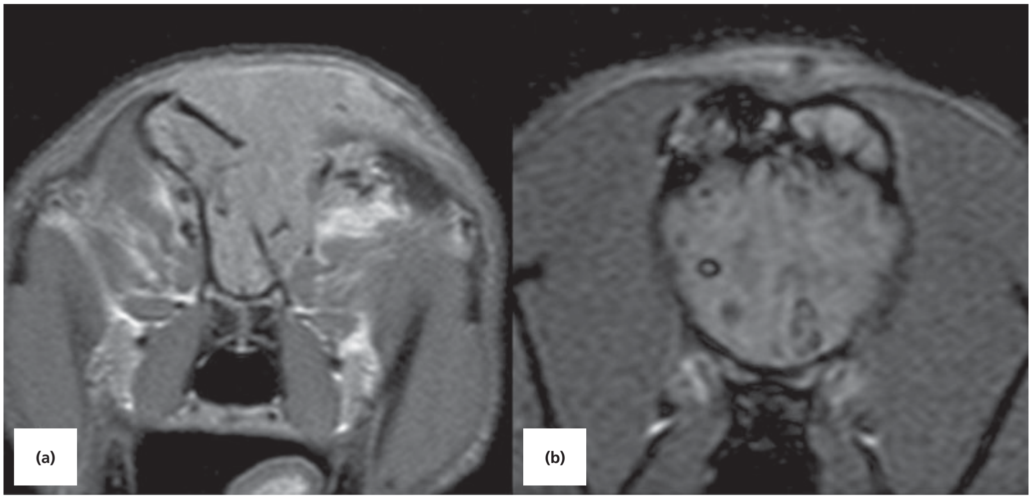

Figure 6.41 Head trauma in a dog after being hit by a car. (A) The PD-W image at the level of the olfactory bulbs demonstrates multiple skull fractures with displacement of bone fragments and compression of brain parenchyma. Subcutaneous soft-tissue swelling and soft-tissue intense material within the frontal sinuses is also noted. (B) In addition, the T2*-W image at the level of the frontal lobes shows multiple foci of intraparenchymal hemorrhage.

Meningioangiomatosis is a rare benign lesion characterized by a proliferation of meningothelial cells surrounding small blood vessels. MR examination in a 2-yr-old Alaskan Malamute showed a large T2 hyperintense mass associated with the cerebrum.

Cholesterol granulomas due to progressive cholesterol accumulation are most commonly reported in horses. In small animals they manifest as large extra-axial well-circumscribed masses of variable intensity and contrast enhancement that originate from ventricular system, brain surface/subarachnoid space, or fissures between cerebral hemispheres and result in severe compression of adjacent brain tissue.

An MR diagnosis of intracranial extension of a large *nasal mucocele* has been reported in a dog. The mass was multilobulated and relatively sharply marginated, hyperintense on T2-W and FLAIR images, isointense on T1-W images, with peripheral ring-enhancement. Concurrent findings included mass effect and brain edema.

Meningeal tumors[96, 98, 118, 124, 130, 144, 147, 202, 222, 227, 241, 245, 261, 312, 322, 330, 336, 360]

Meningiomas originate from the meningeal lining of the brain and are the most common brain tumors in dogs and cats. They are typically single lesions, but multiple tumors may be found on occasion. Meningiomas are typically in broad-based contact with adjacent bone, have round/ovoid or plaque-like shape, are smoothly marginated, show expansile rather than infiltrative growth, are hypointense to isointense on T1-W images, hyperintense on T2-W/FLAIR images, and show strong and homogeneous to heterogeneous contrast enhancement (see Fig. 6.6). Mineralization or hemorrhage may be present, which is best demonstrated on T2*-W images. Possible concurrent findings include hyperostosis, pressure atrophy, or invasion of adjacent bone, brain edema, and mass effect. A “dural tail sign” (thickening and enhancement of the dura adjacent to an extra-axial mass) is frequently present and is strongly suggestive of but not specific for meningioma. Cystic meningiomas have been described and predominantly occur in the rostral cranial fossa (Fig. 6.42).

Other tumor types such as *disseminated histiocytic sarcoma*, *lymphoma*, *granular cell tumor*, or *metastases* (meningeal carcinomatosis) can affect the meninges and have variable appearance on MRI.

Glial tumors[74, 103, 122, 176, 182–185, 200, 214, 225, 244, 273, 322, 324, 348, 360, 379, 395, 403]

Glial tumors typically appear as single intra-axial lesions, although cases of multiple concurrent tumors have been reported.

Astrocytomas and *oligodendrogliomas* cannot be reliably distinguished using MRI. They are variable in appearance, with shapes ranging from an ovoid or amorphous mass to a diffuse infiltrate with distinct to poorly defined margins. They are most commonly located in the cerebrum or thalamus. Lesions are hypointense to isointense on T1-W and hyperintense on T2-W images, with contrast enhancement ranging from none to strong with uniform, nonuniform, and ring-enhancing patterns (Fig. 6.43). Cystic regions in the mass, intralesional hemorrhage, concurrent brain edema, and brain herniation are common.

MRI features of *glioblastoma multiforme* include heterogeneous increased T2 signal intensity with iso- to hypointense T1-W signal, sharp borders, necrosis, and peritumoral edema. Cyst formation is possible. Irregular margins and a pedunculated shape have been reported in one dog. Ring enhancement is commonly seen.

Gliomatosis cerebri/cerebelli is a rare tumor-like disease of glial cells characterized by diffuse, widespread infiltration with preservation of brain structures. MRI findings include focal

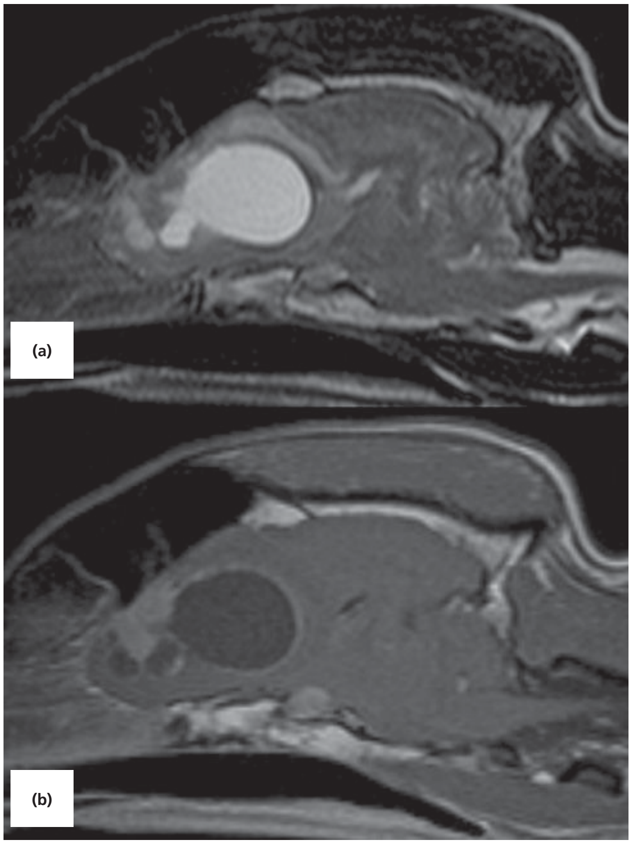

Figure 6.42 Cystic meningioma in an 11-yr-old Labrador Retriever. Parasagittal T2-W (A) and postcontrast T1-W (B) images show a large smoothly marginated cyst and several small cystic lesions in contact with a strongly and homogeneously contrast-enhancing extra-axial mass in the left olfactory and frontal lobe. The large cyst has mild ring-enhancement. Additional findings include perilesional edema, mass effect, subtentorial herniation, and compression of the cerebellum.

or multifocal ill-defined T2/FLAIR hyperintense noncontrast-enhancing areas associated with the brain and/or spinal cord.

Ventricular tumors[182, 183, 202, 266, 290, 296, 333, 348, 359, 377, 386]

Choroid plexus tumors originate from the choroid plexus located within the ventricular system and predominantly occur in the third and fourth ventricles. Both choroid plexus papillomas (CPP) and carcinomas (CPC) are predominantly isointense to hyperintense on both T1-W and T2-W images, typically with intense and homogeneous contrast enhancement (Fig. 6.44). Signal heterogeneity can be observed secondary to cyst formation, mineralization, hemorrhage, or necrosis. The most important feature in differentiating different tumor types is evidence of intraventricular or subarachnoid metastases detected in 35% of CPC but not in CPP. Concurrent ventriculomegaly and perilesional and periventricular edema are common.

Ependymal tumors (ependymomas) are uncommon in animals. On MRI, ependymomas manifest as fairly well circumscribed smooth or lobulated tumors associated with the

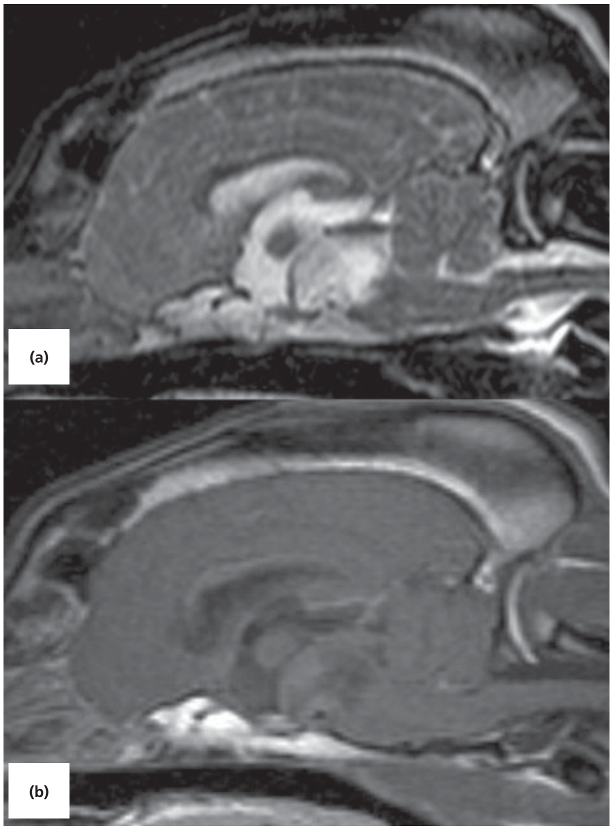

Figure 6.43 Oligodendroglioma in a 7-yr-old Boxer. Sagittal T2-W (A) and postcontrast T1-W (B) images show a heterogeneous T2 hyperintense mass within the thalamus and mesencephalon which exhibits only minimal contrast enhancement.

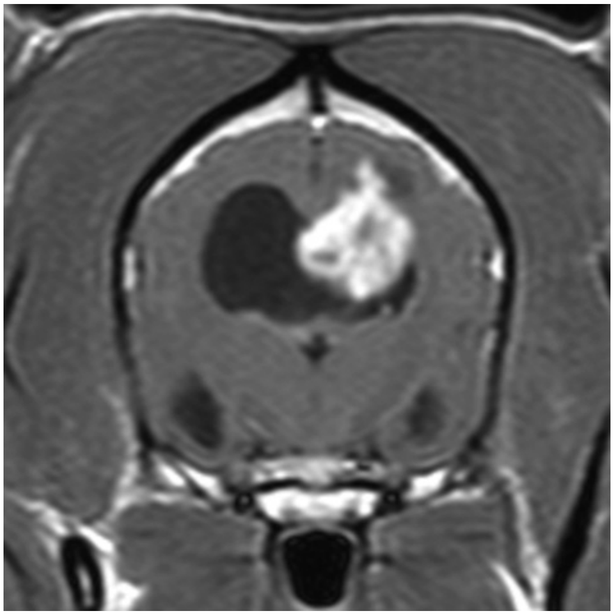

Figure 6.44 Choroid plexus tumor (presumptive) in a 9-yr-old English Bulldog. T1-W postcontrast image demonstrates a large, irregularly marginated, strongly contrast-enhancing mass associated with the roof of the left lateral ventricle and concurrent hydrocephalus.

ventricular system. Extension into adjacent brain parenchyma or vice versa is possible. Ependymomas are isointense on T1-W and hyperintense on T2-W images, exhibit variable contrast enhancement, and are often associated with hydrocephalus and brain herniation.

The ventricular location of *meningiomas* has been reported in dogs and cats. They are characterized by smooth margination and homogeneous contrast enhancement. Concurrent hydrocephalus and brain herniation are common.

Intraventricular *neurocytomas* have been reported in dogs and appear as T1-isointense, T2 and FLAIR hyperintense, and markedly contrast-enhancing mass lesions within the ventricular system.

Primitive neuroectodermal tumors (PNET) and medulloblastomas[54, 169, 187, 214, 233, 322, 333]

Primitive neuroectodermal tumors (PNET) are a group of poorly differentiated neoplasms derived from primitive neuroectodermal cells. MR findings reported in dogs include intra-axial masses which were hypointense to isointense on T1-W images, hyperintense on T2-W images, and showed moderate to strong heterogeneous contrast enhancement.

Medulloblastomas are almost exclusively located in the cerebellum. MRI features include a more or less well-defined heterogeneous cerebellar mass which is predominantly isointense to hypointense on T1-W images, hyperintense on T2-W images, and shows variable contrast enhancement (Fig. 6.45). Concurrent hemorrhage and/or cysts are possible.

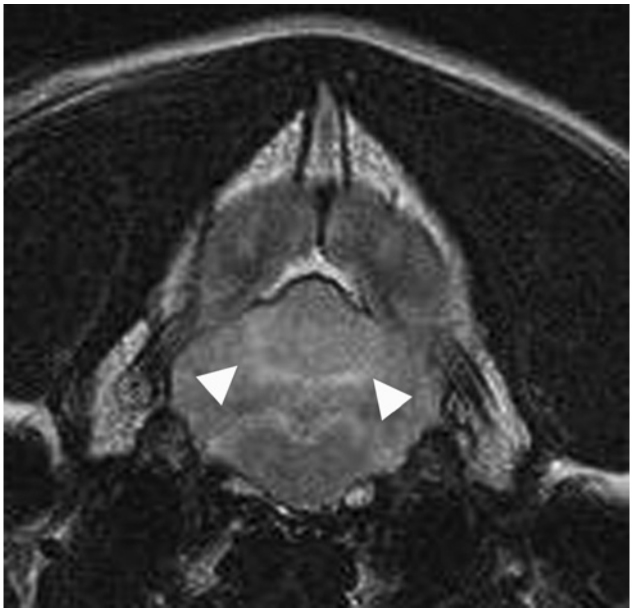

Figure 6.45 Medulloblastoma in a 3-yr-old mixed-breed dog. Transverse FLAIR image shows indistinct T2 hyperintensity associated with the cerebellar vermis (arrowheads). No additional abnormalities were detected on other MR sequences. (Hecht and Adams, 2010. Reproduced with permission from Elsevier.)[131]

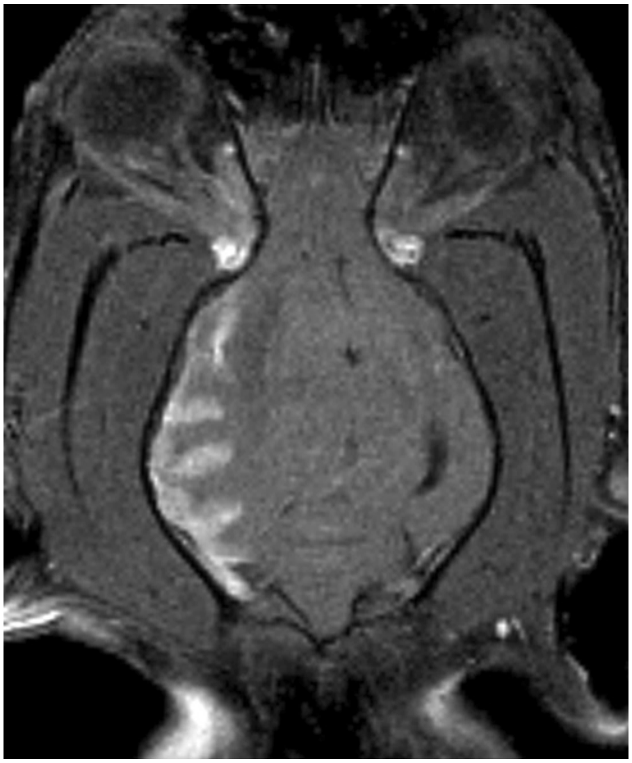

Figure 6.46 Intracranial histiocytic sarcoma in a 12-yr-old mixed-breed dog. The dorsal postcontrast T1-W image with fat suppression shows extensive meningeal and parenchymal contrast enhancement of the right cerebrum. Midline shift of the falx cerebri and compression of the right lateral ventricle is consistent with mass effect due to vasogenic edema.

Other CNS tumors[139, 156, 203, 241, 247, 252, 261, 312, 315, 322, 336, 349, 360, 362]

MR findings have been reported in *CNS lymphoma* in dogs and cats and *disseminated histiocytic sarcoma* in dogs. Lesions can appear as ill- or well-defined, single or multifocal, intra-axial or extra-axial masses. These are typically isointense to hypointense on T1-W images and hyperintense on T2-W images, show moderate to strong contrast enhancement, and may be associated with edema and mass effect (Fig. 6.46). In cats with extra-axial lymphoma and dogs with extra-axial histiocytic sarcoma, a "dural tail sign" after contrast medium administration has been reported, mimicking a common finding in meningiomas.

Granular cell tumor is a descriptive term for a heterogeneous group of tumors. Intracranial granular cell tumors can be intra- or extra-axial, are typically hyperintense on T2-W images, and show strong contrast enhancement. Concurrent findings include mass effect as well as transcalvarial extension and meningeal enhancement.

Central nervous system-associated tumors[9, 10, 16, 22, 77, 88, 119, 173, 182, 183, 201, 239, 243, 246, 277, 306, 333, 348, 360, 397]

Pituitary tumors are characterized by typical location in the pituitary fossa, which is best demonstrated on sagittal images

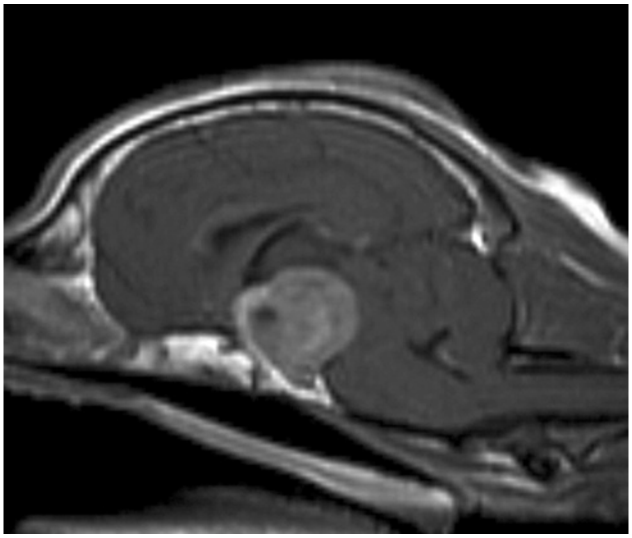

Figure 6.47 Pituitary macrotumor in an 11-yr-old mixed-breed dog. Sagittal T1-W postcontrast image shows a smoothly marginated, fairly homogeneously contrast-enhancing mass extending dorsally from the pituitary fossa.

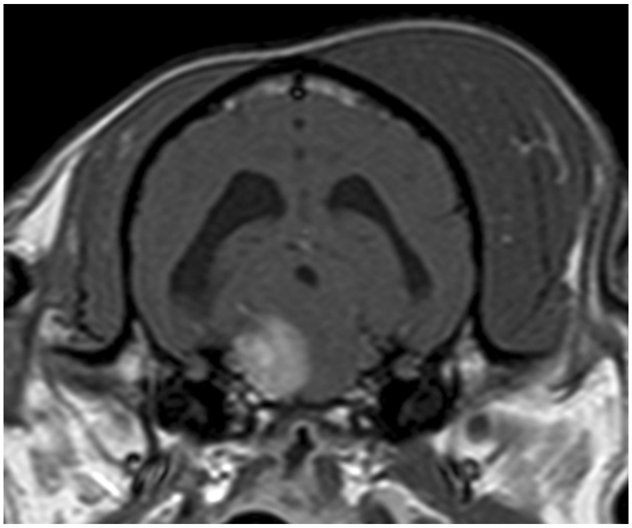

Figure 6.48 Trigeminal nerve sheath tumor in a 12-yr-old Pembroke Welsh Corgi. Transverse T1-W postcontrast image demonstrates a rounded smoothly marginated contrast-enhancing mass associated with the right brainstem and atrophy of the right temporalis and masseter muscles.

(Fig. 6.47). Pituitary microadenomas may not be readily apparent on conventional MR sequences, and dynamic studies or specific thin-slice sections might be necessary to establish a diagnosis. Pituitary macroadenomas usually appear as relatively well-circumscribed expansile T1 iso- to hypointense and T2/FLAIR hyperintense masses with strong contrast enhancement. Invasive adenomas and carcinomas show more invasive growth than adenomas and may invade adjacent structures. Pituitary hemorrhage may occur in any pituitary macrotumor, resulting in susceptibility artifacts on GRE (T2*-W) images and alteration of signal intensity of the mass on pre- and postcontrast images. Metastases from pituitary carcinoma are not usually observed on MRI. In acromegalic cats with pituitary tumors concurrent thickening of the frontal bone and soft-tissue accumulation in nasal cavity, sinuses, and pharynx may be seen.

Craniopharyngiomas originate from remnants of the craniopharyngeal duct ectoderm which are located above the sella turcica and, by expansion, compress the pituitary gland, optic chiasm, and hypothalamus. MRI examination in two cats revealed large masses at the skull base, with extensive bone lysis and cerebral displacement.

Trigeminal nerve sheath tumors are not uncommon in dogs. MRI features include an extra-axial solitary or lobulated mass in the middle or caudal fossa which is typically isointense on T1-W images, isointense or hyperintense on T2-W images, and shows contrast enhancement (Fig. 6.48). Atrophy of the temporalis and masseter muscles with increase in signal intensity of these muscles on T1-W images is typically present. Possible additional findings include distortion of the adjacent brain stem and enlarged skull foramina.

Nasal tumors (e.g. adenocarcinoma, squamous cell carcinoma, chondrosarcoma, neuroesthesioblastoma) may invade the brain through the cribriform plate. Imaging findings include nasal masses of variable size, intensity and contrast enhancement with destruction of cribriform plate, and intracranial extension of nasal mass. Cystic/necrotic areas associated with the tumor and brain edema are frequently present (Fig. 6.49).

Tumors of the skull such as multilobular osteochondrosarcoma or masses originating from adjacent structures may also extend into the cranial vault.

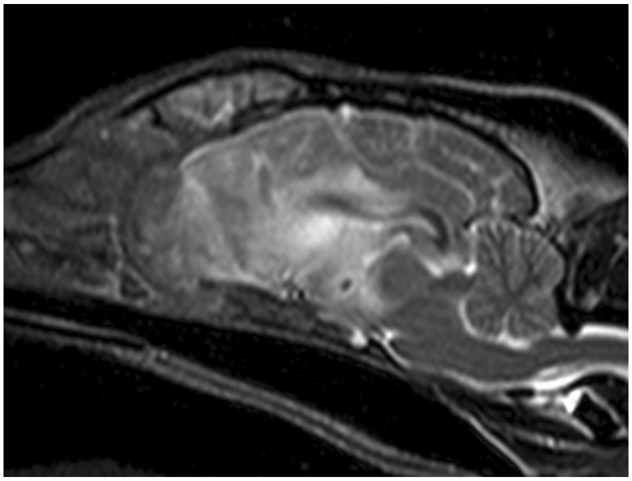

Figure 6.49 Nasal mass (adenocarcinoma) with intracranial extension in a 4-yr-old dog. The sagittal T2-W image shows a large heterogeneous mass associated with nasal cavity and frontal sinuses which results in destruction of turbinates, cribriform plate, and frontal bones. The mass extends into the cranial vault and is associated with vasogenic edema, mass effect, and subtentorial herniation.

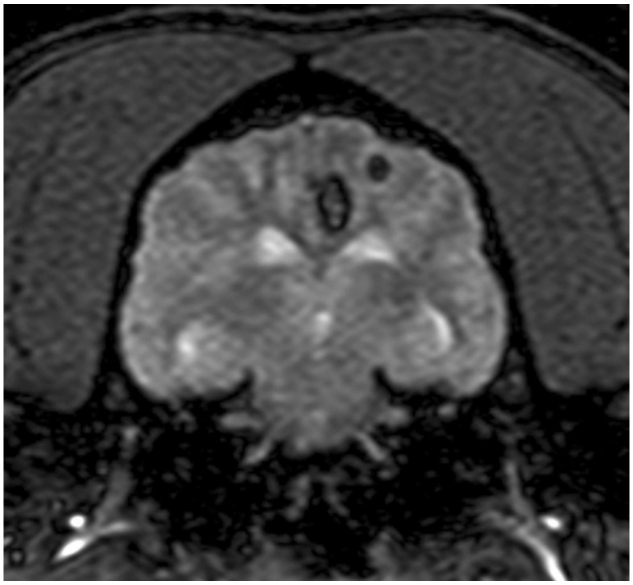

Figure 6.50 Hemangiosarcoma metastases to the brain (presumptive) in a dog presented with hemoabdomen, a cavitary splenic mass and multiple liver masses. The transverse T2*-W image shows two of multiple hemorrhagic intra-axial lesions of variable size and shape.

Metastatic CNS tumors[47, 87, 182, 317, 321, 333]

Many primary tumors including hemangiosarcomas and carcinomas have the potential for wide dissemination including spread to the CNS. Metastases can appear as single or multiple lesions associated with brain parenchyma and/or meninges, often with associated brain edema. They are commonly rounded to ovoid, appear iso- to hypointense on T1-W images and hyperintense on T2-W images. Hemangiosarcoma metastases may be associated with hemorrhage (Fig. 6.50). Strong and homogeneous or ring enhancement are commonly noted, although nonenhancing carcinoma metastases have been reported.

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Magnetic resonance imaging (MRI) of the vertebral column

Ronaldo C. da Costa

Generalities of Vertebral Column MRI[1–10, 12–51, 53–66, 68–70]

Magnetic resonance imaging (MRI) of the vertebral column has revolutionized the diagnosis of many spinal conditions such as fibrocartilaginous embolic myelopathy or type III intervertebral disc disease. MRI is the only modality that allows direct visualization of soft-tissue structures such as the spinal cord and nerve roots, thus allowing characterization of spinal disorders well beyond those achieved with myelography and computed tomography (CT). The applications of spinal MRI are many and are expanding progressively. In addition to routine MRI sequences, such as T2- and T1-weighted (W) images, special sequences, such as diffusion tensor imaging and angiography, are beginning to be used, and may become routine in the future.

Advanced imaging modalities offer significant advantages over survey radiographs and myelography. There is a wealth of data in people supporting the significant benefits of MRI versus myelography, and the few comparative studies available support the findings seen in people. The overall diagnostic sensitivity of MRI is superior to CT, and as such MRI can be used to image the vast majority of spinal disorders, with few exceptions (e.g. spinal trauma caused by gunshot). CT and MRI allow visualization of different structures, so ideally should be seen as complementary imaging modalities. Routine survey radiographs are always recommended prior to proceeding with advanced imaging because the area of interest may be more specifically localized, reducing scanning time, and severe spinal/osseous lesions, such as hemivertebrae or discospondylitis, may be identified without the need of advanced imaging studies. However, depending on the clinical status and treatment plan, advanced imaging may still be needed.

Compared to CT, MRI provides superior contrast resolution and is better suited for imaging soft tissues, such as the spinal cord, nerve roots, and intervertebral discs. MR images can be acquired in multiple planes, whereas CT images can only be acquired in one plane (typically transverse). Whereas myelography is still often used in conjunction with CT of the spine, this is not necessary with MRI because of the ability to alter tissue contrast by applying different acquisition sequences. Thus, the associated morbidity often accompanying myelography is avoided. Disadvantages of MRI compared to CT are the prolonged acquisition time and increased expenses.

MRI imaging techniques[2, 3, 15, 16, 16, 37–39, 42, 49, 62]

Positioning

Straight spinal alignment is extremely important for MRI to allow direct comparison of multiple sites on sagittal images. A trough may be necessary to achieve this in deep-chested dogs. The spinal segment(s) to be imaged must be in close contact to the RF coil for a satisfactory signal-to-noise ratio. As table surface coils designed for spinal imaging are used in most instances, patients are typically positioned in dorsal recumbency.

Plane of acquisition

- Sagittal: often used as the survey series to localize a specific site of pathology as a long segment of the spine can be imaged. The T2-W sequence is preferred for initial assessment.
- Dorsal: useful to evaluate lateralized compressions, mainly when multiple lesions are present.
- Transverse: typically limited to specific sites of pathology as imaging extended lengths of spine in this plane is time intensive.

Image sequences and slice

- T2-W: fluid, such as cerebrospinal fluid (CSF) or edema, will be hyperintense.
- T1-W: fluid, such as CSF or edema, will be hypointense.
- FLAIR (fluid attenuated inversion recovery): pure fluid, such as normal CSF, will be hypointense, whereas edema or abnormal fluids will be increased in intensity.
- STIR (short tau inversion recovery) or fat saturation: the typically hyperintense fat (on both T1- and T2-W sequences) will be of low signal intensity. If a sequence is T2-W, CSF can be more readily differentiated from epidural fat. If a sequence is T1-W, a contrast-enhancing lesion can be more readily differentiated from fat.
- Gradient echo (GRE): a fast sequence that is very sensitive to inhomogeneities in the magnetic field, though less sensitive to motion artifact because of its speed of acquisition. It is often used to detect areas of hemorrhage, as excessive iron concentrations in hemorrhagic areas of the spinal cord will cause field inhomogeneity.
- MR myelogram sequence (single-shot turbo spin echo), HASTE (half-Fourier acquisition single-shot turbo spin echo), or heavily T2-W: this sequence is primarily useful to evaluate the dorsal and ventral subarachnoid spaces, thus it is useful to characterize arachnoid diverticula and intradural neoplasms.

Recommended standard planes, slice thicknesses and sequences

- 2–3 mm thick T2-W sagittal images followed by 2–3 mm thick T1-W sagittal images. A 0.5 mm gap between slices, to avoid image cross-talk and resultant decreased signal to noise, or interleaved (no interval/gap) acquisition is typical.

- Sagittal MR myelogram sequence (single-shot turbo spin echo, heavy T2).
- 2–3 mm transverse images through the lesion identified on the sagittal images.
- 2–3 mm dorsal images for lateralized lesions identified on the prior sequences.
- T1-W images after intravenous gadolinium injection may be obtained in all three image planes according to the lesion characteristics.
- STIR, FLAIR, fat saturation, and GRE sequences may be necessary depending on lesion characteristics.

Field of view (FOV)

Field of view is defined as the vertical or horizontal distance across an image. It should be set specific to the spinal column, which is dependent on patient size. By decreasing FOV to a specific area, the signal-to-noise ratio decreases and thus increases in sampling (NEX; see below) or increases in slice width are necessary to maintain adequate spatial and contrast resolution. By increasing NEX, scan time is also increased.

Number of excitements (NEX)

This refers to the number of repeat signal samplings acquired in any given sequence. In general, the more times an area is sampled, the greater the signal-to-noise ratio (improved tissue contrast). The downside is that the greater the NEX, the longer the overall imaging time. NEX values between 2 and 4 are typically required for field strengths over 1 tesla.

Saturation bands

As MRI is extremely sensitive to motion artifact secondary to respiration and blood flow, saturation bands may be placed over the abdomen and thorax to suppress the effects of motion from these areas during scanning.

Contrast imaging

Gadolinium diethylenetriaminepentaacetic acid (MRI) contrast: indications include identification of vascular lesions like those secondary to neoplasia, infectious/noninfectious inflammatory lesions other than related to intervertebral disc herniation, and vascular malformations.

Normal anatomy

The anatomic features of the spinal region being studied must be taken into consideration when interpreting advanced imaging studies. Each region of the vertebral column (cervical, thoracic, lumbar, sacral) has specific anatomic features. A larger degree of anatomic variation is seen in the cervical vertebrae compared to other vertebral regions. Not only are the cervical vertebrae different but also the shape and relationship of the spinal cord to the vertebral canal varies according to the location within the cervical column (Fig. 6.51). The anatomic features of the cervical spine and lumbosacral spine have been reported in detail using CT, MRI, or both.

Due to the exquisite sensitivity of MRI, it is important to assess the imaging findings in the light of the patient's clinical signs and examination findings. The presence of asymptomatic spinal abnormalities is widely recognized in human medicine. The presence of multiple spinal abnormalities is commonly seen in aged dogs and cats. Clinically silent spinal cord compression, intervertebral disc degeneration, intervertebral disc protrusion, nerve root compression, intervertebral foraminal stenosis, and vertebral canal stenosis have all been reported without concurrent clinical signs in dogs. Similarly, no correlation exists between the severity of spinal cord or nerve root compression with the severity of clinical signs.

Vascular diseases

Fibrocartilaginous embolic myelopathy (FCEM)[1, 18, 20]

MRI is the imaging modality of choice for the diagnosis of fibrocartilaginous embolic myelopathy. MRI depicts the spinal

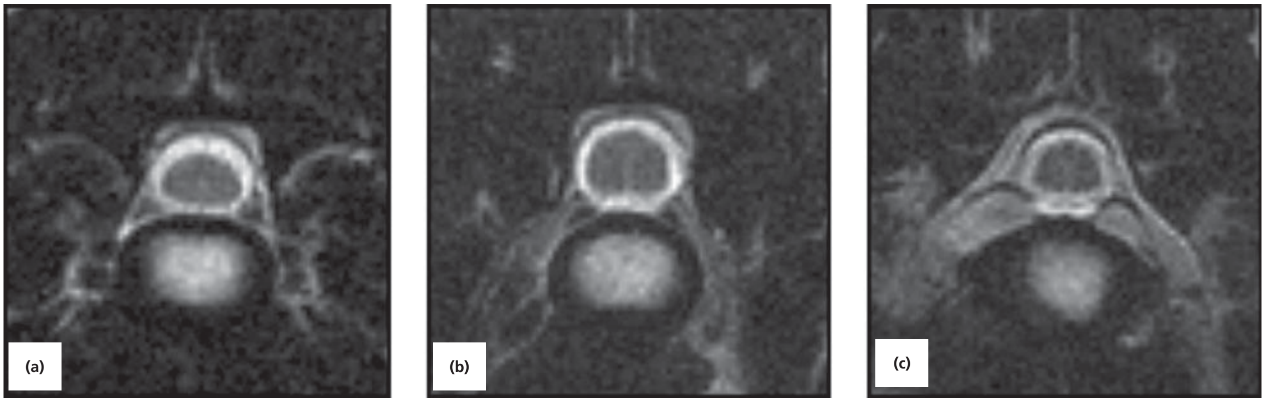


Figure 6.51 Transverse T2-W images (WI) at the level of the C2–C3 (A), C5–C6 (B), and C7–T1 (C) intervertebral discs of a clinically normal Doberman Pinscher. Notice the different shapes of the spinal cord at each cervical level. The normal spinal cord at C7–T1 has a trapezoid shape. (da Costa *et al.*, 2006. Reproduced with permission from American Veterinary Medical Association.)[15]

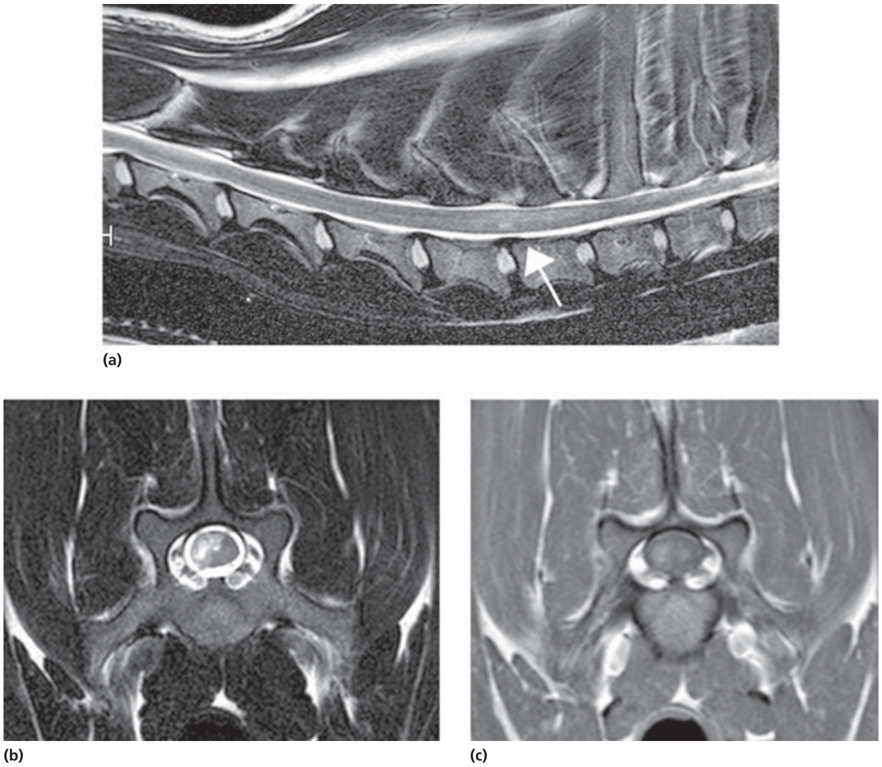


Figure 6.52 Fibrocartilaginous embolic myelopathy (FCEM). (A) Sagittal T2-WI of the cervical spine of a dog with the presumptive diagnosis of FCEM. Hyperintensity is seen at the level of the seventh cervical vertebra (C7) (arrow). (B) Transverse T2-WI at the level of C7 showing the asymmetric hyperintensity. (C) Transverse T1-WI postcontrast administration. Note mild contrast enhancement at the same level of the hyperintensity seen on 2B.

cord parenchyma allowing visualization of the ischemic spinal cord region. The appearance of FCEM on MRI is typically of a focal (although sometimes extensive) hyperintense T2-W lesion affecting primarily the gray matter and usually clearly asymmetric (Fig. 6.52). The lesion is commonly isointense on T1-W images but can also be hypointense. Contrast enhancement is not commonly seen, it was observed in only 12% of cases in a study. It is more likely to see contrast enhancement when MR imaging studies are performed five to seven days after the ischemic event. Spinal cord swelling is a common feature of FCEM. The severity of intramedullary lesions seen on MRI has been correlated with the severity of neurologic signs at presentation and with outcome. Interestingly, the presence of MRI changes was not associated with the timing of imaging. In some cases, primarily those imaged within 24 to 72 hrs after the ischemic injury, no signal changes are seen on MRI. These cases could be diagnosed with diffusion weighted MR imaging, although application of this technique in dogs is challenging.

Inflammatory spinal diseases

Discospondylitis[8, 10, 28, 29]

Discospondylitis has been, by convention, a radiographic diagnosis. Clinical signs often precede radiographic evidence of vertebral endplate lysis and medullary sclerosis, typically seen with more advanced disease. MRI is much more sensitive for detecting soft-tissue inflammation of the disc that usually precedes bony changes. MRI may be preferred to CT in order to screen for early cases of discospondylitis where bony changes are not observed radiographically. Two recent studies reported the MRI findings in dogs with discospondylitis. The vertebral body was typically hypointense or isointense in both T2- and T1-W images. The endplates were hypointense or had mixed intensity in T1-W images, with hyperintensity in STIR-W images in most dogs (Fig. 6.53). Contrast enhancement of endplates and paravertebral tissues was also frequently seen. The intervertebral discs were frequently hyperintense in T2-W and STIR images, isointense in T1-W images and had contrast enhancement in most cases.

Myelitis[24]

Myelitis is best evaluated with pre- and postintravenous contrast MR studies because contrast enhancement is a frequent finding (Fig. 6.54). Imaging features are very similar to, and are difficult to distinguish from, neoplasia. CSF analysis, surgical biopsy, and the patient's overall clinical picture are necessary to substantiate the diagnosis of myelitis. A recent study reported STIR muscle hyperintensity in the deep cervical muscles (longus colli) in dogs with meningomyelitis. The finding had a strong association with CSF changes.

Epidural empyema[21]

Epidural empyema is a neurologic emergency characterized by the accumulation of purulent material within the vertebral canal

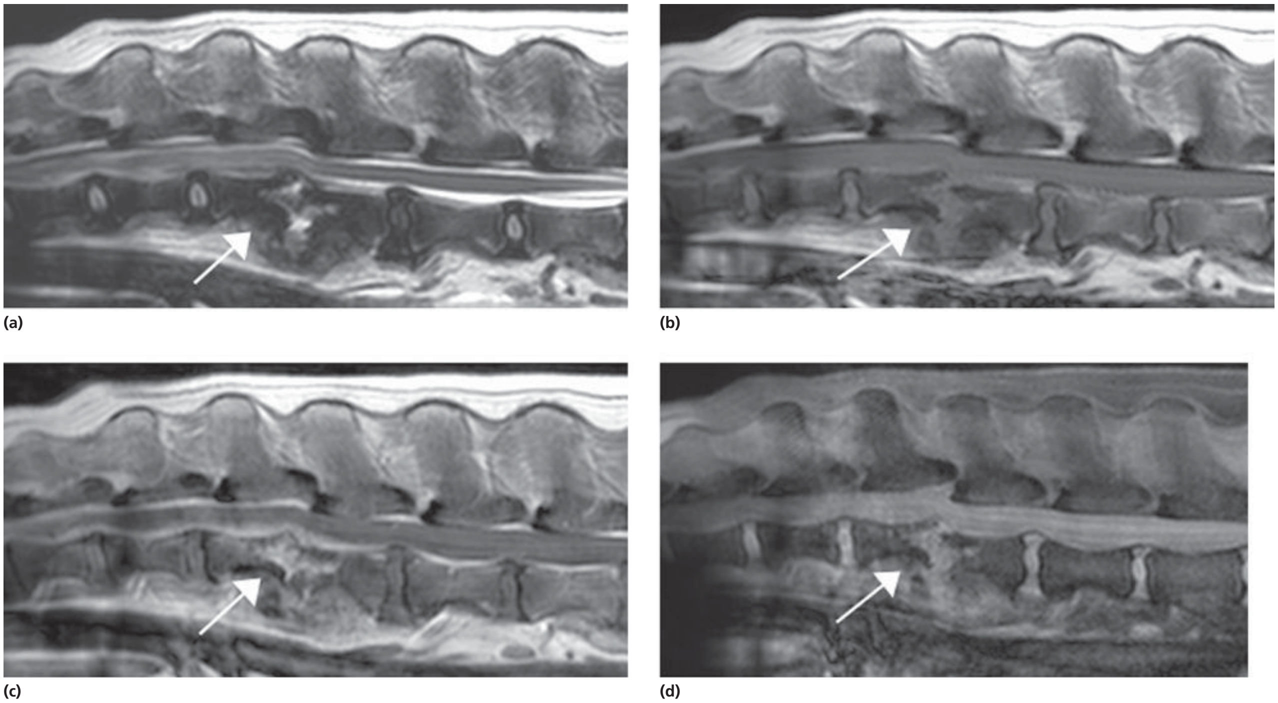


Figure 6.53 Discospondylitis. (A) Sagittal T2-WI showing subluxation between L1 and L2 with lysis of the endplates and intervertebral disc with heterogeneous hyperintensity of the endplates (arrow). Mild ventral spinal cord compression and spinal cord hyperintensity are also seen. (B) Sagittal T1-WI showing markedly irregular endplates with isointense signal of the intervertebral disc space. (C) Sagittal T1-WI postcontrast injection. Observe marked contrast enhancement of the intervertebral disc space, endplates, and peridural region. (D) STIR WI showing hyperintensity of the disc space and endplates.

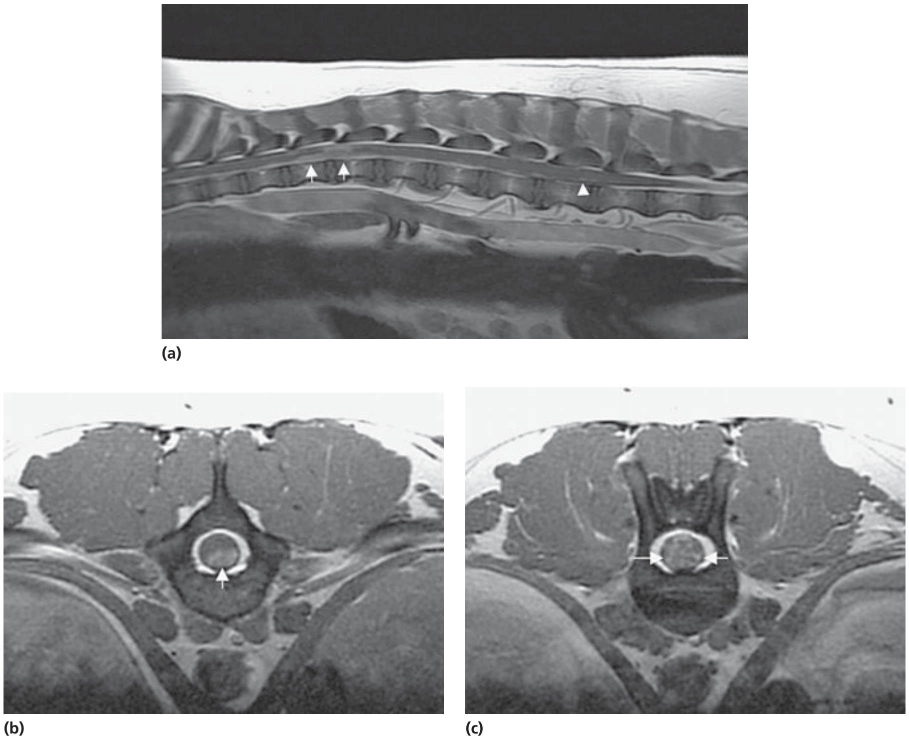


Figure 6.54 Myelitis—sagittal (A) and transverse (B, C) T1-W MR images after IV gadolinium injection showing the irregular areas of contrast enhancement in the spinal cord (arrows).

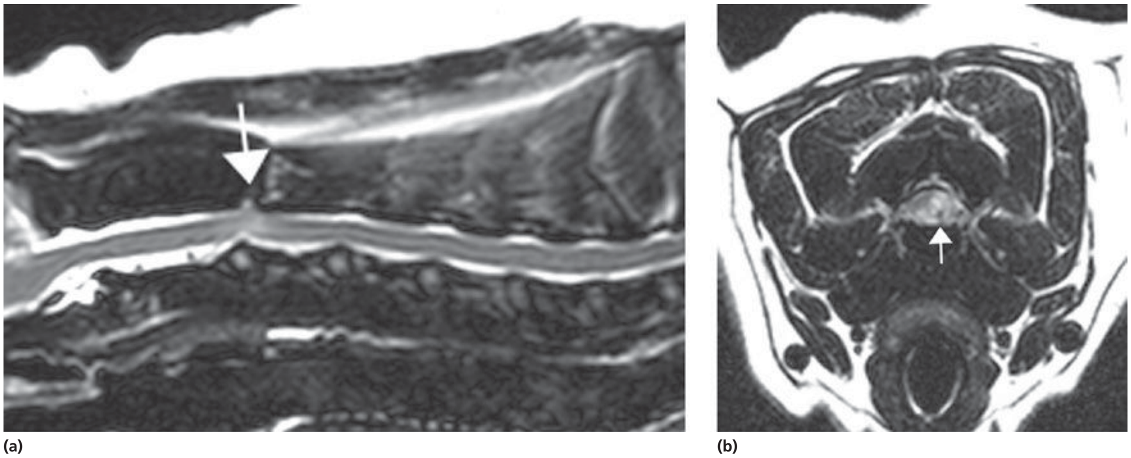


Figure 6.55 Traumatic intervertebral disc herniation. The patient suffered a traumatic injury and had an acute onset of tetraparesis. (A) Sagittal T2-WI shows a focal area of spinal cord hyperintensity between C2–C3. (B) Transverse T2-WI shows the hyperintensity within the spinal cord parenchyma with a focal area of hypointensity (arrow) thought to be a fragment of extruded disc material within the spinal cord (type III disc).

causing fever, spinal pain, and progressive neurologic dysfunction. Neurologic signs are secondary to the combined effects of regional tissue inflammation and spinal cord compression by an epidural mass effect. The epidural masses were hyperintense or had mixed intensity on T2-W, and were hypointense on T1-W images. Mild to moderate contrast enhancement was frequently observed. Spinal cord hyperintensity on T2-W images was a common finding in a study suggesting ischemia, extension of the infection, or focal malacia.

Spinal trauma[31, 32, 36, 41, 46]

Limited information is available on MRI and spinal trauma. In a study of 11 dogs with spinal fracture or subluxation, MRI identified rupture of soft-tissue structures and/or fracture of two vertebral compartments (based on the three-compartment theory; see Chapter 15) in most dogs. The majority of dogs had spinal cord changes (hyperintensity on T2-W images), hemorrhage, or swelling. Epidural hematoma was also identified in most dogs. Another study compared the diagnostic sensitivity of survey radiographs and CT in dogs with confirmed spinal fractures and luxations. Radiographs missed approximately 25% of the lesions detected on CT. CT is routinely used as the screening imaging of choice for spinal trauma in people due to its availability and rapidity of imaging. Studies in humans suggest that MRI and CT should be used as complementary modalities, as CT has exquisite bone resolution whereas MRI has superior soft-tissue resolution. It should be pointed out that large case series in people indicated that MRI may miss a significant proportion of osseous lesions identified on CT.

Traumatic intervertebral disc extrusion is important to be considered in cases of external trauma. In a recent series, the majority (71%) of traumatic disc extrusions did not cause spinal cord compression. MR of the affected area identified spinal cord hyperintensity on T2-W images and reduced the volume of nucleus pulposus of the intervertebral disc ventral to the area of hyperintensity. (Fig. 6.55).

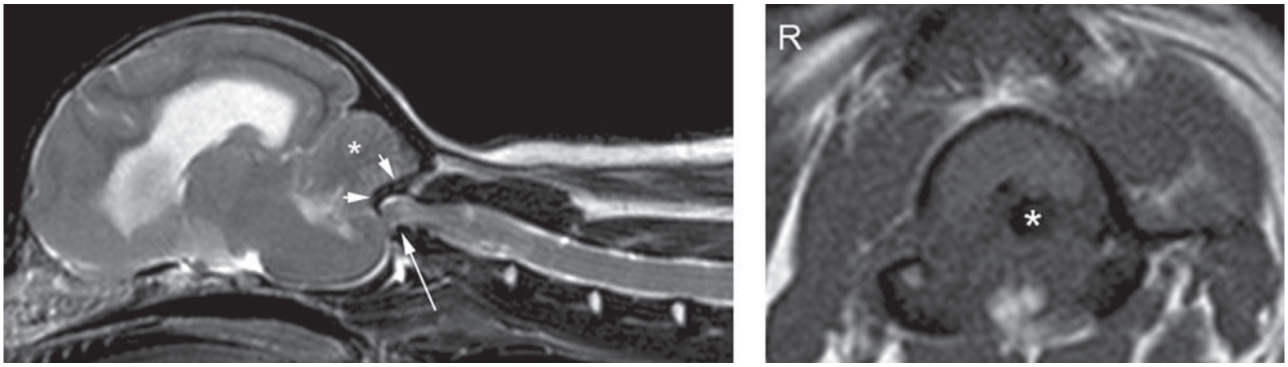
Congenital spinal diseases

Atlantoaxial subluxation[9, 50, 52]

Atlantoaxial subluxation or instability (AAS) is seen primarily in toy-breed dogs. Anatomic abnormalities associated with atlantoaxial subluxation include odontoid process (dens) malformation, hypoplasia, or aplasia, and/or weak or poorly developed supporting ligamentous structures of the odontoid process. The result may be subluxation or luxation of the atlantoaxial articulation, usually resulting in ventroflexion and a widened angle or space between the dorsal lamina of the atlas and spinous process of the axis (Fig. 6.56). If the odontoid process is intact and normally or partially formed, it may deviate dorsally within the spinal canal resulting in severe compression of the spinal cord, exacerbated by increased ventroflexion of the cranial cervical spine. MRI is sensitive for detecting secondary trauma to the spinal cord (hemorrhage, edema) secondary to instability at the articulations. The supporting ligaments can be visualized using high-field MRI and thin slices. Considering the possibility of concurrent neurologic diseases in these toy/small-breed dogs, it may be necessary to perform lumbar CSF collection to rule out inflammatory diseases.

Hemivertebra[4, 35]

Hemivertebra is commonly recognized in brachycephalic, screw-tail breeds. Besides the tail, the mid- to caudal thoracic spine is often affected to varying degrees. It results from abnormal, uneven growth between the two halves of one or more vertebrae during development, with often, incomplete fusion between the halves. Because of the abnormal vertebral



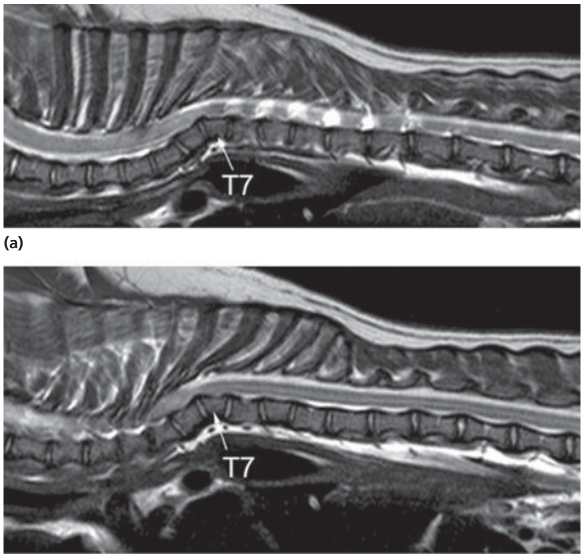
(a) (b)

Figure 6.56 Atlantoaxial subluxation. (A) Sagittal T2-WI showing the odontoid process as a hypointense structure ventral to the spinal cord (long white arrow). A curvilinear hypointensity caudal to the cerebellum (*) represents caudal occipital overlapping with medullary kinking (short white arrows). (B) Transverse T1-WI through the odontoid process (*). The normally oval spinal cord has a kidney-bean shape secondary to ventral compression by the dorsally deviated odontoid process.

conformation, secondary spinal canal stenosis and spinal cord compression may occur. One of the greatest challenges in imaging these patients is that most patients have associated varying degrees of kyphosis, lordosis, and scoliosis. Achieving well-positioned planar images is difficult. CT is preferred for a better definition of bone. If neurologic deficits are present, MRI is preferred for spinal cord imaging (Fig. 6.57).

Spinal arachnoid diverticula ("cysts")[26,40,61,62,69]

These diverticula consist of outpouchings of the arachnoid matter or focal dilatations in the subarachnoid space that are filled with CSF. The use of the term "cyst" to describe these lesions is a misnomer, as these outpouchings are not lined by epithelium.



(a)

(b)

Figure 6.57 Hemivertebrae. Sagittal (A, B) T2-WI of the thoracolumbar spine of a French Bulldog with severe lordosis and scoliosis secondary to T7, T8, and T9 hemivertebrae.

These diverticula are commonly located in the cranial cervical (C2–C4) region in large-breed dogs (mainly the Rottweiler), whereas in small-breed dogs the thoracic and thoracolumbar region is more commonly affected. The clinical appearance of these cases is of a chronic progressive cervical or thoracolumbar myelopathy (depending on the location of the diverticulum) frequently associated with fecal and/or urinary incontinence. There is still discussion as to whether these diverticula are congenitally acquired or secondary to trauma, arachnoiditis, intervertebral disc disease, previous surgery, hematomas, or meningitis. It has also been postulated that the arachnoid adhesions, rather than the subarachnoid outpouchings, are the cause of spinal cord compression and the resultant neurologic deficits. As the Rottweiler breed is overrepresented, a genetic or hereditary component is likely in at least some patients. CT myelography and MRI are equally adept at identifying cyst-like lesions of the subarachnoid space. MRI appearance is of a focal accumulation of CSF, usually dorsally, with the cranial aspect ending abruptly with a "tear-drop" appearance. The MR myelogram sequence may be particularly useful to identify these dilations (Fig. 6.58). Spinal cord hyperintensity on T2-W images may also be seen associated with the subarachnoid dilation.

Spinal neoplasia[7,14,22,23,42,43,51,59,60]

Spinal neoplasia is an important differential diagnosis for dogs presenting with either chronic or acute neurologic signs. Several classification systems are used to categorize spinal neoplasms. A common classification categorizes the tumors according to the location into: extradural, intradural extramedullary, and intramedullary. Extradural tumors such as osteosarcoma and fibrosarcoma are the most common.

Both CT and MRI are sensitive techniques for the diagnosis of spinal tumors. Due to the superior soft-tissue resolution, MRI is usually the preferred imaging method; however, CT is excellent for the visualization of osseous lesions, which are commonly observed in spinal tumors.

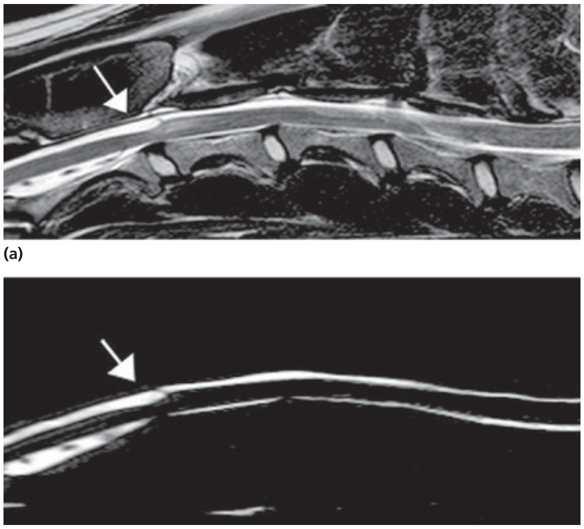

(a)
(b)

Figure 6.58 Spinal arachnoid diverticula. (A) Sagittal T2-WI showing a teardrop shape accumulation of CSF dorsally between C2–C3 (arrow). (B) HASTE sequence (MR myelogram) showing the conspicuous dilation of the dorsal subarachnoid space.

Lytic and proliferative regions observed on imaging need to be differentiated from infections such as discospondylitis or vertebral osteomyelitis. As a general rule, lytic and proliferative lesions located in the vertebra itself are typical or neoplasia, while lytic/proliferative lesions centered at the disc space are caused by infections (discospondylitis). In one study, myelography was more useful in differentiating between intradural extramedullary and intramedullary tumors than CT. This same observation was made when comparing myelography and MRI in another study. Careful evaluation of the images in all three planes (transverse, sagittal, dorsal) may assist in defining the location of the tumor. Dorsal images are particularly useful. The MRI findings of spinal meningiomas, the most common intradural tumor, have been well described. Most meningiomas are iso- to hyperintense on T1-W images and hyperintense on T2-W images. Homogeneous, strong contrast enhancement, and presence of dural tail are also consistently observed (Fig. 6.59).

MRI findings for other spinal tumors have not been well described. Osseous tumors have very variable signal intensity, ranging from iso- to hyper- or hypointense on both T1- and T2-W images. Contrast enhancement is also variable. It is important to use fa- suppression techniques (e.g. STIR) when observing hyperintense lesions on T1- and T2-W images within osseous structures, as these changes may be caused by fat infiltration. Intramedullary tumors have more consistent imaging patterns. Due to the common presence of edema, hyperintensity on T2-W images and hypointensity on T1-W images, in relation to the surrounding spinal cord, is commonly observed. The pattern of enhancement is variable.

Primary or secondary nerve sheath tumors (NSTs) are the most common cause of neurogenic lameness. Approximately 45% of the tumors are located in the nerve roots proximal to

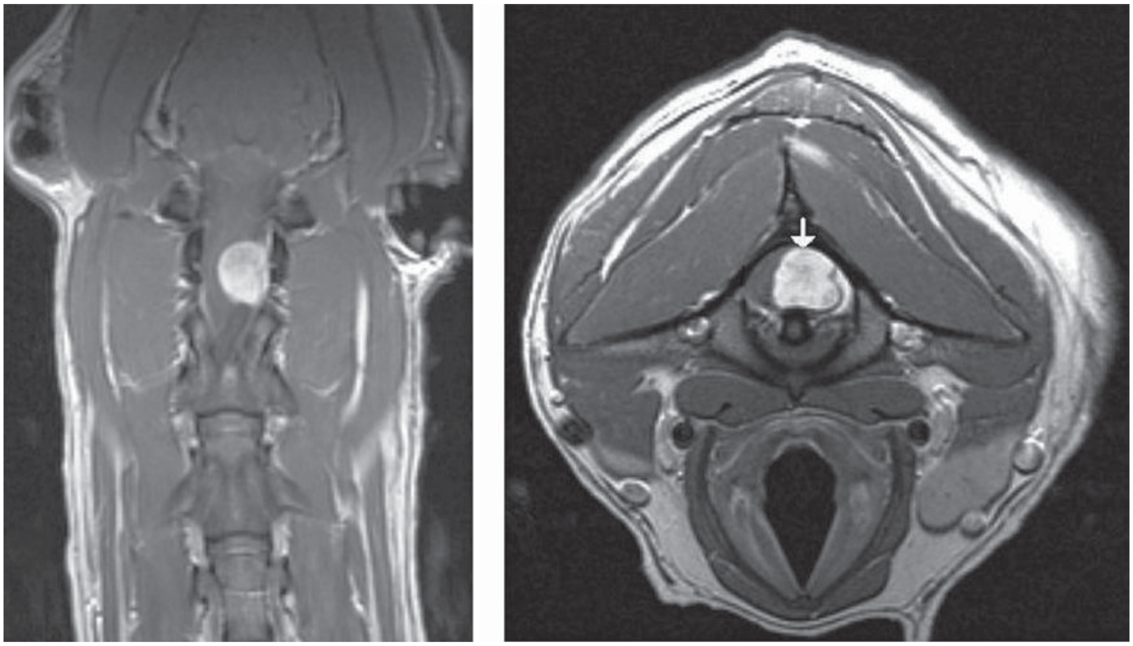

(a)
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Figure 6.59 Meningioma. T1-W MR images after IV gadolinium injection. (A) Dorsal and (B) transverse images show a large, mostly homogeneous, contrast-enhancing mass at the level of C1 and C2 (arrow). (From da Costa, RC. In Daleck CR, de Nardi AB, Rodaski S. *Oncologia em cães e gatos*. Guanabara: Koogan; 2009. Reproduced with permission.)

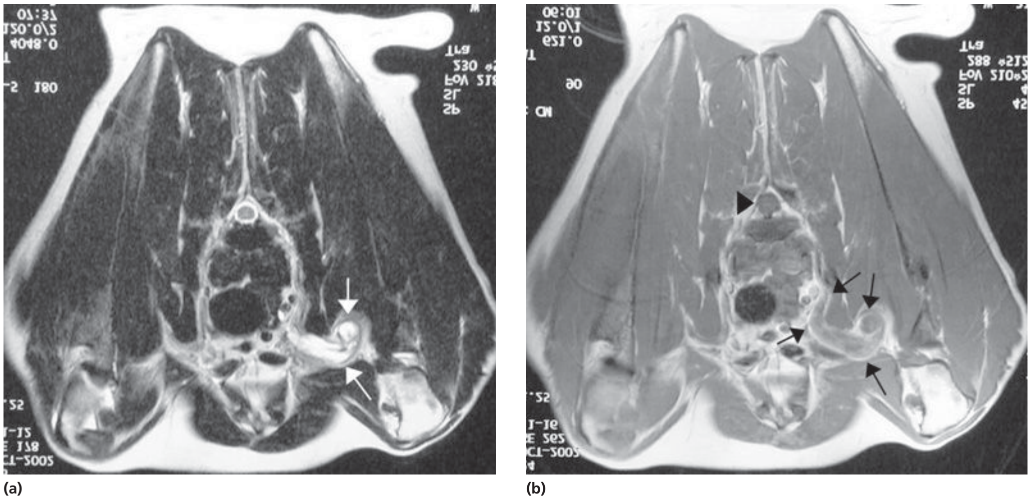

Figure 6.60 Primary malignant nerve sheath tumor—distal location. (A) Transverse T2-W MR image reveals a large hyperintense mass at the level of the left axilla just lateral to the first rib (arrows). (B) Transverse T1-W MR image post-IV gadolinium injection shows an inhomogeneously enhancing mass at the same level of (A; arrows). Arrowhead indicates the spinal cord.

the spinal cord, while 55% are located in the plexus area or peripheral nerves. This emphasizes the importance of using a larger field of view when imaging patients suspected of having NSTs. The imaging features of NSTs have been described using CT and MRI. The visualization of NST is facilitated using MRI. CT findings commonly observed in dogs with NSTs are rim enhancement and a hypodense center. On MRI, NSTs are consistently hyperintense on T2-W images, hypointense on T1-W images, and show homogeneous or inhomogeneous contrast enhancement (Fig. 6.60). The tumor may appear as a diffuse brachial plexus nerve thickening or a circumscribed mass (Fig. 6.61).

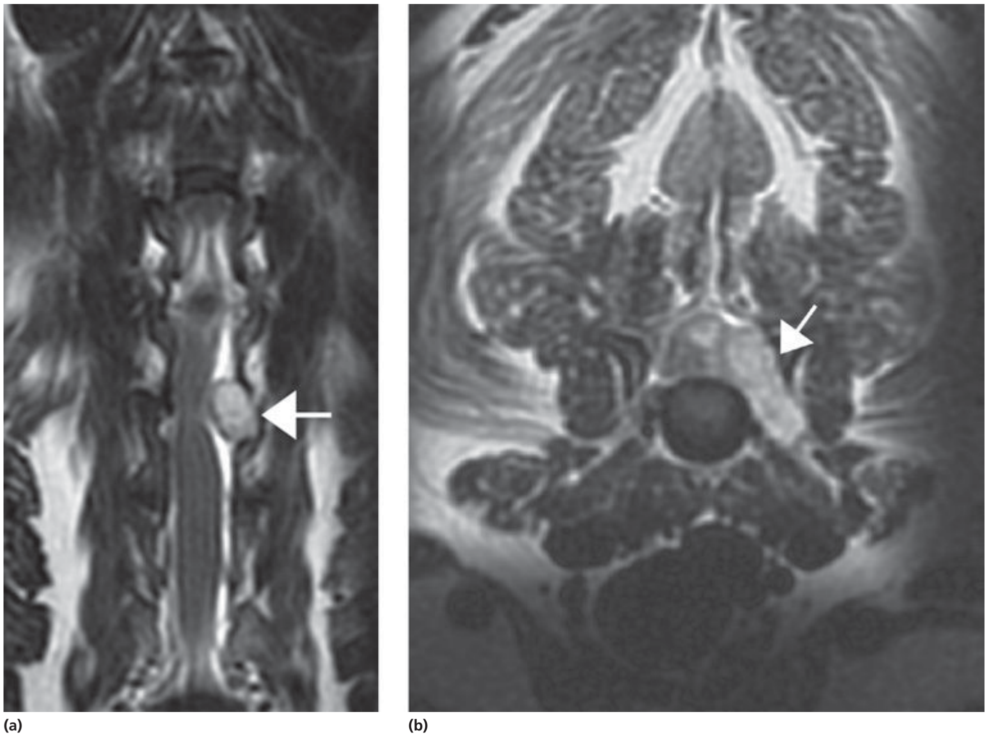

Figure 6.61 Primary malignant nerve sheath tumor—proximal location. (A) Dorsal T1-W MR image post-IV gadolinium injection shows an oval contrast-enhancing mass that appears to be displacing the spinal cord medially at the level of C5–C6 (arrow). (B) Transverse T1-W MR image at the level of C5–C6 shows a large contrast-enhancing mass involving the nerve roots and infiltrating into the spinal cord (arrow). (From da Costa, RC. In Daleck CR, de Nardi AB, Rodaski S. *Oncologia em cães e gatos*. Guanabara: Koogan; 2009. Reproduced with permission.)

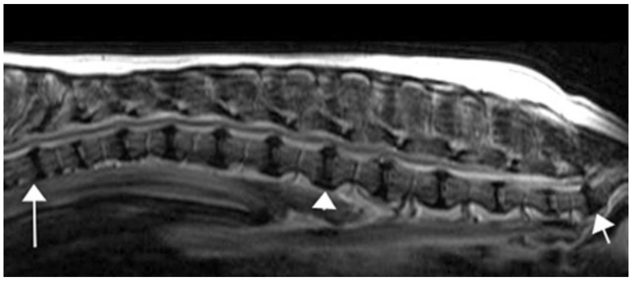

Figure 6.62 Multiple sites of thoracolumbar intervertebral disc protrusion in a 9-yr-old German Shepherd. Variable degrees of spinal cord compression are seen at almost every single disc space starting at T9–T10 (long arrow). Compression is also seen at the lumbosacral space (short arrow). Intervertebral disc degeneration and spondylosis is also observed at multiple sites (arrowhead).

Biopsy is always needed to confirm the diagnosis of spinal or nerve sheath tumors, and to define the specific type of tumor. Depending on the location of the tumor, biopsy can be guided using CT or ultrasonography.

Degenerative and developmental diseases

Intervertebral disc disease (IVDD)[3, 5, 19, 25, 34, 45, 48, 56, 58, 62, 66, 68]

Intervertebral disc disease is the most common spinal disease of dogs, and should be a differential diagnosis in any dog older than 1 yr of age with spinal pain and myelopathic signs.

MRI allows clear visualization of IVDD. The normal nucleus pulposus of the intervertebral disc appears a hyperintense ellipsoid area on sagittal T2-W images. Intervertebral disc degeneration leads to a decrease in signal intensity and the degenerated disc becomes isointense to hypointense relative to the surrounding annulus fibrosus. The degree of brightness of the T2 signal of the nucleus pulposus correlates with the proteoglycan concentration but not with water or collagen concentration. MRI allows the detection of disc degeneration at earlier stages of the degenerative process, before mineralization occurs, which is when it can be visualized using CT and radiographs. It is important to emphasize that disc degeneration per se does not lead to clinical signs, except in uncommon cases of discogenic spinal pain. MRI also allows visualization of the spinal cord, which facilitates comparison when multiple sites are affected (Fig. 6.62). The size of the spinal cord and vertebral canal varies according to different spinal locations, so the same degree of disc protrusion may lead to different degrees of spinal cord compression according to the spinal location. Sagittal and transverse images should be used concurrently to assess the severity and lateralization of spinal cord compression (Fig. 6.63). It is common to observe lateralized disc extrusions causing nerve root compression, and this may not be seen on midsagittal images. Parasagittal images allow visualization of lateralized disc herniations and nerve root compression. Hemorrhage associated with disc extrusion can cause a signal void on MR images. GRE sequences can confirm the presence of hemorrhage.

MRI also allows assessment of the spinal cord parenchyma and detection of spinal cord signal changes. In cases with multiple sites of spinal cord compression, identification of hyperintensity on T2-W images indicates the site with the worst compression. The spinal cord hyperintensity seen on T2-W images correlate with the severity of clinical signs. The degree of severity of spinal cord compression, however, does not correlate with the severity of clinical signs. Three studies in dogs have indicated that the presence and extension of spinal cord signal changes have prognostic implications. A study suggested that areas of hyperintensity three times longer than the body of L2 were associated with poor prognosis, with only 20% of dogs with this signal change regaining ambulatory status. The presence of hyperintensity was a more reliable prognostic indicator than absence of nociception (deep pain perception). Even in noncompressive intervertebral disc extrusions, the extent of spinal cord hyperintensity predicted the outcome.

Chronic disc extrusions may be associated with inflammatory reaction surrounding the extruded disc leading to a ring enhancement pattern surrounding the disc (Fig. 6.64). The image may be mistaken as a granulomatous or neoplastic lesion. It is important to be aware of this imaging feature of IVDD to avoid misdiagnosing it as other conditions. Intervertebral disc herniation can cause many different types of imaging patterns and should always be considered in the differential diagnosis for unusual MRI findings. In contrast to nonenhanced CT, normal MRI findings in all three imaging planes rules out the diagnosis of IVDD.

Cervical spondylomyelopathy (CSM)[11–13, 17, 44, 47, 53, 63, 64]

Cervical spondylomyelopathy is characterized by static and dynamic spinal cord compressions. The disease is commonly caused by osseous compressions in young, giant-breed dogs and by disc protrusion in middle-age to older large-breed dogs. Both MRI and CT have been used in the diagnosis of CSM in dogs. When planning advanced imaging studies of the cases suspected of having CSM, it is important to plan the FOV to cover the entire cervical spine up to the third thoracic vertebrae. A recent study found compressions at T1–T2 and T2 associated with other cervical compressions in almost 10% of dogs.

MRI has been considered the best imaging technique for humans with cervical spondylotic myelopathy for more than 20 yrs. CT myelography is still used in humans for equivocal cases where cervical radiculopathy secondary to foraminal stenosis is the main clinical problem. The main advantage of MRI over CT myelography is the ability to directly visualize the spinal cord. This allows the detection of spinal cord signal changes that are helpful to determine the primary spinal cord lesion(s) in cases with multiple compressions (Fig. 6.65). Two studies indicate that multiple spinal compressions are seen in 63% of dogs with CSM.

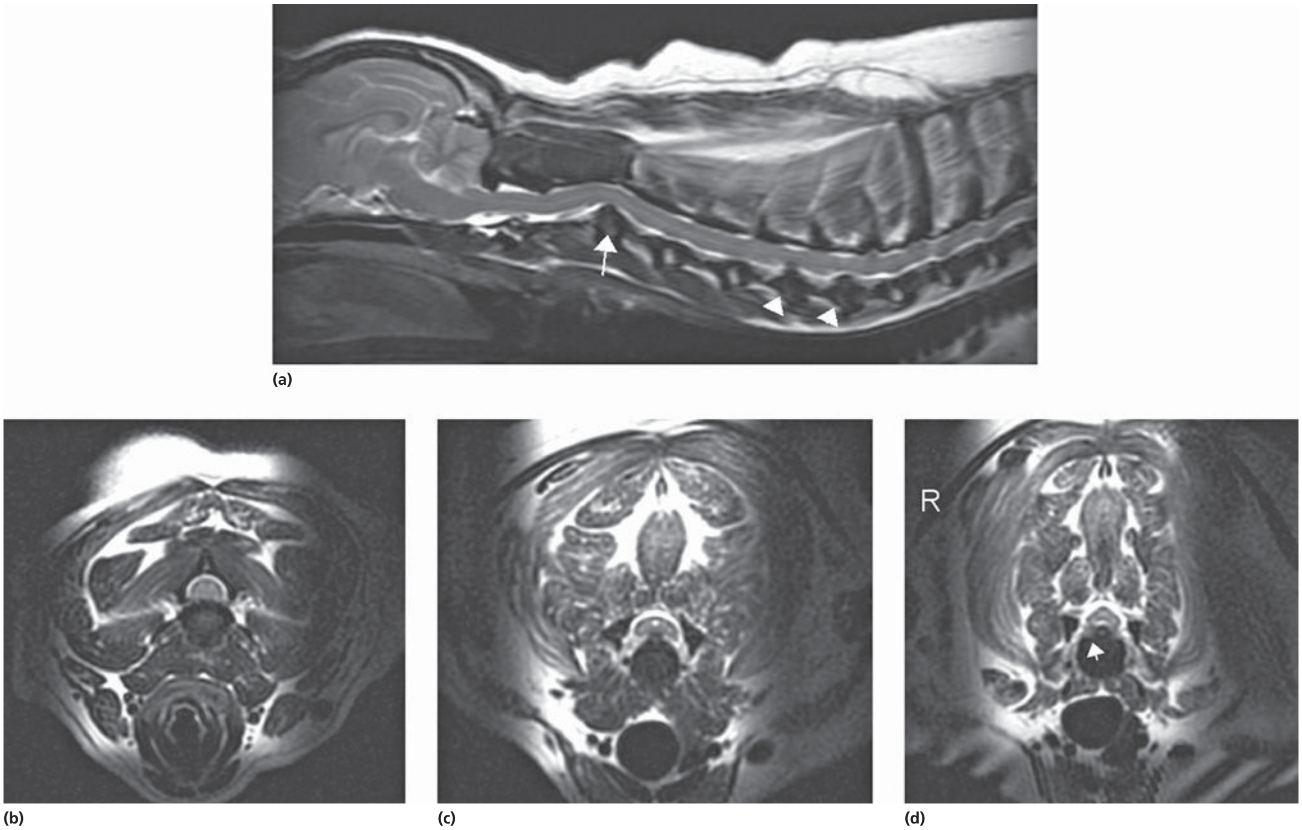

Figure 6.63 Multiple sites of cervical intervertebral disc disease. (A) Sagittal T2-W MR image shows a large ventral extradural compressive lesion at the level of C2–C3 (arrow), with less severe disc protrusions at C5–C6 and C6–C7. Intervertebral disc degeneration is seen at all these sites. (B) Transverse T2-W MR image at the level of C2–C3 with a broad spinal cord compression. (C) Transverse T2-W MR image at the level of C5–C6 shows a centrally located disc protrusion with dilation of the central canal of the spinal cord. (D) Transverse T2-W MR image at the level of C6–C7 shows ventral compression of the spinal cord and nerve root on the right side (arrow). The nerve root compression was causing lameness of the right thoracic limb.

A study compared MRI and myelography for dogs with CSM. It was concluded that MRI allows the identification of more sites of abnormalities than cervical myelography. Although myelography could identify the location of the lesion in most patients, MRI was more accurate in predicting the site, severity and nature of the spinal cord compression. Spinal cord signal changes were seen in the majority of patients and provided assistance in precise lesion identification. A study looked specifically at factors

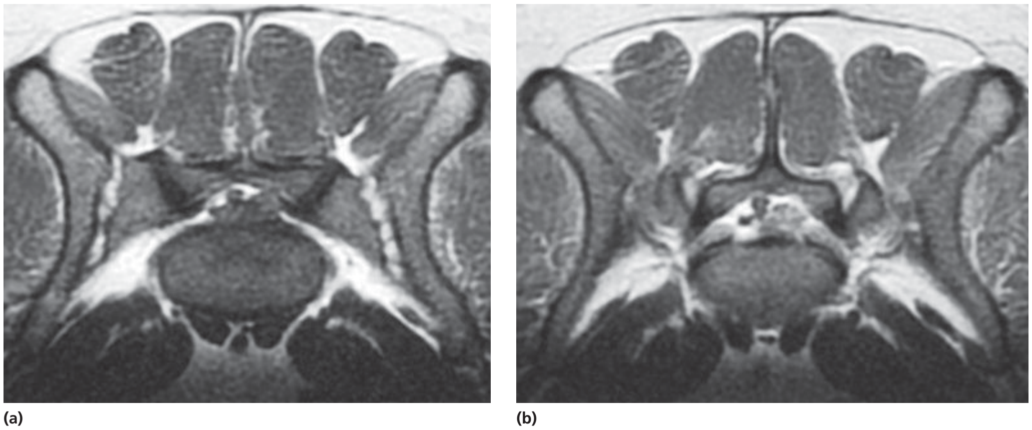

Figure 6.64 Transverse T1-WI at the level of L6–L7 before (A) and after (B) administration of contrast showing a focal area of contrast enhancement. The mass was confirmed to intervertebral disc extrusion at surgery.

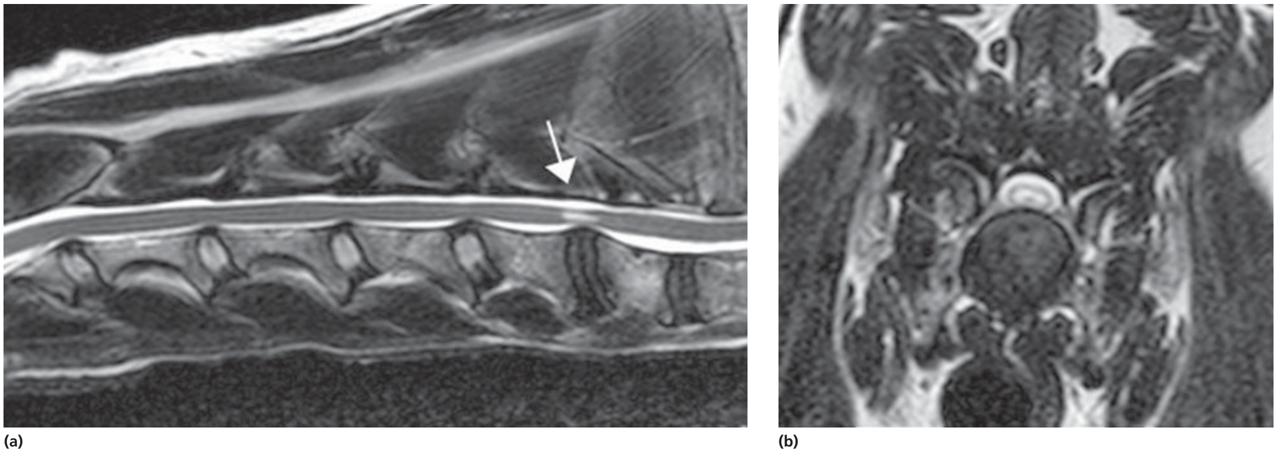

Figure 6.65 Cervical spondylomyelopathy—disc-associated. (A) Sagittal T2-W MR image showing ventral spinal cord compression at the level of C6–C7 with spinal cord hyperintensity (arrow). Mild spinal cord compressions are seen at C4–C5 and C5–C6. The intervertebral discs at C5–C6, C6–C7, and C7–T1 show various stages of disc degeneration. (B) Transverse T2-WI shows the location and extensive distribution of the area of hyperintensity.

associated with spinal cord signal changes (SCSC) in 102 dogs with CSM. The overall incidence of SCSC was 55.9%. SCSC were significantly more common in dogs with a chronic history, more severe neurologic deficits, and with moderate or severe spinal cord compressions. The location and direction of the compressive lesions had no influence on the development of SCSC in dogs with CSM. A recent study compared myelography, CT myelography, and MRI in 22 dogs with disc-associated CSM. The study found moderate agreement of all modalities in identifying the most severe compressive lesions and the authors conclude that CT myelography and MRI could be seen as complementary modalities. Another study in Great Danes with the osseous form of CSM also concluded that CT and MRI are complementary modalities.

Lumbosacral (LS) disease[3, 37, 38, 49, 67]

Lumbosacral disease, also known as degenerative lumbosacral stenosis (DLSS) or cauda equina syndrome, is a common disease of large-breeds dogs associated with nerve root compression at L6–L7 or L7–S1 vertebrae. Dogs with lumbosacral disease often present with lameness, paresis, and caudal lumbar or lumbosacral pain.

The degree of lumbosacral compression detected using MRI has no correlation with the severity of clinical signs. Fecal and urinary incontinence were observed in dogs with minimal LS compression, while other dogs had severe compression of the LS region and showed pain only without neurologic deficits. MRI usually reveals ventral compression caused by intervertebral disc degeneration and protrusion (Fig. 6.66). Intervertebral disc protrusion can be seen with the loss of the normal bright hyperintense signal of the intervertebral disc. Dorsal compression can also be observed caused by joint capsule thickening, osteophyte formation, and hypertrophy of the ligamentum flavum. Foraminal stenosis is an important component of the complex of the DLSS and the parasagittal and transverse images should be carefully examined. Transverse images allow assessment of the dorsoventral diameter of the foramina, while the parasagittal images allow evaluation of the craniocaudal diameter of the

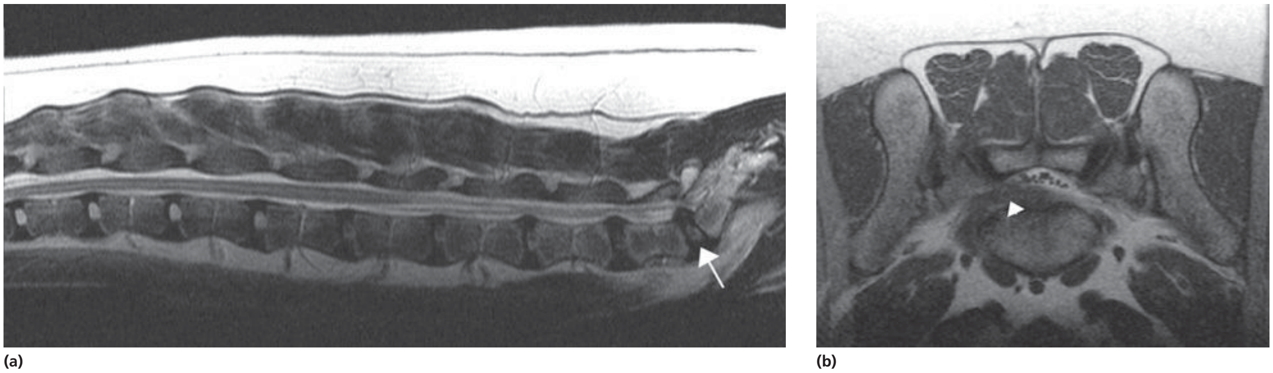

Figure 6.66 Degenerative lumbosacral stenosis. (A) Sagittal T2-WI showing severe ventral compression at the level of L7–S1. Milder compressions are also seen at L5–L6 and L6–L7, along with degeneration of the caudal lumbar intervertebral discs. (B) Transverse T2-WI at the level of the lumbosacral junction showing foraminal stenosis and nerve root compression secondary to asymmetric disc protrusion.

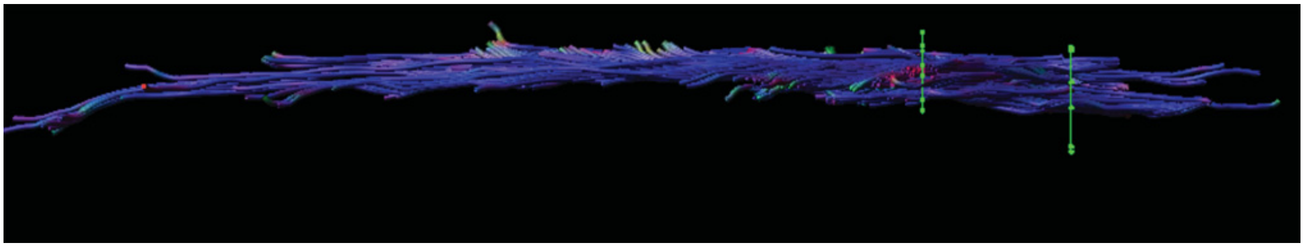

Figure 6.67 Tractographic image of the spinal cord of a dog with cervical spondylomyelopathy.

foramina. Dynamic studies of the LS spine can be performed; however, criteria for testing and normal reference ranges have not been established and so interpretation of the results can be problematic.

CT and MRI findings for LS disease showed a high agreement between both modalities; however, the correlation between CT or MRI findings with surgical findings is low. MRI and CT findings also had no correlation with outcome. It is also important to remember that clinically normal dogs can have imaging characteristics of LS diseases without clinical signs.

Closing remarks

The field of advanced imaging, primarily MRI, is continually growing in veterinary medicine and will likely expand to the routine application of advanced techniques such as diffusion tensor imaging (Fig. 6.67), MR angiography, and MR spectroscopy in the near future. These technical advances will likely have a remarkable impact in our ability to understand several disease processes of the brain and spinal cord.

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CHAPTER 7

Encephalopathies: Disorders of the Brain

Curtis W. Dewey

Introduction

This chapter focuses on brain diseases other than head trauma and cerebellar disorders. These latter subjects are discussed in detail in Chapters 8 and 12, respectively. There are a large number of diseases that can affect the brain, the majority of which are discussed in this chapter. Seizures will be mentioned where appropriate, but the important subject of seizure disorders and their management is discussed in detail in Chapter 9. Many of the disease processes that affect the brain can cause dramatic clinical signs, which can be very upsetting to the owner and even the clinician. However, many of these diseases can be successfully treated. The clinician should be cautious not to rush into making prognostic decisions based primarily on clinical appearance.

Clinical signs of brain dysfunction (see also Chapters 2 through 4)

A. Cerebrum/diencephalon (forebrain)
   Dogs and cats with forebrain dysfunction may exhibit clinical signs that include altered mental status (obtundation more likely than stupor or coma), behavioral changes, circling in a wide arc, head-pressing, visual impairment, focal and/or generalized seizure activity, and hemi-inattention (unilateral hemineglect) syndrome. The combination of conscious proprioceptive deficits with a normal to near-normal gait is characteristic of forebrain dysfunction. Neck pain may be appreciable in patients with structural brain lesions.

B. Brain stem (caudal to the diencephalon)
   Lesions from the midbrain (mesencephalon) through the medulla myelencephalon) may lead to altered mental status (stupor or coma more likely than with forebrain lesions), proprioceptive and gait abnormalities, deficits in s (CN) III–XII, and central vestibular dysfunction.

Disorders affecting the brain in dogs and cats (Table 7.1)

A. Degenerative
   1. Lysosomal storage disease (Table 7.2)[19, 21, 23, 24, 28, 35, 43, 44, 49, 66, 68, 77, 78, 89, 98, 106, 107, 113, 114, 145, 149, 150, 172–174, 176, 178, 183, 184, 194, 195, 202, 225–227, 255, 278, 279, 281, 296, 324–328, 336–338, 340, 343, 345, 355, 356, 363, 371, 372, 379, 384, 386, 435, 436, 441, 442, 453, 459, 477, 489, 490, 498, 500, 506, 527, 566, 567, 577, 579, 590, 616, 619, 622–624, 627, 643, 654, 656, 659, 660, 663, 665, 670, 678, 684, 691, 704, 708, 722, 753–756, 760–762, 765, 781–787]
      a. This disease category comprises a wide variety of inherited (most are autosomal recessive) abnormalities, which have in common the intracellular accumulation of one or more products of an interrupted degradative metabolic pathway. In the normal animal, substances that need to be catabolized within the cell typically undergo a stepwise degradation by a sequential chain of specific lysosomal enzymes. If one or more than one enzyme (acid hydrolase) in the chain of degradation is absent or defective (e.g. deficiency of an activator protein for that enzyme, deficiency of a lysosomal transport protein for the substance to be degraded), the substance prior to that enzymatic step accumulates. The accumulated by-product(s) will lead to cellular dysfunction, presumably due to cellular swelling, a toxic effect of the accumulated material(s), or both. In globoid cell leukodystrophy (Krabbe's disease), the deficient enzyme leads to the accumulation of a sphingolipid called psychosine. Psychosine is toxic to oligodendrocytes and Schwann cells, so white matter in both the central (CNS) and peripheral nervous systems (PNS) is affected. The lysosomal storage diseases are subdivided into groups in Table 7.2, according to the nature of accumulated storage products. For many of these diseases, the specific genetic defect responsible for the enzymatic deficiency has been identified. Specific breeds reported with these various conditions are provided in the table.

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Table 7.1 Encephalopathies of dogs and cats.

Degenerative	Lysosomal storage disease Leukodystrophy/spongy degeneration Neuronal vacuolation of Rottweilers and Boxer dogs Multisystem neuronal degeneration/abiotrophy of Cocker Spaniels Cognitive dysfunction syndrome (CDS)
Anomalous/ Developmental	Congenital hydrocephalus Caudal occipital malformation syndrome (COMS) Intracranial arachnoid cyst (IAC) Neuronal migration disorders Dandy–Walker syndrome (DWS) Miscellaneous malformations
Metabolic	Hepatic encephalopathy Renal-associated encephalopathy Hypoglycemic encephalopathy Electrolyte-associated encephalopathy Miscellaneous endocrine-related encephalopathies Acid-base disturbance encephalopathy Mitochondrial encephalopathy Organic acidurias
Neoplastic	Primary brain tumors Secondary brain tumors
Nutritional	Thiamine deficiency
Inflammatory/ Infectious	Bacterial meningoencephalitis Fungal meningoencephalitis Viral meningoencephalitis Protozoal meningoencephalitis Rickettsial meningoencephalitis Verminous meningoencephalitis Miscellaneous infections meningoencephalitides Granulomatous meningoencephalitis (GME) Necrotizing meningoencephalitis of small-breed dogs Eosinophilic meningoencephalitis Hydrocephalus with periventricular encephalitis (HPE)
Ischemic/Vascular	Global ischemia Thromboembolic disease (nonhemorrhagic/hemorrhagic infarcts)

b. For most of these diseases, affected animals are normal at birth, and develop a progressive multifocal to diffuse encephalopathy within the first several weeks to several months of life. Many of the storage disorders have the common feature of cerebellar dysfunction as an early sign of disease. Examples include mannosidosis, the gangliosidoses (GM1, GM2), globoid cell leukodystrophy (Krabbe's disease), glucocerebrosidosis (Gaucher's disease), and sphingomyelinosis (Niemann–Pick disease). Forebrain dysfunction predominates, at least in the disease's early stages, in neuronal glycoproteinosis (Lafora's disease), ceroid lipofuscinosis (Batten's disease), and fucosidosis. Dogs with Lafora's disease typically develop clinical signs of dysfunction (seizures, dementia) within the first year of life (Video 14). Ceroid lipofuscinosis and fucosidosis are unique among the lysosomal storage disorders in their relatively late onset of clinical signs. Although clinical signs of neurologic dysfunction occasionally occur in dogs less than 1 yr of age for these two diseases, disease onset is typically in young adult dogs. Encephalopathic signs of ceroid lipofuscinosis initially manifest at 1–2 yrs of age, although the age range of disease onset is 6 mos to 10 yrs. Behavior changes and visual deficits are usually the first abnormalities noticed. The disease typically progresses over one to several years to include neurologic abnormalities such as seizures, ataxia, tremors, and hypermetric gait. Two cats that were reported with ceroid lipofuscinosis exhibited rapid deterioration of neurologic status. A form of ceroid lipofuscinosis that selectively involves neurons in the cerebellum and thalamus of adult dogs has been described. These dogs exhibited signs of progressive cerebellar dysfunction. Although the age range for onset of neurologic dysfunction in fucosidosis is 4–24 mos, most dogs begin to exhibit signs of an abnormality between 12 and 18 mos of age. Forebrain dysfunction (e.g. behavior change, circling) is evident initially, and progresses over 2–3 yrs to include signs such as ataxia, dysphagia, vision and hearing loss, nystagmus, and dysphonia. Enlargement of the ulnar nerves is often palpable in dogs with fucosidosis. The enlargement is due to both edema and infiltration of the nerves with lipid-filled phagocytes and Schwann cells.

Involvement of areas other than the brain is a feature of the lysosomal storage diseases that may affect the clinical manifestation of a particular disease, the accessibility of tissue for diagnostic purposes, or both. Organomegaly (e.g. hepatomegaly, splenomegaly) is apparent upon physical examination for some of these diseases, due to accumulation of storage products in cells of the abdominal organs. Skeletal abnormalities (e.g. craniofacial malformation, joint immobility) are a common feature of mannosidosis, the mucopolysaccharidoses, and mucolipidosis II. Pelvic limb paresis often develops in cases of mucopolysaccharidosis and mucolipidosis, due to impingement of the spinal cord by bony vertebral growths invading the vertebral canal. Skeletal abnormalities and widened intervertebral disc spaces may also occur in gangliosidosis of English Springer Spaniels and Portuguese Water dogs. Dwarfism associated with gangliosidosis has been described in English Springer Spaniels. Involvement of the PNS may occur with fucosidosis, globoid cell

Table 7.2 Lysosomal storage diseases of dogs and cats.

Disease subgroup	Storage disease	Deficiency	Reported breeds
Glycoproteinoses	Fucosidosis	α-L-fucosidase	English Springer Spaniel
	Mannosidosis	α-D-mannosidase	Domestic Shorthaired cat Domestic Longhaired cat Persian cat
	Neuronal glycoproteinosis (Lafora's disease)	Unknown	Basset Hound Beagle Poodle Wire-haired Miniature Dachshund Mixed-breed dog
	Galactosialidosis	Protective protein/cathepsin A (protects lysosomal degradation of β-galactosidase and neuraminidase)	Schipperke
Oligosaccharidoses	Glycogenosis type Ia (von Gierke disease)	Glucose-6-phosphatase	Maltese[a]
	Glycogenosis type II (Pompe's disease)	α-glucosidase	Lapland dog Domestic Shorthaired cat
	Glycogenosis type IIIa	glycogen debranching enzyme (AGL gene)	Curly-Coated retriever
	Glycogenosis type IV (Andersen's disease)	glycogen debranching enzyme	Norwegian Forest cat
Sphingolipidoses	Gangliosidosis (GM1) type I (Norman-Landing disease)	β-galactosidase	Beagle cross[b] English Springer Spaniel Domestic Shorthaired cat Siamese cat
	Type II (Derry's disease)	β-galactosidase	Alaskan Husky Portuguese Water dog Shiba dog Korat cat Domestic Shorthaired cat Siamese cat
	Gangliosidosis (GM2)type I (Tay-Sachs' disease)	Hexosaminidase A	German Shorthaired Pointer Japanese Spaniel
	Type II (Sandhoff's disease)	Hexosaminidase A and B	Golden Retriever Domestic Shorthaired cat Korat cat
	Glucocerebrosidosis (Gaucher's disease)	β-D-Glucocerebrosidase	Sydney Silky Terrier
	Globoid cell leukodystrophy (Krabbe's disease)	β-D-Galactocerebrosidase	Basset Hound Beagle Blue Tick Hound Cairn Terrier Irish Setter Miniature Poodle Pomeranian West Highland White Terrier Domestic Shorthaired cat Domestic Longhaired cat
	Sphingomyelinosis (Niemann–Pick disease)		
	Type A	Sphingomyelinase	Miniature Poodle Balinese cat Siamese cat
	Type B	Cholesterol esterification deficiency	Boxer dog Domestic Shorthaired cat
	Type C	NPC1 mutation (protein function unknown)	Domestic Shorthaired cat
	Metachromatic leukodystrophy	Arylsulfatase A	Domestic Shorthaired cat

(*continued*)

Table 7.2 (*Continued*)

Disease subgroup	Storage disease	Deficiency	Reported breeds
Mucopolysaccharidoses	Mucopolysaccharidosis type I (Hurler's disease, Scheie disease, Hurler/Scheie disease)	α-L-iduronidase	Mixed-breed dog Plott hound Rottweiler Domestic Shorthaired cat[c]
	Mucopolysaccharidosis type II (Hunter disease)	Iduronate-2-sulfatase	Labrador Retriever Miniature Pinscher Domestic Shorthaired cat Siamese cat
	Mucopolysaccharidosis type III A and B (Sanfilippo disease)	Heparan-N-sulfatase (type A)N-acetyl-α-D-glucosaminidase (type B)	Dachshund (type A) New Zealand Huntaway dog (type A) Schipperke dog (type B)
	Mucopolysaccharidosis type VI (Maroteaux-Lamy disease)	Arylsulfatase B	Chesapeake Bay Retriever Miniature Pinscher Miniature Schnauzer Welsh Corgi Domestic Shorthaired cat Siamese cat
	Mucopolysaccharidosis type VII (Sly disease)	β-D-glucuronidase	German Shepherd dog Mixed-breed dog Domestic shorthaired cat
	Mucolipidosis II (I-cell disease)	N-acetylglucosamine-1-phosphotransferase	Domestic Shorthaired cats
Proteinoses	Ceroid lipofuscinosis (Batten's disease)	Cathepsin D[d]	American Bulldog American Pit Bull Terrier[e] American Staffordshire Terrier[e] Australian Cattle dog
		CLN5[d]	Border Collie Chihuahua Cocker Spaniel Corgi
		CLN2 (TTP1)[d]	Dachshund Dalmatian
		CLN8[d]	English Setter Golden Retriever Labrador Retriever Miniature Schnauzer Polish Owczarek Nizinny dog Queensland Blue Heeler Saluki Terrier crossbreed Tibetan Terrier Yugoslavian Sheepdog Domestic Shorthaired cat Siamese cat

[a] Puppies display generalized seizures, obtundation, tremors, and weakness associated with hypoglycemia.

[b] Exhibited features of type I and type II disease.

[c] These cats have an increased risk for developing intracranial meningioma.[230]

[d] Specific enzyme and/or genetic defect has been identified for this breed.

[e] Exhibited adult onset degeneration of cerebellar and thalamic nuclei with lipopigment accumulation in affected cells.[529]

leukodystrophy, the glycogenoses, and sphingomyelinosis (Niemann–Pick disease). Several genes necessary for normal myelin assembly have been shown to be down regulated in dogs afflicted with fucosidosis. Myopathy is a prominent feature of the glycogenoses, but forebrain dysfunction may result from secondary hypoglycemia in some of these disorders. Corneal abnormalities have been observed in both gangliosidosis and mannosidosis of cats, and mucopolysaccharidosis type VII in dogs. Retinal degeneration has been reported in some dog breeds with ceroid lipofuscinosis (e.g. Tibetan Terrier, Miniature Schnauzer, Cocker Spaniel), and in cats with mucolipidosis II. Cardiac abnormalities can occur with the glycogenoses.

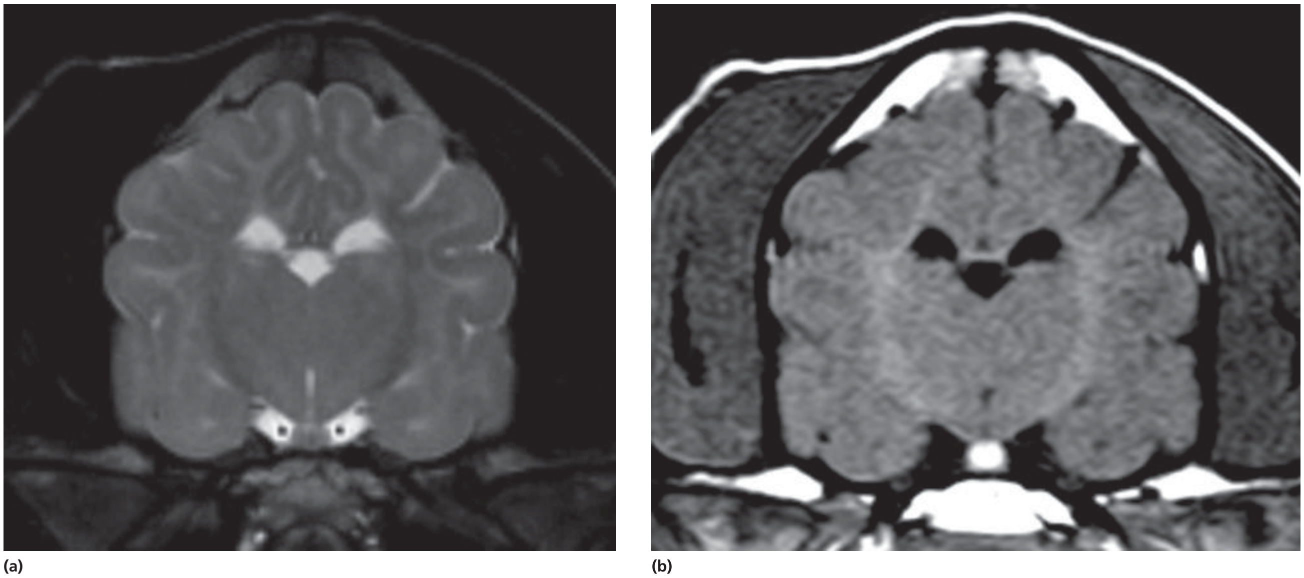


Figure 7.1 Transaxial T2-weighted (A) and FLAIR (B) brain images of a dog with gangliosidosis (GM1) demonstrating diffuse cerebral white matter hyperintensity. (Hasegawa *et al.*, 2012.)[279]

c. Tentative diagnosis of a lysosomal storage disease is based upon clinical signs of a progressive, multifocal/diffuse encephalopathy in a young animal, especially in a susceptible breed. Cerebrospinal fluid (CSF) analysis is usually normal but may reveal increased protein levels with a normal cell count. Abnormalities of the brain may be evident on computed tomography (CT) or magnetic resonance imaging (MRI; e.g. ventriculomegaly, brain atrophy, abnormal brain tissue density). In one study of canine gangliosidosis (GM1) in which sequential brain MR imaging was performed, early evidence (by 2 mos of age) of diffuse cerebral white matter hyperintensity on T2-weighted (T2-W) and FLAIR images was found, in addition to brain atrophy later (around 9 mos of age) in the disease course (Fig. 7.1). Definitive diagnosis of a specific lysosomal storage disease is typically made by the identification of the storage product (antemortem or postmortem; Fig. 7.2), documenting the deficient enzyme activity, and/or demonstrating the presence of the defective gene responsible for the disease. Whole blood leukocytes, tissue biopsy samples (e.g. liver), or

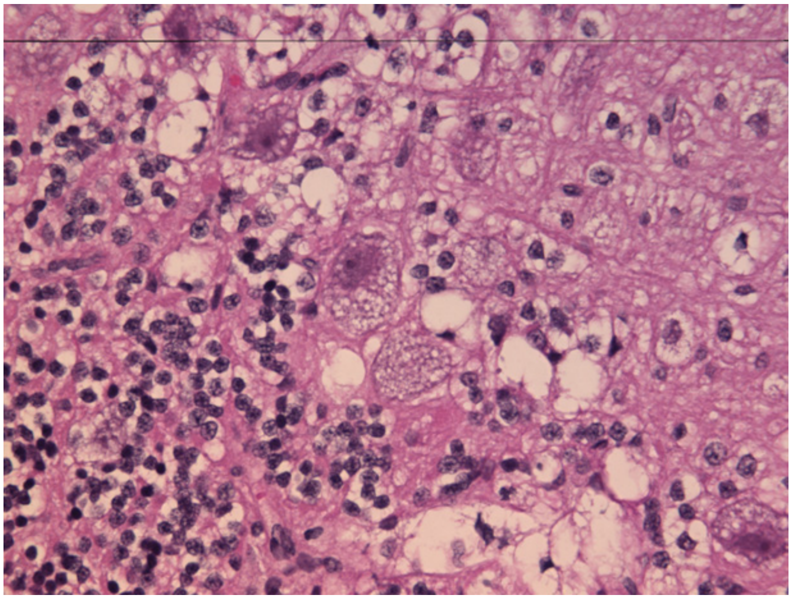


Figure 7.2 Brain histopathology of a cat with mannosidosis. Neurons swollen with storage product are evident. (Dr. Charles Vite, 2014. Reproduced with permission from Dr. Charles Vite.)

cultured fibroblasts can be used to demonstrate storage material and assay for deficient lysosomal enzyme activity. In some of the storage diseases (e.g. mannosidosis, mucopolysaccharidosis, fucosidosis), accumulated storage product can be identified in urine using specific assays. For many of the lysosomal storage diseases identified in veterinary patients, the specific genetic mutations responsible for the enzyme deficiencies have been identified and sequenced. It is now possible to diagnose some of the lysosomal storage diseases in dogs and cats by demonstrating the defective gene using a blood sample.

d. Treatment of lysosomal storage diseases is directed at reducing the accumulation of cellular storage products. Various methods are used in people to increase the specific deficient enzyme activity in order to achieve this effect. They include bone marrow transplantation (transplanting stem cells that produce the deficient enzyme), enzyme replacement therapy (recombinant enzyme administered parenterally to the patient), and gene therapy (transferring normal copies of the malfunctioning gene to the patient's cells for the specific disease using a viral vector). It has been shown that, in general, only about 5% of normal enzyme activity is necessary to prevent or reverse clinical signs associated with lysosomal storage diseases. Substrate reduction therapy (administering drugs that inhibit enzymes that produce the accumulated product) is a method to reduce the amount of substrate that should normally be degraded by the deficient enzyme. All of these options are associated with problems such as autoimmune responses to a transplanted foreign material, transient duration of effect, and inability to cross the blood–brain barrier. Despite these challenges, several successful interventions have been reported in dogs and cats with lysosomal storage diseases. Intravenous and/or intrathecal recombinant enzyme replacement therapy has been successfully used to treat canine fucosidosis, mucopolysaccharidosis type I, mucopolysaccharidosis type IIIA, and feline mucopolysaccharidosis type VI. Another promising therapeutic approach is the delivery of functional copies of the specific defective gene directly to the patient's brain (either intrathecally or intraparenchymally) using a viral vector. The functional copy of the gene becomes incorporated into the target cell, which then begins to produce the deficient enzyme (cell transduction). This therapeutic approach has been shown to be effective in the treatment of feline α-mannosidosis and canine mucopolysaccharidosis types I and IIIB. In one study, the oral treatment of cats afflicted by Niemann–Pick disease type C with an imino sugar called miglusat resulted in the delayed onset of neurologic signs and increased lifespan, as well as decreased accumulation of gangliosides (GM2) in neurons and prolonged Purkinje cell survival.

At present, the prognosis for lysosomal storage diseases remains guarded to poor. For many of these disorders, affected animals are euthanized due to progressively worsening neurologic dysfunction within the first year of life. For the more slowly progressive disorders (e.g. fucosidosis, ceroid lipofuscinosis), continuous neurologic dysfunction leads to death or euthanasia usually within 1–2 yrs of diagnosis. However, continued advances in molecular diagnosis as well as enzyme replacement and gene therapy for these disorders will likely lead to a more favorable prognosis for many lysosomal storage diseases in the near future.

2. Leukodystrophy/spongy degeneration[70, 98, 329, 436, 483, 485, 502, 615, 691, 752, 778, 794]

a. The leukodystrophies are thought to be due to abnormal synthesis (by oligodendrocytes) and/or maintenance of myelin in the CNS. This is a diverse group of rare, poorly understood, suspected heritable, progressive diseases. However, some of these enigmatic disorders are either suspected or have been proven to be mitochondrial encephalopathies or organic acidurias (discussed in this chapter). Some of these diseases produce clinical signs of a myelopathy rather than encephalopathy, and are discussed elsewhere (see Chapter 13). Leukodystrophy/spongy degeneration of the brain has been described as primarily affecting the white matter in Labrador Retrievers, Dalmatians, Silky Terriers, Samoyeds, Shetland Sheepdogs, Bull Mastiffs, a Scottish Terrier, a Miniature Poodle, and Egyptian Mau cats. The white matter leukodystrophy in Bull Mastiffs is a unique disorder that appears to represent an oligodendroglial dysplasia, an inherited primary disorder of oligodendroglial cells. Primarily gray matter spongy degeneration has been described in Bull Mastiffs, Salukis, Malinois/Shepherd mixed-breed dogs, Cocker Spaniel littermates, and Birman kittens.

b. Neurologic dysfunction typically begins within the first 6 mos of life, and progressively worsens. Clinical signs are variable, depending upon breed, but may include visual deficits, behavior changes, obtunded mental status, seizures, cerebellar dysfunction (tremors, ataxia), dysphagia, paraparesis, and tetraparesis. Similar to lysosomal storage diseases, a multifocal/diffuse disorder may be evident.

c. Tentative diagnosis is based upon typical clinical signs of dysfunction in a breed previously reported with leukodystrophy/spongy degeneration. Since these are progressive, fatal diseases, definitive diagnosis is based upon postmortem histologic findings of extensive CNS white matter loss, often with attendant vacuolation of the brain tissue (spongiform change). In some cases (e.g. Scottish Terrier, Miniature Poodle), astrocytic inclusion bodies, referred to as Rosenthal fibers, are identified. These latter cases have been termed fibrinoid leukodystrophy and are similar to a leukodystrophy in people called Alexander's disease. Histopathologic findings in Shetland Sheepdogs are reminiscent of another human leukodystrophy called Kearns–Sayre syndrome, which is now considered a mitochondrial encephalopathy.

d. There are no effective treatments for leukodystrophy/spongy degeneration of the brain of unknown cause. Potential treatments and prognoses for various mitochondrial encephalopathies and organic acidurias are discussed in those sections, respectively. The prognosis for the majority of leukodystrophy/spongy degeneration disorders is typically grave.

3. Neuronal vacuolation and spinocerebellar degeneration in Rottweilers and Boxer dogs[15,17,122,126,168,221,222,375,572,617,618,743]

a. This is a progressive, multifocal, degenerative CNS disorder of unknown etiology. It has been reported in 15 Rottweilers and one Rottweiler/German Shepherd cross. A nearly identical disorder was recently reported in two Boxer dog littermates. In addition, a very similar disorder has been reported in a mixed-breed dolichocephalic dog, with no apparent parentage from either Rottweiler or Boxer dog breeds. The hallmark of this disease is the histopathologic finding of intraneuronal vacuoles primarily in the brain stem, cerebellum, and spinal-cord gray matter. The vacuoles are reminiscent of scrapie-associated spongiform change, but there is no evidence for an infectious cause for this disease. In addition to widespread neuronal vacuolation in the CNS, axonal necrosis was demonstrated primarily affecting the dorsolateral and ventromedial funiculi of the cervical and thoracic spinal cord. Similar axonal necrosis has also been shown in the lumbar spinal cord, cerebellum, and brain stem. A selective distal neuropathy of the recurrent laryngeal nerves has also been shown to be a feature of this degenerative condition.

b. All Rottweiler dogs exhibited clinical signs of a progressive neurologic disorder between 6 and 16 wks of age, most within 2 mos of age. The Boxer dogs were presented at 6 mos of age. Affected puppies typically exhibit generalized weakness and ataxia (more prominent in the pelvic limbs), with a hypermetric gait. Proprioceptive placing reactions are abnormal. With the exception of one dog with hyporeflexive patellar reflexes, the spinal reflexes remain intact. A consistent clinical feature of the disease is inspiratory stridor, due to laryngeal nerve dysfunction. Other frequent abnormalities include positional strabismus, intention head tremor, and nystagmus. Pharyngeal dysfunction has also been reported. Some dogs with this disorder had concurrent congenital ocular abnormalities (cataracts, persistent pupillary membrane, microphthalmia, retinal dysplasia). Clinical signs progress over several weeks to include worsening of the paresis, laryngeal and pharyngeal dysfunction, and development of behavioral changes (in some dogs).

c. A tentative diagnosis is based upon the typical clinical signs and progression in a young Rottweiler. A definitive diagnosis is based upon histopathologic findings postmortem consistent with the disorder.

d. There is no treatment and the prognosis is grave. With the exception of one dog who survived for 9 mos following onset of clinical signs, these dogs were all euthanized within several months of disease onset due to disease progression.

4. Multisystem neuronal degeneration/abiotrophy in Cocker Spaniels[97,319,436,691]

a. A number of breeds have been described with suspected neuronal abiotrophy. Abiotrophy refers to the premature death of cells, presumably due to the lack of some factor necessary for cellular survival. Most of the abiotrophies described cause signs primarily or exclusively related to cerebellar dysfunction. A group of related Red-haired Cocker Spaniels was described with suspected neuronal abiotrophy. These dogs exhibited signs of both forebrain and cerebellar dysfunction.

b. The reported dogs developed clinical signs of neurologic dysfunction at approximately 1 yr of age. The clinical signs reflect both forebrain and cerebellar dysfunction and include behavior change, generalized seizures, intention tremor, ataxic and hypermetric gait, circling, vision loss, and proprioceptive deficits. The disease progresses slowly over several months.

c. Tentative diagnosis is based on clinical signs of a progressive multifocal/diffuse encephalopathy in a Cocker Spaniel dog. Definitive diagnosis is attained histopathologically. Widespread neuronal cell loss is evident throughout the brain in affected dogs.

d. Although this disorder is slowly progressive, there is no treatment and the prognosis is grave.

5. Cognitive dysfunction syndrome (CDS)[13,16,36,57,119,153,236,263–265,273,280,287–292,306,314,315,351,382,390–394,433,469–472,494,504,533,569–571,582,586,588,593,595–597,620,621,660,685,689,705,789,792]

a. An age-related syndrome similar to Alzheimer's disease (AD) in people occurs in elderly dogs and cats. Cognitive dysfunction syndrome is best described for the dog, and this species appears to be the best animal model available for human AD. Similar to AD of people, the pathophysiology of CDS is uncertain. There are pathologic similarities between the brains of humans with AD and dogs and cats with CDS.

Cerebral vascular changes, meningeal thickening, gliosis, and ventricular dilatation occur in the brains of both AD and CDS patients. More specifically, the progressive accumulation of a neurotoxic protein called beta-amyloid in the brain (in and around neurons) is a consistent feature in both AD and CDS. These accumulations coalesce to form plaques (neuritic plaques) and are most prominent in the frontal cerebral cortex and in the hippocampus in both human and veterinary disorders. In both disorders, the degree of beta-amyloid accumulation correlates with the extent of cognitive impairment. In addition to the accumulation of neurotoxic beta-amyloid (Aβ) protein in the aged canine and feline brain, intraneuronal accumulation of a hyperphosphorylated microtubular-associated protein (tau protein) has also been demonstrated. Tau protein is the precursor to neurofibrillary tangles (NFTs), another prominent histopathologic feature of human AD. The absence of mature NFTs in the brains of dogs and cats with CDS has been argued as evidence against CDS of dogs and cats being analogous to human AD. However, the absence of NFTs in dogs and cats has a number of potential explanations. It is possible that dogs and cats do not live long enough for the tau proteins to develop into NFTs as they do in people. While the amino acid sequence of Aβ protein is identical between humans and dogs, this is not the case for tau protein. The amino acid sequence of dogs and cats differs from that in people; this different sequence may affect the ability of tau protein to form NFTs. Other structural abnormalities found in the aging canine brain that are similar to those in humans include cerebral atrophy, ventricular enlargement, blood vessel wall fibrosis, and amyloid deposition (meningeal and parenchymal), microhemorrhages and infarcts, axonal degeneration with myelin loss, astroglial hypertrophy and hyperplasia, and intraneuronal accumulation of several substances (lipofuscin, polyglucosan bodies, ubiquitin). The pathophysiology of CDS and AD is multifactorial and complex. There is evidence in both diseases that increased oxygen free radical mediated cellular damage, decreased endogenous antioxidant defenses, inflammation (from various processes), decreased mitochondrial function, DNA damage, altered gene expression, vascular compromise, decreased capacity for neurogenesis (likely associated with hippocampal degeneration), synaptic dysfunction, and neurotransmitter imbalance are all interrelated processes that are involved in progressive cognitive impairment. There is some evidence in people with AD that neurovascular damage precedes the accumulation of Aβ protein. Since brain hypoxia can stimulate the production of Aβ protein (by altering amyloid metabolism enzymes) and accumulated Aβ protein around brain blood vessels leads to progressive vascular damage, it is clear that a self-perpetuating cycle of vascularly mediated brain damage occurs in AD and CDS.

Neurochemical changes that occur in the aging brain are thought to contribute to progressive cognitive impairment. An age-associated decline in the brain's neurotransmitter levels of acetylcholine, dopamine, norepinephrine, serotonin, and gamma-aminobutyric acid (GABA) have been documented in CDS and AD. Other neurochemical abnormalities identified in the brains of CDS and AD patients include increased acetylcholinesterase levels (associated with cholinergic decline), increased monoamine oxidase B (catalyzes the breakdown of dopamine, with a subsequent formation of free radicals), and elevated CSF levels of lactate, pyruvate, and potassium.

b. Cognitive dysfunction syndrome is recognized primarily in elderly dogs (more than 9 yrs) and cats (more than 12 yrs), but should be suspected in animals 7 yrs or older that are demonstrating progressive cognitive impairment. It is likely that many pets with mild cognitive impairment are not reported as such and that the majority of CDS patients seen by veterinarians are severely impaired, similar to human AD patients. Clinical signs of CDS are numerous and often nonspecific. They include inattentiveness, inactivity, aimless wandering (often pacing at night), walking in circles, demented behavior, disturbance of the sleep/wake cycle, urinary and/or fecal incontinence, difficulty navigating stairs, becoming lost in previously familiar environments, attempting to pass through narrow spaces (Fig. 7.3), failure to recognize previously

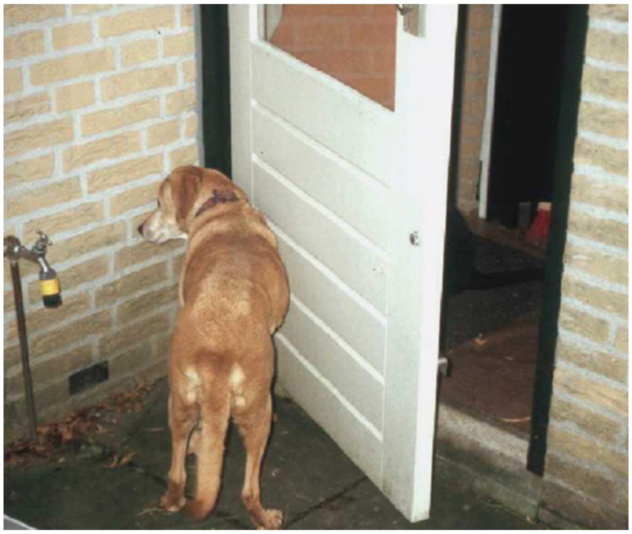


Figure 7.3 A dog with cognitive dysfunction syndrome (CDS) attempting to pass through the wrong end of the door. (Rofina *et al.*, 2006. Reproduced with permission from Elsevier.)[586]

Table 7.3 CDS checklist.[1]

Signs: DISHAAL	Age first noticed	Score 0-3[a]
D: Disorientation/Confusion—Awareness, Spatial orientation		
Gets stuck or cannot get around objects		
Stares blankly at walls or floor		
Decreased recognition of familiar people/pets		
Goes to wrong side of door; walks into door/walls		
Drops food/cannot find		
Decreased response to auditory or visual stimuli		
Increased reactivity to auditory or visual stimuli (barking)		
I: Interactions—Social Relationships		
Decreased interest in petting/avoids contact		
Decreased greeting behavior		
In need of constant contact, overdependent, "clingy"		
Altered relationships other pets, less social/irritable/aggressive		
Altered relationships with people, less social/irritable/aggressive		
S: Sleep–Wake Cycles—Reversed Day/Night Schedule		
Restless sleep/waking at nights		
Increased daytime sleep		
H: House Soiling (Learning and Memory)		
Indoor elimination at sites previously trained		
Decrease/loss of signaling		
Goes outdoors, then returns indoors and eliminates		
Elimination in crate or sleeping area		
A: Activity—Increased/Repetitive		
Pacing/wanders aimlessly		
Snaps at air/licks air		
Licking owners/household objects		
Increased appetite (eats quicker or more food)		
A: Activity—Apathy/Depressed		
Decreased interest in food/treats		
Decreased exploration/activity/play		
Decreased self-care (hygiene)		
A: Anxiety		
Vocalization, restlessness/agitation		
Anxiety, fear/phobia to auditory or visual stimuli		
Anxiety, fear/phobia to places (surfaces, locations)		
Anxiety/fear of people		
Separation anxiety		
L: Learning and Memory—Work, Tasks, Commands		
Decreased ability to perform learned tasks, commands		
Decreased responsiveness to familiar commands and tricks		
Inability/slow to learn new tasks		

[a] Score: 0 = none; 1 = mild; 2 = moderate; 3 = severe.
Source: Adapted from Landsberg GM, Hunthausen W, Ackerman L. *The Effects of Aging on the Behavior of Senior Pets: Handbook of behavior problems of the dog and cat*. 2nd ed. Philadelphia: W.B. Saunders; 2003:273; with permission.

familiar people or animals, decreased interaction with family members, hearing loss, and excessive vocalization (often at night). Cats with CDS occasionally exhibit overresponsive and aggressive behavioral patterns as well as excessive vocalization. The acronym DISHAAL (disorientation; alterations in interactions with owners, other pets, and the environment; sleep/wake cycle disturbances; house soiling; changes in activity; perceived anxiety; and learning or memory deficits) can be used as a checklist for patients suspected of being affected by CDS (Table 7.3). Owners of CDS pets often describe their pets as acting "senile." Aging dogs appear to fall into three categories of cognitive function, similar to people. These categories are successful aging, mild cognitive impairment, and severe cognitive impairment (dementia). The third, most severe category is consistent with a diagnosis of AD. Standardized cognitive testing of older dogs (almost exclusively done in a research setting) has enabled a more objective determination of the extent of cognitive dysfunction in individuals, as well as the response to therapeutic interventions. Such testing includes the delayed nonmatching to position (DNMP) memory task (Fig. 7.4) and the

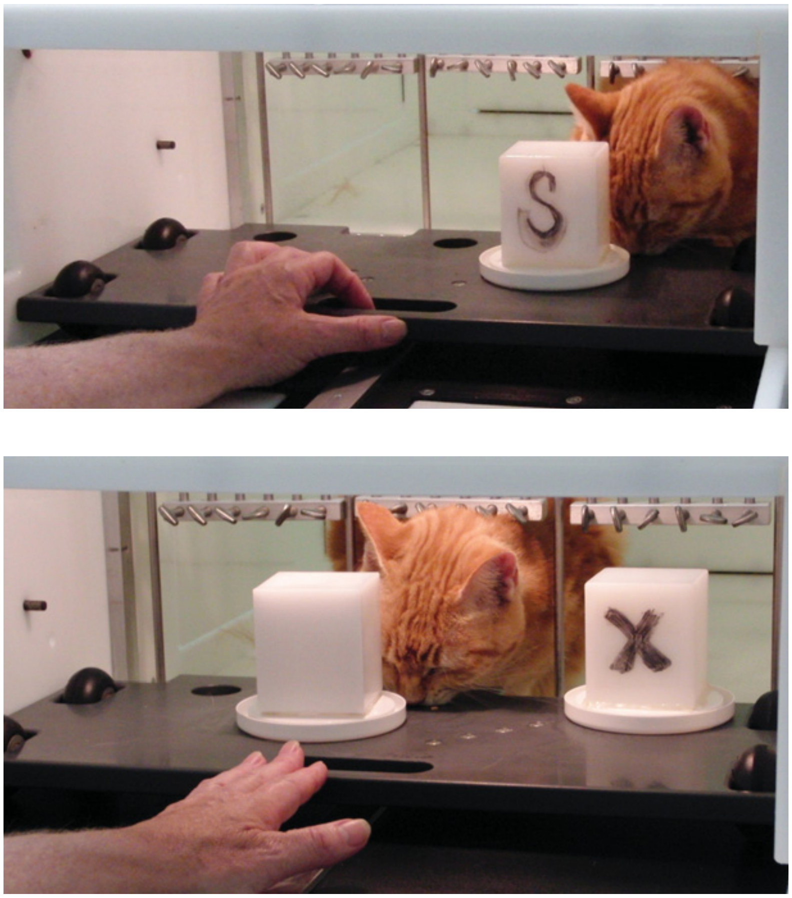


Figure 7.4 The DNMP is a test of short-term visuospatial working memory. The test consists of two phases. In the sample phase, the subject is required to displace an object placed over one of three possible locations on a food well (top); in this case the cat is required to displace block S covering food reward in the well on cat's right. The second stage (bottom) occurs after a delay and the subject is presented with two objects identical to that used in the sample phase. One object (marked with an X) is located in the same position as the sample object. The correct object is located in one of the remaining two positions (the nonmatch), and if the subject displaces the object, it can retrieve the food reward beneath. Initially, subjects are trained using a 5-second delay between the phases, but when the cat learns the rule that the food will always be found under the block in the nonmatch position, gradually longer delays can be introduced to assess memory. (Landsberg *et al.*, 2012. Reproduced with permission from Elsevier.)[394]

attention task (Fig. 7.5). In addition to the classic behavioral abnormalities indicative of CDS in dogs, the author occasionally encounters suspected CDS dogs with either transient central vestibular dysfunction or seizure activity of recent onset. Although not yet reported as a clinical feature of canine CDS, vestibulocerebellar dysfunction and seizures are reported as a potential consequence of AD in people. Seizure activity has been reported associated with feline CDS.

c. Similar to AD of people, a diagnosis of CDS in a dog or cat is based primarily on historical complaints

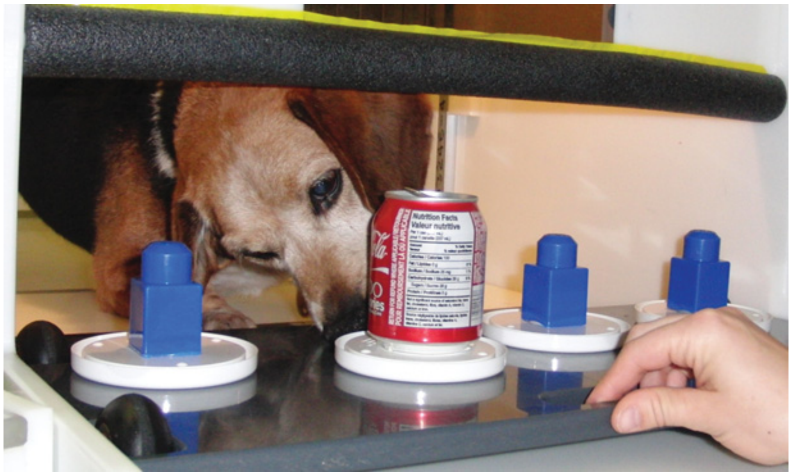


Figure 7.5 In the attention task, the dog must select the correct object (covering a food reward), which is presented concurrently with either one, two, or three incorrect objects (distracters). Studies have demonstrated that performance declines and latency increases with increased distracter number, consistent with a test that assesses selective attention. (Landsberg *et al.*, 2012. Reproduced with permission from Elsevier.)[394]

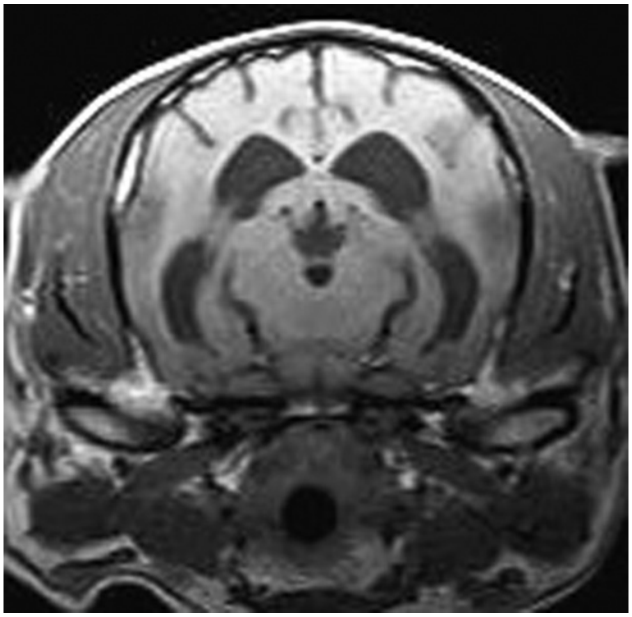


Figure 7.6 Transaxial MR image of a dog with cognitive dysfunction, demonstrating typical characteristics of brain aging.

indicative of progressive cognitive impairment. Before arriving at a presumptive diagnosis of CDS, the clinician should rule out other potential causes of cognitive dysfunction, such as metabolic disorders (e.g. hepatic encephalopathy) and structural brain disorders (e.g. brain tumor). In AD, CT or MR imaging of the brain is usually performed as part of the diagnostic workup, and should ideally be part of the diagnostic plan for CDS patients. The brain imaging of AD patients can be normal, but may reveal brain atrophy, ventricular enlargement, and lesions in the medial temporal lobes of the cerebral cortex (Fig. 7.6). Age-related changes appreciated on MR imaging of the brain in CDS patients are primarily reflective of brain atrophy and include ventricular enlargement, widened and well-demarcated cerebral sulci, and diffuse and scattered areas of T2 hyperintensity, in periventricular white matter. Although these are consistent findings associated with the aging brain, they may be found in older patients without evidence of CDS. In one study, the thickness of the interthalamic adhesion as measured on transaxial T1- and T2-W MR images was found to be significantly smaller in dogs with CDS compared with dogs without CDS (Fig. 7.7). An interthalamic adhesion thickness of 5.0 mm or less was found to be consistent with a diagnosis of CDS in dogs. Positron emission tomography (PET) scanning with radioactively labeled glucose (to evaluate brain glucose utilization) is often used in the evaluation of human AD; this has been investigated as a potential tool for evaluating brain function in dogs.

d. As with human AD, there is no known cure for CDS. There are multiple proposed therapeutic and preventative approaches to CDS, with variable evidence of efficacy in improving cognitive function and/or delaying the progression of cognitive decline. These treatments include a variety of drugs (Table 7.4) and dietary supplements/modifications (Table 7.5). There is evidence of efficacy for some of these treatments in dogs. Information pertaining to treatment efficacy for such interventions in cats is mainly anecdotal. The use of oral L-deprenyl (selegiline), an irreversible inhibitor of monoamine oxidase B (MAOB), has been purported to improve cognitive function and slow the progression of the disease in the majority of dogs and cats with CDS. There is considerable variability in the degree of response achieved among patients, however. L-deprenyl is thought to exert its beneficial effects in the brain by restoring dopaminergic balance, as well as enhancing catecholamine levels, and decreasing levels of damaging free radical species. The dosage for dogs is 0.5–1.0 mg/kg every 24 hrs. Cats are administered 0.5 mg/kg every 24 hrs. Most patients will exhibit a positive response within the first month of therapy. Despite apparent positive responses of both canine and feline CDS patients to selegiline, there is some evidence that this drug does not have a significant effect on cognitive function in these patients, or in people with AD. The clinical efficacy studies supporting selegiline use in CDS are based primarily on owner response to questionnaires, rather than on standardized comparative cognitive testing procedures of treated and untreated patients. Since selegiline may produce nonspecific low-level hyperactivity by increasing brain catecholamine levels, the “response” observed by owners may not truly be representative of improved cognitive ability. Selegiline is not considered an effective drug for human AD, due to variable responses and overall minimum improvement of cognitive function. The acetylcholinesterase inhibitor phenserine has exhibited efficacy in improving cognitive function in both dogs with CDS and humans with AD in clinical trials; to the author’s knowledge, this drug is not yet commercially available for dogs. Nicergoline and propentofylline are drugs that theoretically can improve cognitive function by improving cerebral blood flow. There is little to no evidence of efficacy for these two drugs. The noradrenergic-enhancing drugs adrafanil and modafinil have shown some efficacy in improving locomotion and learning in dogs, but seem to further impair memory. Behavioral changes (especially anxiety) in CDS patients may be alleviated with the use of GABA-ergic drugs, such as gabapentin or pregabalin. Other drugs that may alleviate anxiety include buspirone, fluoxetine, and benzodiazepine

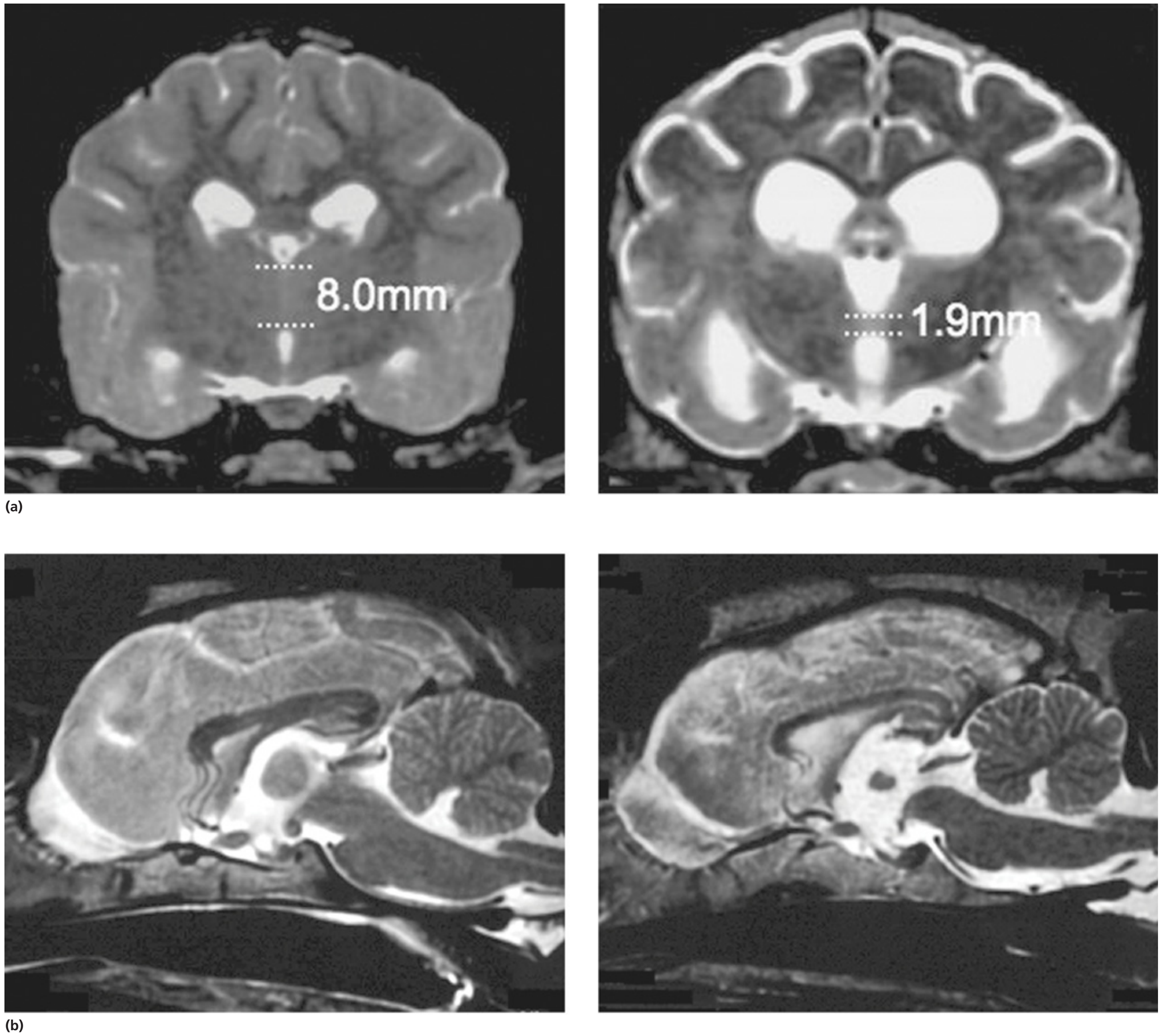


Figure 7.7 Transaxial (A) and midsagittal (B) T2-weighted MR images, demonstrating normal (left) and abnormal (right-cognitive dysfunction patient) interthalamic adhesion thicknesses in dogs. (Hasegawa *et al.*, 2005. Reproduced with permission from Wiley.)[280]

derivatives. Because inflammatory changes have been identified in the brains of CDS dogs, the use of anti-inflammatory drugs (e.g. carprofen) has also been proposed. A large number of complementary therapies have been suggested for the treatment of CDS, with the primary goals of calming the patient, reducing anxiety, and normalizing the sleep/wake cycle. These include melatonin, valerian root, dog-appeasing pheromone (DAP), and lavender essential oils. The evidence for efficacy of all these complementary therapies is largely anecdotal.

There is convincing evidence that providing a diet fortified with antioxidants, mitochondrial cofactors, and essential fatty acids improves cognitive function and delays cognitive decline in dogs with CDS. A commercially available canine diet (Hills b/d) contains a mixture of fruits and vegetables, in addition to vitamins C and E, and mitochondrial cofactors (L-carnitine, DL-α-lipoic acid). Another commercially available diet for dogs (Purina One Vibrant Maturity 7+ Formula) has been shown to improve cognitive function in dogs; this diet contains medium-chain triglycerides (MCTs) which are converted to ketones by the liver. Since reduced brain glucose utilization occurs in CDS and AD, MCTs provide an alternative brain energy source. In addition, MCTs have been shown to increase brain mitochondrial function, increase polyunsaturated fats in the brain, and

Table 7.4 Doses for drugs for behavior therapy of senior pets (oral dosing).

	Dog	Cat
Selegiline (CDS)	0.5–1 mg/kg sid in am	0.5–1 mg/kg sid in am
Propentofylline (CDS)	2.5–5 mg/kg bid	1/4 of a 50 mg tablet daily
Oxazepam[a]	0.2–1 mg/kg sid–bid	0.2–0.5 mg/kg sid–bid
Clonazepam[a]	0.1–1.0 mg/kg bid–tid	0.02–0.2 mg/kg sid–bid
Lorazepam[a]	0.025–0.2 mg/kg sid–tid	0.025–0.05 mg/kg sid–bid
Diphendydramine[a]	2–4 mg/kg	1–4 mg/kg
Fluoxetine	1.0–2.0 mg/kg sid	0.5–1.5 mg/kg sid
Paroxetine	0.5–2 mg/kg	0.5–1.5 mg/kg
Sertraline	1–5 mg/kg sid or divided bid	0.5–1.5 mg/kg sid
Buspirone	0.5–2.0 mg/kg sid–tid	0.5–1 mg/kg bid
Trazodone	2–5 mg/kg (up to 8–10) prn–tid	Not determined
Phenobarbital	2.5–5 mg/kg bid	2.5 mg/kg bid
Memantine	0.3–1 mg/kg sid	Not determined
Gabapentin	10–30 mg/kg q 8–12 h	5–10 mg/kg q 12 h
Pregabalin	2–4 mg/kg q 8–12 h	1–2 mg/kg q 12 h

[a] Use single dosing prior to sleep or anxiety-evoking event, up to maximum daily dosing for control of ongoing anxiety.

decrease the level of brain amyloid precursor protein (APP). Although similar commercially available diets for CDS are not available for cats, a number of dietary supplements with antioxidant activity are available for this species. Phosphatidylserine and S-Adenosyl-L-methionine (SAMe) are two natural dietary supplements that have shown some efficacy in the treatment of CDS in dogs. Both of these supplements are thought to have beneficial antioxidant properties. A calcium-buffering protein called apoaequorin has recently been shown to have some efficacy in enhancing learning and attention in older dogs. Though not yet evaluated in dogs and cats, there are several naturally occurring phytochemicals that exhibit anti-amyloidogenic, antioxidative and anti-inflammatory properties. These include resveratrol (found in grapes,

Table 7.5 Ingredients and doses of natural therapeutics for senior pets.

	Ingredients	Dose
Senilife	Phosphatidylserine, *Gingko biloba*, vitamin B6 (pyridoxine), vitamin E, resveratrol	Dogs and cats (see label)
Aktivait	Phosphatidylserine, omega-3 fatty acids, vitamins E and C, L-carnitine, alpha-lipoic acid, coenzyme Q, selenium Note: no alpha-lipoic acid in feline version	Separate dog and cat products See label
Novifit	S-Adenosyl-L-methionine disulfate tosylate (SAMe)	Dog: 10–20 mg/kg sid Cat: 100 mg sid
Neutricks	Apoaequorin	Dogs: 1 tablet per 18 kg
Prescription diet b/d Canine aging and alertness	Flavonoids and carotenoids from fruits and vegetables, vitamin E, vitamin C, beta-carotene, selenium, L-carnitine, alpha-lipoic acid, omega-3 fatty acids	Dogs
Purina One Vibrant Maturity 7 + Senior	Medium chain triglycerides (from coconut oil)	Dogs
Melatonin	Endogenous-based peptide	Dogs: 3–9 mg Cats: 1.5–6 mg
Anxitane	Suntheanine	Dogs: 2.5–5 mg/kg bid Cats: 25 mg bid
Harmonease	Magnolia and phellodendron	Dogs: up to 22 kg 1/2 tablet daily; > 22 kg 1 tablet daily Cats: N/A
Zylkène	Alpha-casozepine	Dogs: 15–30 mg/kg/d Cats: 15 mg/kg/d
Pheromones	Adaptil collar, diffuser, or spray for dogs Feliway spray or diffuser for cats	As per label
Lavender	Aromatherapy for dogs	As per label

red wine, and berries), curcumin (a spice used in several Indian foods), and catechin (found in green tea).

Environmental enrichment, such as regular exercise and introduction of new toys, has also been demonstrated to improve cognitive function and delay cognitive decline in dogs with CDS. Progression of CDS appears to be more rapid in castrated versus intact male dogs, suggesting a potential role for hormone replacement therapy in this disease. The prognosis for CDS is guarded. Most affected patients are euthanized within 18–24 mos of the onset of clinical signs, either due to progressive cognitive impairment or unassociated medical problems.

B. Anomalous/developmental

1. Congenital hydrocephalus[96, 99, 127, 134, 135, 139, 180, 198, 203, 204, 260, 272, 309, 316, 321, 323, 342, 349, 350, 352, 357, 362, 408, 418, 425, 454, 484, 581, 583, 612, 643, 652, 657, 673, 694, 716]

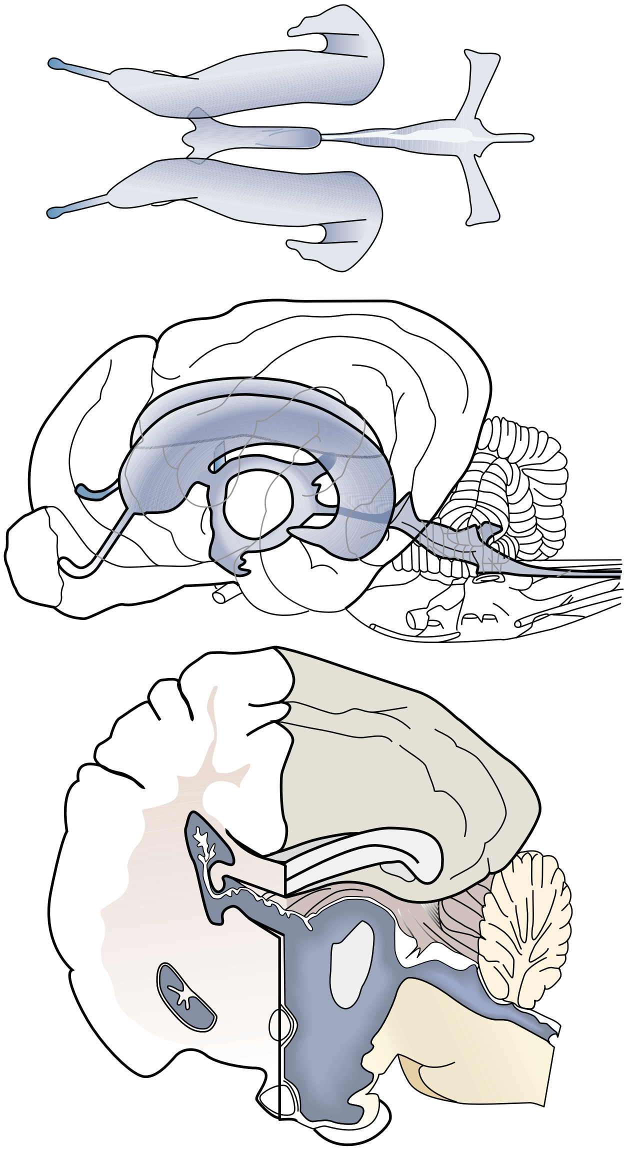


Figure 7.8 Schematic illustration depicting the normal ventricular anatomy of the canine brain. Illustration by Michael Simmons. (Dewey and Marino, 2012. Reproduced with permission from Elsevier.)[142]

a. The anatomy of the ventricular system of the dog is summarized in Fig. 7.8. The pathophysiology of CNS damage associated with hydrocephalus is complex, and involves the destruction of the ependymal lining of the ventricles, neuronal injury in the cerebral cortex, compromise of cerebral vasculature, and damage to periventricular white matter. The phenomenon of excessive CSF in the ventricular system of the brain occurs commonly in young dogs, especially of the toy and brachycephalic breeds, and less commonly in cats. Congenital hydrocephalus is most commonly reported in dogs, especially small breeds (e.g. Chihuahua, Yorkshire Terrier, Maltese, Boston Terrier, English Bulldog, Toy/Miniature Poodle, Lhasa Apso, Pomeranian, Pekingese). Congenital hydrocephalus may be an autosomal recessively inherited trait in the Siamese cat. The list of potential causes for congenital hydrocephalus (i.e. evident from birth) is diverse and extensive, and involves disturbances to the developing fetus or the neonate, including the following: intraventricular hemorrhage (e.g. dystocia-related); viral infections (e.g. parainfluenza virus in dogs, coronavirus in cats); teratogen exposure; nutritional deficiencies (e.g. vitamin A); and heritable malformations. Traditional/historical theories to explain the ventriculomegaly of congenital hydrocephalus are based on the "bulk flow" concept of CSF accumulation and contend that excessive fluid accumulation results from obstruction of CSF flow within the ventricular system (e.g. mesencephalic aqueduct stenosis) and/or insufficient absorption of CSF into the venous system at the arachnoid villi level. These mechanisms may contribute to some cases of congenital hydrocephalus, but likely are not responsible for the development of this disease in the majority of cases. A more recently proposed theory, called the "hydrodynamic theory," maintains that the hydrocephalus develops due to abnormal (reduced) intracranial compliance and the resultant effect of this compliance defect on brain capillaries. In the normal animal, individual brain capillaries remain open during the entire cardiac cycle (systole and diastole). This is important because much of the CSF absorption actually occurs at the capillary level, rather than the arachnoid villi. Hydrocephalic patients are believed to have poor intracranial compliance as an underlying disorder that leads to hydrocephalus. The increased capillary pulse pressure caused by decreased compliance leads to a pulsatile transmantle pressure gradient directed from the cerebral tissue toward the lateral ventricles. These abnormal capillary pulsations occur within normal mean intracranial pressure (ICP) limits. The rebound pressure from the recurring gradient as well as hyperdynamic CSF flow in the mesencephalic aqueduct leads to progressive ventricular enlargement. The result is that congenital hydrocephalus often develops within the confines of normal ICP (i.e. normal pressure hydrocephalus). Hydrocephalus, especially if progressive, can cause neurologic dysfunction from compression and stretching of brain parenchyma, as well as from brain ischemia and interstitial edema.

It is the rule, rather than the exception, that a specific cause for congenital hydrocephalus is not apparent at the time of clinical presentation; this lack of an active causative process (e.g. inflammation, hemorrhage) helps define this form of hydrocephalus. Hydrocephalus, especially if progressive, can cause neurologic dysfunction from the compression and stretching of brain parenchyma, as well as from brain ischemia and interstitial edema. Many animals, especially of the predisposed breeds, have hydrocephalus based upon ventricular enlargement yet have no discernible neurologic dysfunction. There is generally an inconsistent relationship between the extent of ventricular dilation and clinical signs of disease in most of these breeds, so that clinical hydrocephalus should not be diagnosed on imaging findings alone. One study, however, evaluated both ventricular-to-brain (VB) ratio and basilar artery resistive index (RI) via Doppler ultrasonography in dogs with ventriculomegaly and varying signs of neurologic dysfunction. It was found that RI and VB ratio were both significantly higher in clinically hydrocephalic dogs compared with dogs having ventriculomegaly and no signs of neurologic dysfunction. Combining these measurements provided a sensitivity and specificity of identifying clinical hydrocephalic patients of 77% and 94%, respectively. In addition, it was found that RI changed with changes in neurologic status (but not VB ratio) and that nonclinical dogs with ventriculomegaly and a VB ratio of more than 60% eventually developed clinical hydrocephalus. Although hydrocephalus typically denotes dilation of the internal ventricular system, external hydrocephalus occasionally occurs in people and has been described in dogs and cats. In this text, a patient is considered to have congenital hydrocephalus only if all three of these criteria are met: (1) ventriculomegaly is demonstrated; (2) there is no active, potentially causal disease process identifiable; and (3) the patient exhibits clinical signs of brain dysfunction. Hydrocephalus may exist concurrently with other anomalous conditions that affect the CSF pathways, such as Dandy–Walker syndrome (DWS), Chiari-like malformation (CLM; also termed caudal occipital malformation syndrome, or COMS), and SM (typically associated with CLM).

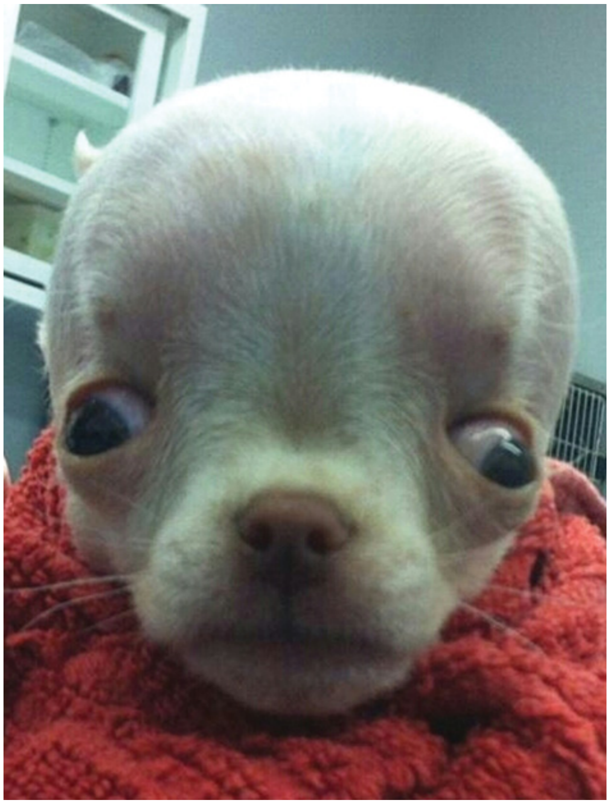


Figure 7.9 Chihuahua with congenital hydrocephalus, exhibiting enlarged calvarium and bilateral ventrolateral strabismus.

b. Dogs and cats with congenital hydrocephalus typically are presented for signs of neurologic dysfunction within the first 6 mos of life. The rate of the clinical progression of congenital hydrocephalus is highly variable, and a considerable proportion of hydrocephalic animals may not develop clinical signs of encephalopathy until adulthood. Common physical characteristics of hydrocephalic patients include a large, dome-shaped head, open fontanelles or larger calvarial defects, and bilateral ventrolateral strabismus (Fig. 7.9). The strabismus may be due to orbital skull malformations, rather than to vestibular dysfunction, and has been referred to as the "setting sun sign." Dogs and cats with congenital hydrocephalus often appear unthrifty and smaller than normal. Clinical signs of neurologic dysfunction usually reflect a forebrain disorder and include obtundation, behavior abnormalities, difficulty with house-training, decreased vision or blindness, circling, pacing, restlessness, and seizure activity. In the author's experience, seizures are not commonly associated with congenital hydrocephalus, in comparison with behavioral abnormalities and abnormal mentation. In one report of hydrocephalic

Maltese dogs, less than 20% exhibited seizures. Some hydrocephalic patients may also exhibit vestibular and/or cerebellar dysfunction. Concurrent congenital abnormalities of the brain (e.g. intracranial arachnoid cyst, DWS, CLM) occasionally occur in hydrocephalic dogs, accounting for cerebellovestibular dysfunction. Progressive neurologic dysfunction over weeks to months is often a reason for medical and/or surgical intervention. However, some dogs progress more slowly and some stabilize. Occasionally, a previously stable animal will rapidly decompensate neurologically following what would be considered a minor traumatic event; this may be due to the tenuous compliance state of the hydrocephalic brain in combination with a relatively unprotected brain (large calvarial defects).

c. Diagnosis of congenital hydrocephalus is based upon a combination of characteristic clinical features, demonstration of ventriculomegaly, and the absence of other causes of encephalopathy. Ultrasonography (through open fontanelles or calvarial defects; Fig. 7.10) and advanced imaging (CT/MRI; Fig. 7.11) have largely supplanted more invasive methods of documenting ventriculomegaly (e.g. contrast ventriculography). Electroencephalography (EEG) has been used historically to assist in the diagnosis of congenital hydrocephalus, with affected patients typically exhibiting slow-frequency, high-voltage activity. However, these EEG findings are relatively nonspecific and seldom contribute much to the diagnosis of congenital hydrocephalus.

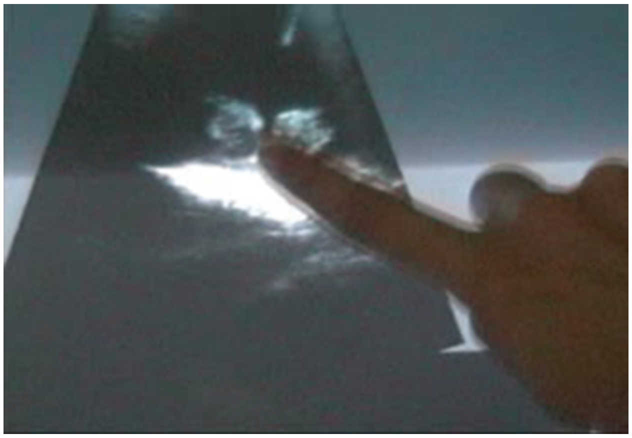


Figure 7.10 Dilated lateral ventricles of a hydrocephalic dog, demonstrated via ultrasonography through an open fontanelle.

d. The medical treatment of congenital hydrocephalus (Table 7.6) is aimed at the reduction of CSF production. Oral prednisone, at an initial dosage of 0.25–0.50 mg/kg q 12 hrs, may decrease CSF production. Prednisone should be reduced over several weeks to the lowest possible dosage required to control clinical signs. Furosemide, a loop diuretic, decreases CSF production via inhibition of the sodium/potassium co-transport system. The recommended dose range is 0.5–4.0 mg/kg body weight PO, q 12–24 hrs. The diuretic acetazolamide is a carbonic anhydrase inhibitor and is typically dosed at 10 mg/kg body weight PO, q 6–8 hrs. Omeprazole, a proton pump

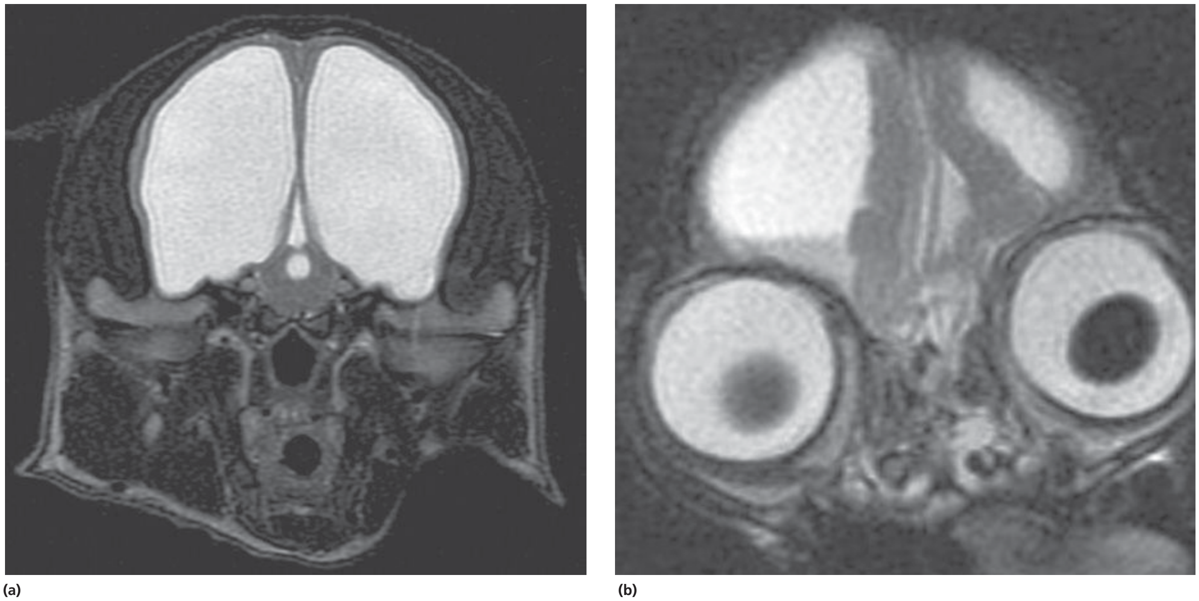


Figure 7.11 Transaxial T2-weighted MR images of (A) a dog with congenital internal hydrocephalus (Coates *et al.*, 2006; reprinted with permission)[96] and (B) a cat with external congenital hydrocephalus. (Dewey *et al.*, 2003. Reprinted with permission from JAAHA, November/December 2003. Copyright © 2003 American Animal Hospital Association (aaha.org). All Rights Reserved.)[139]

Table 7.6 Drugs for the medical treatment of congenital hydrocephalus.

Drug	Dosage
Prednisone	0.25–0.5 mg/kg PO, q 12 hrs
Furosemide	0.5–4.0 mg/kg PO, q 12–24 hrs
Acetazolamide	10 mg/kg PO, q 6–8 hrs
Omeprazole	10 mg q 24 hrs (dogs less than 20 kg); 20 mg q 24 hrs (dogs more than 20 kg) PO

PO = oral.

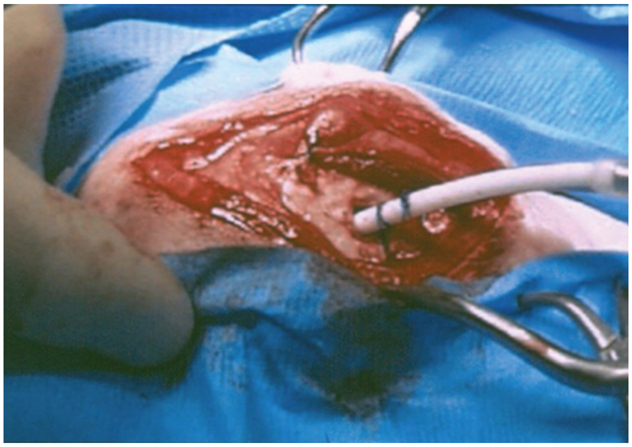


Figure 7.12 Intraoperative image of shunt placement in the lateral ventricle for congenital hydrocephalus. (Coates *et al.*, 2006. Reprinted with permission.)[96]

inhibitor, has been shown to decrease CSF production in dogs by 26%. The oral dose for dogs is 10 mg (dogs weighing less than 20 kg) q 24 hrs and 20 mg (dogs weighing more than 20 kg) q 24 hrs. For all of these drugs, it is recommended that the dose be tapered to the lowest dose needed to control the clinical signs of disease, in order to avoid serious side effects. Anticonvulsant drugs are administered if the patient is experiencing seizure activity. Medical therapy of congenital hydrocephalus may provide some level of disease palliation in mild cases, but often fails in the long term. The potential side effects of long-term corticosteroid and/or diuretic therapy should be considered along with the questionable efficacy of medical therapy for congenital hydrocephalus, when making treatment decisions. Electrolyte depletion (especially potassium) and dehydration are concerns when using diuretics for prolonged time periods, particularly when combined with corticosteroids. The goal of the surgical treatment of hydrocephalus is to continually divert excessive CSF from the ventricles of the brain to either the peritoneal cavity (most commonly performed; Fig. 7.12) or the right atrium of the heart. Both ventriculoatrial and ventriculoperitoneal shunts (Fig. 7.13) have been successfully placed in dogs with congenital hydrocephalus. Ventriculoperitoneal shunt placement is technically more feasible than ventriculoatrial shunt placement, especially in very small patients (Fig. 7.14).The prognosis for dogs and cats with congenital hydrocephalus is variable, but is generally guarded. Medical therapy may be effective in some patients, whereas others require surgical shunting procedures for the long-term control of clinical signs. The prognosis for sustained clinical improvement in neurologic status after surgical shunting procedures varies in the literature from 50 to 90% for dogs. In the author's experience, the success rate is approximately 75–80%. Potential postoperative surgical shunt complications in dogs and cats include shunt obstruction, shunt dislodgement, mechanical damage to the shunt, and shunt infection.

2. Craniocervical junction abnormalities[79–84, 110, 115, 130, 134, 136–138, 143, 144, 156, 157, 211, 213, 228, 234, 259, 409, 411, 423, 425, 437, 473, 488, 499, 510, 536, 538, 560, 587, 598–608, 632–636, 650, 655, 681, 701, 741, 749, 767, 773, 795] (Video 15)
    a. Since the occipital region of the skull and the first two cervical vertebrae develop together embryologically, it makes inherent sense that multiple developmental disorders, as well as combinations of these disorders, should occur in this anatomical region in small animals, as they do in humans. Craniocervical junction abnormalities (CJAs) is an umbrella term that

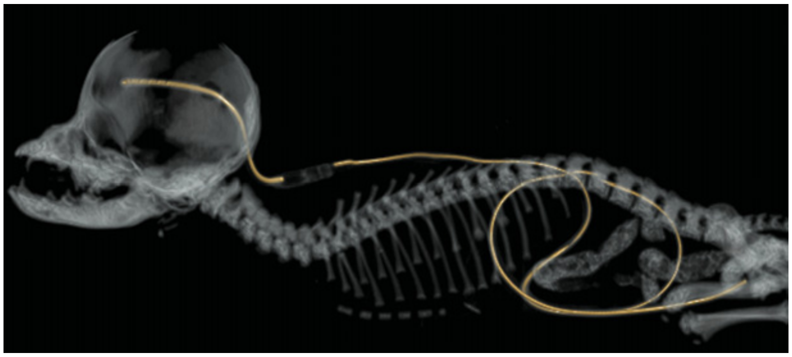


Figure 7.13 Three-dimensional CT reconstruction image of a dog with a ventriculoperitoneal shunt placed.

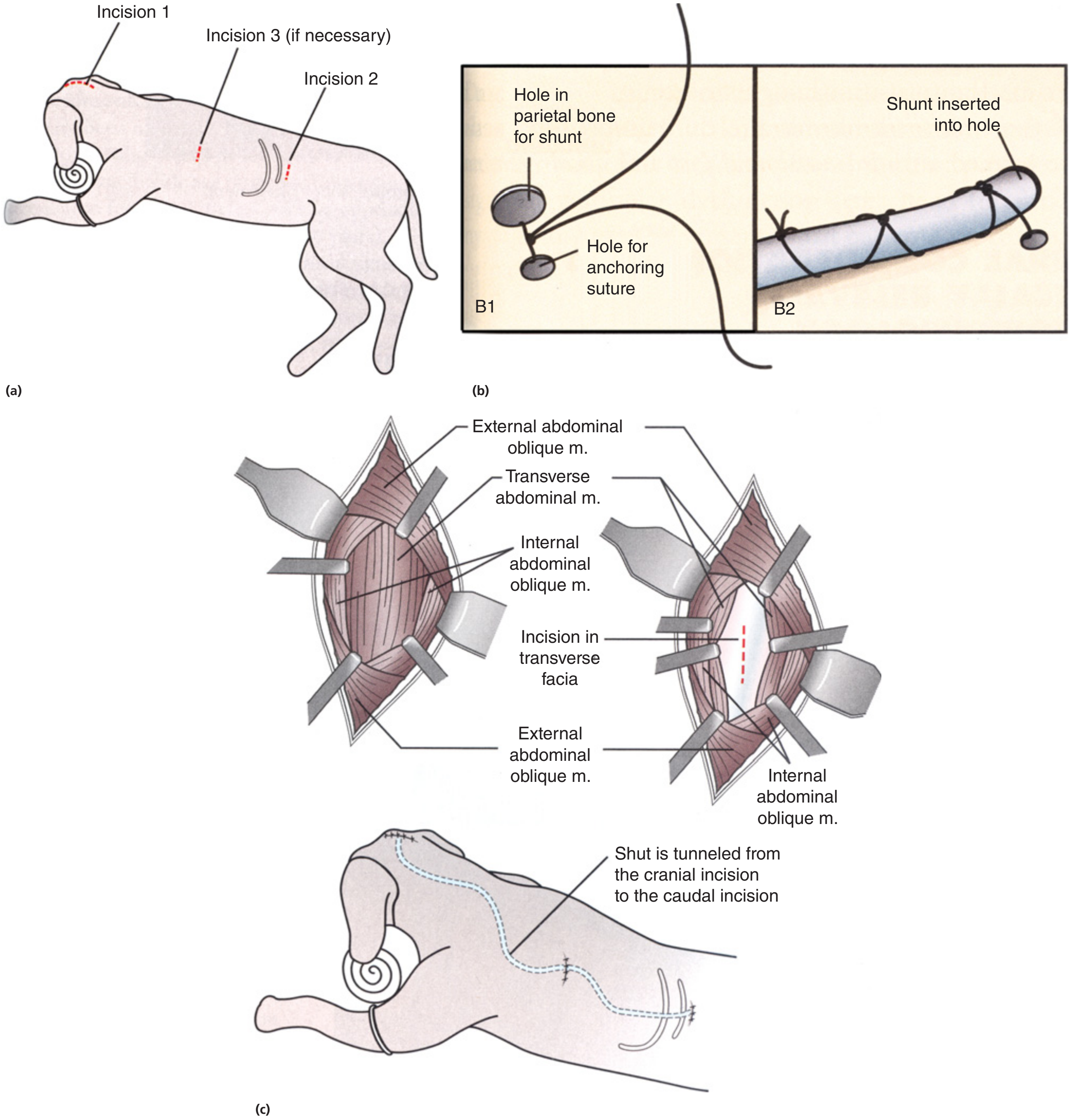

Incision 1
Incision 3 (if necessary)
Incision 2
(a)
Hole in parietal bone for shunt
Hole for anchoring suture
B1
Shunt inserted into hole
B2
(b)
External abdominal oblique m.
Transverse abdominal m.
Internal abdominal oblique m.
Incision in transverse facia
External abdominal oblique m.
Internal abdominal oblique m.
Shut is tunneled from the cranial incision to the caudal incision
(c)

Figure 7.14 Surgical positioning and location of incisions for ventriculoperitoneal shunt (VPS) placement (A). Insertion and anchoring (B1, B2) of the rostral end of the VPS. Grid approach (C) to the peritoneal cavity following subcutaneous tunneling of the VPS. (Dewey, 2013. Reproduced with permission from Elsevier.)[133]

includes Chiari-like malformation (CLM), atlanto-occipital overlapping (AOO), dorsal compression at C1/C2, and atlantoaxial instability. Atlantoaxial instability and dorsal compression at C1/C2 are discussed in Chapter 13. Syringomyelia (SM) refers to the development of fluid cavities within the parenchyma of the spinal cord and can develop as a secondary consequence from any CJA. CLM is the canine analog of Chiari type I malformation of people and has also been termed caudal occipital malformation syndrome (COMS) and occipital hypoplasia. CLM appears to be a very common neurologic disorder in dogs. This disease is almost exclusive to small-breed dogs, with the Cavalier King Charles Spaniel (CKCS) being the most overrepresented. Other CJAs tend to occur in small-breed dogs as well. Occipitoatlantoaxial

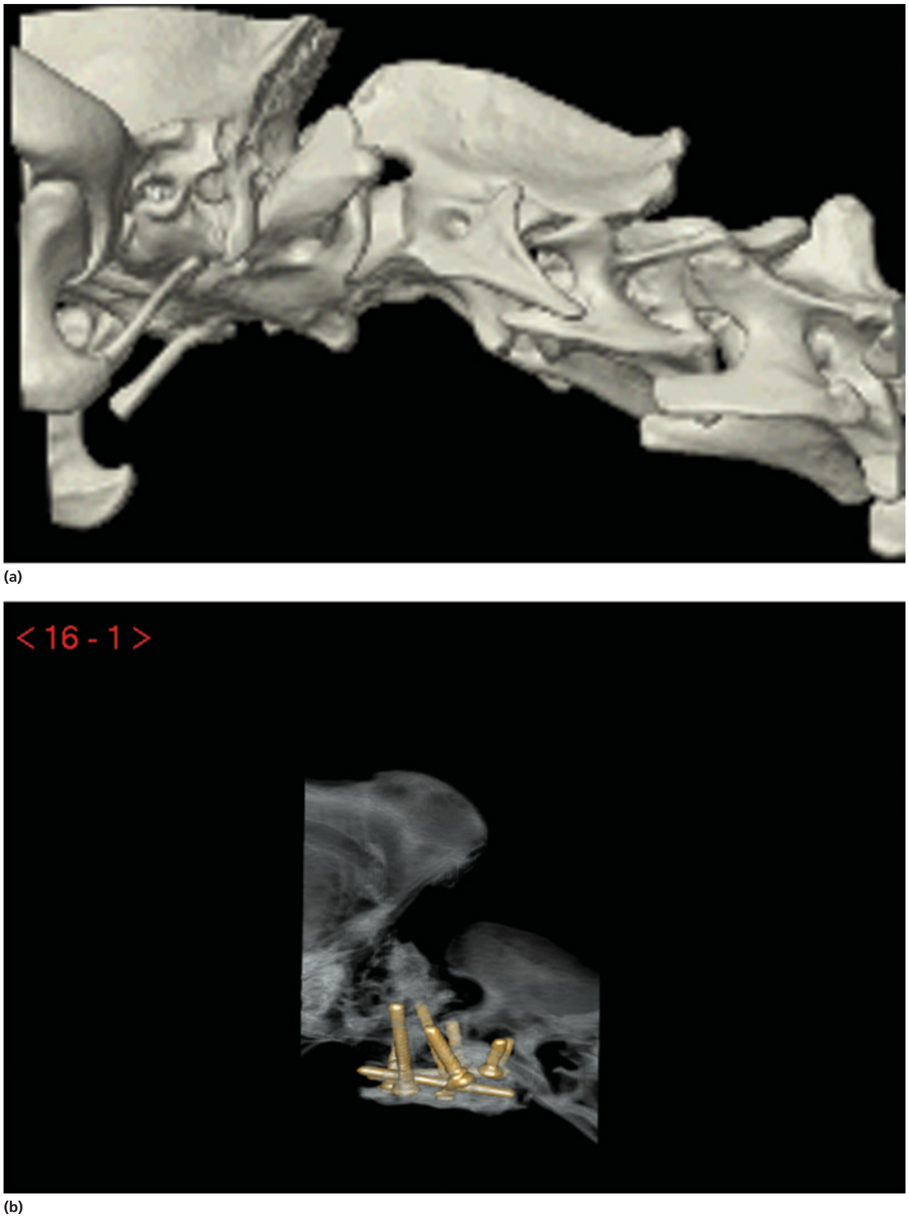


Figure 7.15 Three-dimensional CT reconstruction image of a dog with an occipitoatlantoaxial malformation before (A) and after (B) surgical stabilization.

malformations (OAAMs) are infrequently encountered in dogs and will be only briefly discussed. These disorders have been reported in small- and large-breed dogs and typically involve a shift of the craniocervical junction by one segment. The atlas fuses to the occipital bone and the atlantoaxial joint resembles the atlanto-occipital junction (Fig. 7.15); OAAMs may be asymmetric. Cranial cervical spinal cord and/or brainstem compression may develop due to direct impingement upon parenchyma from malformed bone and/or instability (e.g. atlantoaxial instability). Because CLM is so prevalent in the CKCS breed, much of the available literature regarding pathophysiology, diagnosis, and treatment is centered on this breed. CLM has generally been considered a congenital malformation of the caudal occipital region of the skull, leading to overcrowding of the caudal fossa and compression of the cervicomedullary junction at the level of the foramen magnum (Fig. 7.16). However, the anatomical abnormalities associated with CLM are far more complicated than simply a malformed skull in the caudal-most aspect of the occipital bone region causing a physical constriction near the foramen magnum. There is convincing evidence in CKCS dogs that there is a mismatch between the volume available in the caudal fossa region (CF, also referred to as the caudal cranial fossa) and the parenchyma (cerebellum and brain stem) that resides within this volume; in other words,

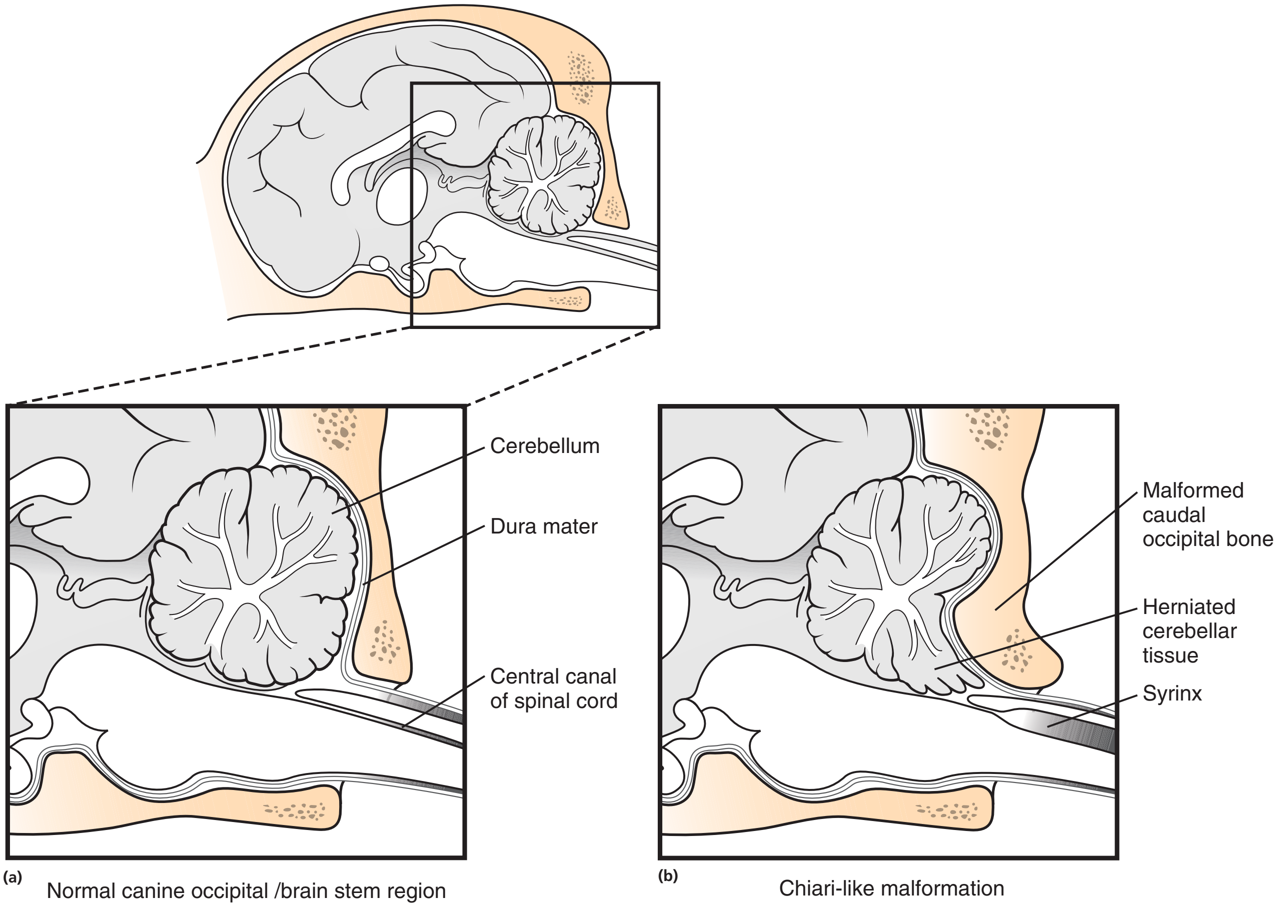

Cerebellum
Dura mater
Central canal of spinal cord
Malformed caudal occipital bone
Herniated cerebellar tissue
Syrinx
(a)
Normal canine occipital /brain stem region
(b)
Chiari-like malformation

Figure 7.16 Schematic illustration of normal canine caudal fossa anatomy (A) and abnormal caudal fossa anatomy (B) associated with Chiari-like malformation. (Dewey, 2013. Reproduced with permission from Elsevier.)[132]

there is too much brain parenchyma in too small a space in the CF of CKCS dogs (compared to other small-breed dogs and Labrador Retrievers). This mismatch between parenchyma and available volume has also been demonstrated in the cranial fossa (rostral and middle fossae) of CKCS dogs. Increased ventricular size, increased relative parenchymal volume in the CF (as a percentage of total brain parenchymal volume), and increased relative cerebellar volume have all been associated with increased likelihood of the presence of SM in the CKCS breed. Increased syrinx width has also been associated with increased ventricular size and relative CF parenchymal volume in this breed. There is some evidence in the CKCS breed that the CF volume itself is often too small compared with other dog breeds. Other anatomic abnormalities of the skull reported in dogs with SM include minute or absent frontal sinuses and abnormally small jugular foramen volumes. For this latter abnormality, it is hypothesized that the constricted venous drainage from the brain due to small jugular foramina leads to intracranial venous hypertension and increased ICP; this would lead to an increased pressure differential between cranial and spinal compartments and an increased likelihood of SM development. In AOO cases, the atlas (C1) is cranially displaced into the foramen magnum, and there is overlap of the occipital bone and the atlas (Fig. 7.17). This displacement tends to compress the caudal aspect of the cerebellum and elevate and compress the caudal medulla (medullary kinking). AOO is likely a form of basilar invagination. Basilar invagination is a human craniocervical junction disorder in which the atlas and/or axis (C2) telescope toward the foramen magnum. It is possible that some cases of atlantoaxial instability in dogs are also analogues of basilar invagination. Since AOO has only recently been described, the bulk of the literature on the topic of CJAs refers to CLM. There is convincing evidence in the CKCS breed that CLM is a heritable disease, although the exact mode of inheritance has not been determined. Other breeds affected by CLM or similar disorders (like AOO) include Brussels Griffon (Griffon Bruxellois), Miniature/Toy Poodle, Yorkshire Terrier, Maltese, Pug dog, Pomeranian, Chihuahua, Staffordshire Terrier, Shih Tzu, Miniature Dachshund, Miniature Pinscher, French Bulldog, Boston Terrier,

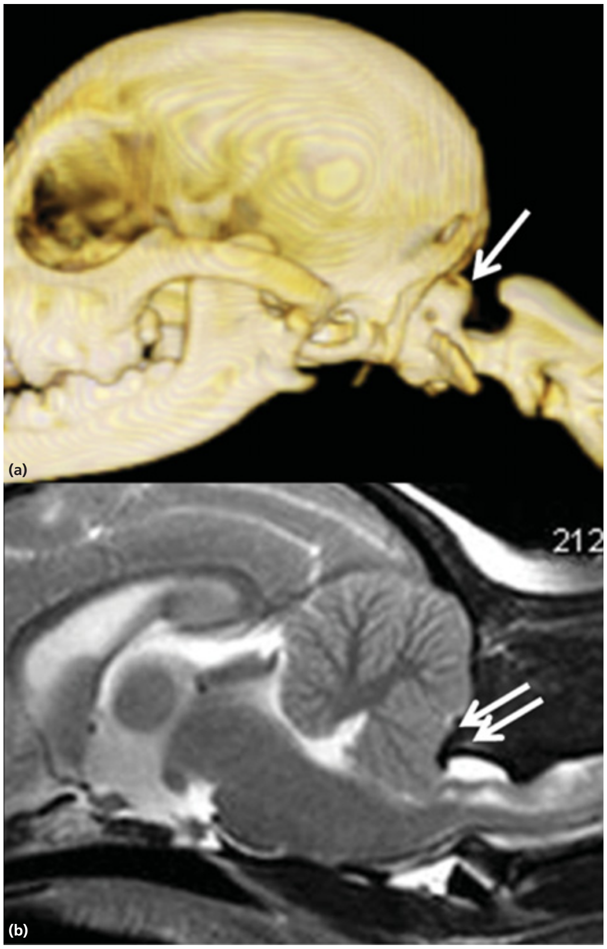


Figure 7.17 Three-dimensional reconstructed CT image (A) and midsagittal T2-weighted MR image (B) of a dog with atlanto-occipital overlap (AOO). (Dr. Dominic Marino, Long Island Veterinary Specialists, Plainview, NY, 2014. Reproduced with permission from Dr. Dominic Marino.)

and Pekingese. Anecdotal reports describe a disorder similar to CLM in several brachycephalic cats. Based on combined MR and CT imaging of dogs with CJAs, there is evidence that a substantial proportion (nearly 30%) of dogs diagnosed with CLM on MR images may actually have AOO as the main anatomic abnormality causing compression at the cervicomedullary junction. Bone is poorly visualized on MR images, but CT images clearly delineate what bony structures are causing compression at the cervicomedullary junction. In short, it is likely that many dogs with constrictive disorders at the cervicomedullary junction diagnosed via MR imaging as having CLM may actually have AOO. The vast majority of dogs with CLM or AOO have SM (usually noted in the cervical spinal cord, but often in multiple regions of the spine if these regions are also imaged), an accumulation of fluid within the spinal cord, as a consequence of the malformation. In patients with CLM or AOO, there tends to be some level of cerebellar compression as well as constriction of the cervicomedullary junction in the vicinity of the foramen magnum. With chronic bony compression at the cervicomedullary junction and probable turbulent CSF flow and pressure changes in this region, it is thought that the underlying meninges become hypertrophied with time. In both humans with Chiari type I and dogs with CLM, there is pathological evidence of dural fibrosis in the region of the malformation. In CLM, as in Chiari type I of people, the caudal aspect of the cerebellum is often projecting into or through (herniation) the foramen magnum, contributing to the obstruction of CSF flow between intracranial and spinal compartments. Progressive alterations in pressure dynamics between the intracranial and spinal compartments are believed to be responsible for the development of clinical signs of CLM. Although aberrant pressure dynamics due to the obstruction of CSF pathways at the level of the foramen magnum are generally agreed to be associated with SM in CJAs, the exact mechanism of this development is unknown and there are multiple theories proposed to explain it. Many of these theories operate on the probably incorrect premise that the SM fluid is CSF which is forced into the central canal of the spinal cord. The newer theories suggest that the SM fluid is actually derived from extracellular fluid from the cord itself, either driven into the central canal via a pulse pressure wave from behind the foramen magnum obstruction and/or drawn into the central canal via a centrifugally directed hydrostatic pressure force within the spinal cord. In normal dogs, there is pulsatile CSF flow across the foramen magnum from intracranial subarachnoid space to cervical spinal subarachnoid space and back again during systole and diastole, respectively. With an obstruction at the foramen magnum and/or substantial pressure differential (due to overcrowding of the caudal fossa), as occurs with CLM, CSF does not flow well in either direction. In this scenario, the pressure exerted during systole may drive either CSF or a pressure wave from the intracranial compartment into the central canal region of the cranial cervical spinal cord, causing it to progressively expand. This has been referred to as the "water-hammer effect." Another theory proposed is that CSF is "sucked" into the central canal region of the cervical spinal cord, especially during maneuvers that lead to sudden increases in intrathoracic an intra-abdominal pressure (e.g. coughing, sneezing, exercising). These Valsalva maneuvers lead secondarily to increased intracranial and intraspinal pressure via epidural venous distension. Because ICP is higher than in the cervical cord region, CSF fluid is drawn into the cervical cord when there are rapid increases in pressure. Pressure within the spinal compartment tends to increase more rapidly in the lumbar versus cervical regions, further promoting CSF movement into the cervical cord via this "suck" effect. The "slosh" phenomenon may also be involved in expansion of a syrinx. With distension of epidural veins during Valsalva events, CSF flows more freely within the syrinx than in the compressed subarachnoid space. Therefore, sudden CSF pressure waves cause CSF within the syrinx cavity to "slosh" around, fissuring surrounding parenchyma and enlarging the syrinx. The combination of spinal epidural vein distension (and the resultant pressurization of the subarachnoid space) and obstruction to CSF flow from the cervical spine to the intracranial compartment may also result in forcing subarachnoid CSF down perivascular spaces into the spinal cord parenchyma, progressively enlarging the syrinx. It has also been proposed that the displaced caudal cerebellum acts like a "piston." The piston theory proposes that the displaced cerebellum moves further caudally during systole, obstructing the subarachnoid space at the foramen magnum and exaggerating the systolic pulse pressure wave that is transmitted from intracranial to spinal compartments; this further forces CSF through perivascular spaces into the syrinx. Although all of the above theories may contribute to the development of a syrinx, none of them is an adequate explanation for this phenomenon. It has been shown that the syrinx usually has a higher pressure than the subarachnoid space, which would argue against theories that propose CSF is being forced or sucked into a low-pressure system from a higher-pressure system. In addition, syrinx fluid is not identical to CSF fluid: it has a lower protein concentration and is more consistent with extracellular fluid. Several related theories have been proposed that are more likely to adequately explain the pathogenesis of SM formation with CLM or Chiari type I malformation. The "intramedullary pulse pressure" theory proposes that the spinal cord parenchyma distal to the foramen magnum compression (or high-pressure region) is subjected to distending forces that tend to pull the tissue in an outward or centrifugal direction. The combination of transmittal of the systolic pulse pressure wave to the spinal cord parenchyma (due to obstruction of the subarachnoid space) and decreased subarachnoid space pressure in the spinal cord region (due to obstruction of the subarachnoid space rostral to the foramen magnum) leads to this mechanical distension. Over time, the distension leads to a cavity formation (syrinx), which is filled with extracellular fluid. The "Venturi effect" describes a similar mechanical spinal cord distension caused by increased CSF velocity distal to an obstruction. The obstruction (i.e. foramen magnum occlusion) causes a narrowing of the subarachnoid space and a resultant increased fluid velocity distal to the obstruction. This increased velocity lowers the hydrostatic pressure, producing a centrifugally directed suction effect, leading to spinal cord distension. This theory also assumes that the accumulated fluid in the syrinx is extracellular fluid and at a higher pressure than the subarachnoid space. Finally, there is a "vascular" theory to explain the development of SM in CLM cases. With increased CSF pressure in the intracranial compartment vs. the spinal compartment due to foramen magnum obstruction and/or caudal fossa overcrowding (especially during Valsalva maneuvers and systole), the venous and capillary beds become collapsed in the intracranial region and distended in the cervical spinal cord region (caudal to the obstruction). This occurs because CSF and venous pressure normally remain closely matched in both cranial and spinal compartments, and the venous system does not become obstructed as does the subarachnoid space with foramen magnum obstruction. With foramen magnum compression, the transmural pressure (difference between intravascular and interstitial pressure) of the venous and capillary system on either side of the obstruction is no longer uniform throughout the spinal cord. The uneven vascular expansion and contraction that ensues causes damage to the surrounding spinal cord. This hydrostatic stress-mediated damage to the spinal cord disrupts the blood-spinal cord barrier, promoting the accumulation of extracellular fluid within the spinal cord (i.e. syrinx development). Common to all theories of syrinx development in CLM is the causative factor of the obstruction or impeding of normal CSF flow at the foramen magnum.

b. Most dogs with CLM and other CJAs (AOO, AA instability) are presented for evaluation as young adults. Most of the OAAMs reported in dogs were presented within the first year of life. The typical age range at presentation for CLM appears to have changed over time, with many dogs developing clinical signs within the first year of life. In general, though the age range at clinical presentation is broad, most dogs present by the time they are 4 yrs old. Dogs that are presented at less than 2 yrs of age often have more severe clinical signs than older dogs. In recent years, there have been an increasing number of younger (< 1 yr of age) patients presenting with CLM or related disorders; whether this trend reflects an increasing severity of the disorder with subsequent generations, increased awareness of the veterinary community and hence earlier diagnosis, or a combination of these two factors is unknown. In the author's experience, AOO is more likely than CLM in toy- and small-breed dogs (e.g. Yorkshire Terrier, Chihuahua), whereas CLM is more likely in the CKCS breed. Similar to Chiari type

I of humans, there is a wide spectrum of possible neurologic presentations for dogs with CLM, including cervical myelopathy, cerebellovestibular dysfunction, and forebrain dysfunction (e.g. seizure activity). By far, evidence of cervical dysfunction and cerebellovestibular dysfunction are the most common and are often both present (e.g. multifocal CNS disease). Most of the CLM cases that the author encounters are presented for signs referable to the cervical region (e.g. neck pain, scratching activity) and subtle signs of central vestibular dysfunction are apparent on neurologic examination (i.e. not noticed by the owner). Occasionally, dogs with CLM and cervical SM present with a specific variant of cervical myelopathy called *central cord syndrome*. In this syndrome, the outwardly expanding syrinx causes more lower motor neuron (LMN) damage to the thoracic limb musculature than white-matter damage (to pelvic limbs); the result is thoracic limb paresis (often LMN in nature) that is notably worse than pelvic limb paresis. In some cases, the pelvic limbs may appear normal. Some specific clinical findings in dogs with CLM include cervical and cranial hyperesthesia, decreased menace responses with normal vision, positional ventrolateral strabismus, thoracic limb weakness, pelvic limb ataxia, persistent scratching (at the head, neck, and shoulder region, often without making skin contact), scoliosis, facial nerve paresis/paralysis (unilateral or bilateral), and hearing abnormalities. The persistent scratching activity and scoliosis are fairly unique clinical signs associated with SM. In the author's experience, these are more commonly encountered in the CKCS breed than in other breeds with CLM and SM. The scratching activity is believed to be due to the syrinx interfering with spinothalamic tracts and/or dorsal horn neurons, resulting in abnormal sensations (dysesthesia/paresthesia). Scoliosis (torticollis) is most likely due to asymmetric syrinx damage to sensory proprioceptive neurons innervating cervical musculature; an alternative, less likely hypothesis is syrinx damage to LMNs innervating cervical musculature. Scratching activity and neck discomfort often are exacerbated by abrupt weather changes, stress or excitement, and physical contact with the neck/shoulder region (e.g. collar). The presence of both pain and scoliosis has been shown to be significantly correlated with syrinx width in CKCS dogs with SM secondary to CLM. It is important to realize that, especially in the CKCS breed, other conditions may account for some of the clinical signs. There are several reports documenting a sizeable proportion of CKCS dogs with either CLM or CLM and SM that were regarded as clinically normal. Since these dogs were recruited for various imaging studies, they are not randomized samples of the CKCS population. Nonetheless, the percentage of clinically normal CKCS dogs with CLM and MR evidence of SM has been reported to range between approximately 25 and 70%; in one study, it was found that the low end of this range was associated with younger dogs (1 yr or less) and the higher end with older dogs (3 yrs or more). As mentioned, syrinx width tends to be smaller in asymptomatic dogs vs. symptomatic dogs. In addition, the syrinxes of asymptomatic dogs tend to be more symmetric and are less likely to extend into the dorsal horn region of the spinal cord. An enigmatic ear problem of the CKCS breed, called primary secretory otitis media (PSOM), has been described. Clinical signs of PSOM include apparent pain around the head and neck area, scratching of the head and neck, facial paralysis, and head tilt. Idiopathic epilepsy is also a prevalent disorder in the CKCS breed. Seizures have been reported to occur in 10 to 12% of humans with Chiari type I malformation; in the author's experience, seizure activity is an infrequent concurrent occurrence in CLM cases, and it is usually not possible to distinguish whether this is due to CLM or concurrent idiopathic epilepsy. Congenital deafness is also well described in the CKCS breed. The severity and rate of progression of CLM in dogs is variable, ranging from asymptomatic (i.e. finding evidence of CLM while imaging for some other reason) to extreme pain and debilitation with rapid worsening. In addition, some dogs with CLM have other concurrent disorders (e.g. disc extrusion, inflammatory brain disease) that could explain observed clinical signs. In such situations, it may be difficult to discern if the CLM is the main problem, contributory, or an incidental finding.

c. Diagnosis of CLM and other CJAs is made by MR imaging (Fig. 7.18). MRI is also the preferred imaging modality for diagnosing SM (Fig. 7.19). The malformation is best visualized on a midsagittal view (preferably T2-W), which includes the caudal fossa and cranial cervical cord. Consistent findings on MR imaging indicative of CLM are attenuation/obliteration of the dorsal subarachnoid space at the cervicomedullary junction and rostral displacement of the caudal cerebellum by the occipital bone. Other common MRI findings in CLM include SM (usually C2 level caudally), herniation of the caudal cerebellum through the foramen magnum (Fig. 7.20), and a "kinked" appearance of the caudal medulla. In one study of CKCS dogs, it was found that a flexed head position during MR imaging was more likely to exacerbate the degree of cerebellar herniation than an extended head position. Phase-contrast MRI (cine-MRI) is often used to measure CSF flow in humans with Chiari type I malformation, and has also been evaluated for use in

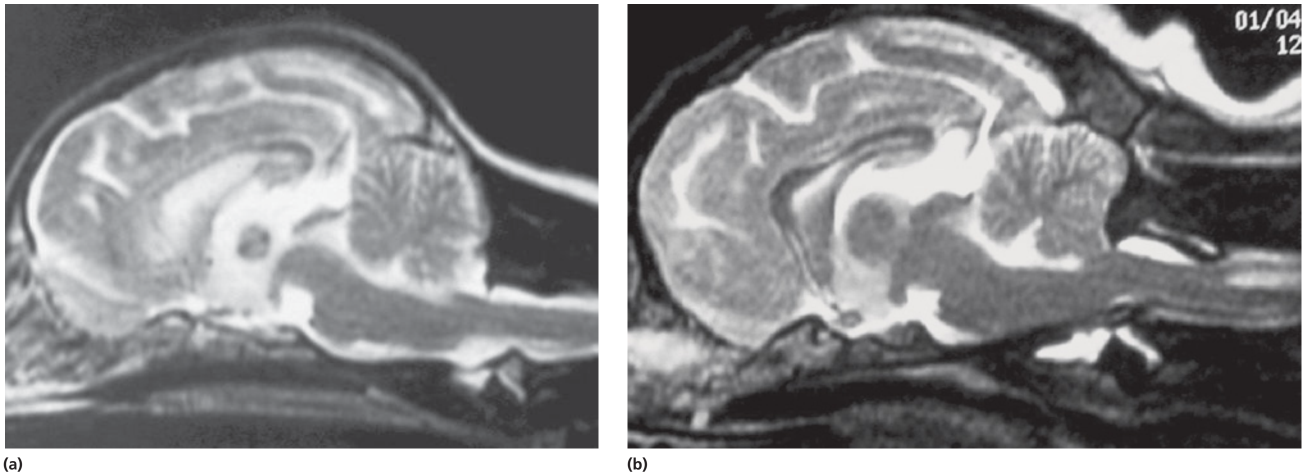


Figure 7.18 Midsagittal T2-weighted MR image of a normal small-breed dog (A) and a dog with Chiari-like malformation (B).

dogs with CLM. In dogs, decreased flow at the foramen magnum and C2/C3 vertebral level, as well as turbulent flow and jets, were predictive of the presence of SM. Dogs with MRI findings consistent with CLM will occasionally have evidence of other congenital disorders such as intracranial arachnoid (quadrigeminal) cyst, malformation of the C1 and/or C2 vertebrae, and hydrocephalus. In the author's opinion, most small-breed dogs normally have large lateral ventricles as a breed characteristic (ventriculomegaly) and are not hydrocephalic. As mentioned previously, the specific anatomic structure causing a constrictive effect at the craniocervical junction can be difficult to ascertain on an MR image. The author and colleagues routinely perform CT scans through the abnormal craniocervical junction following MR imaging to determine whether the abnormality is truly indicative of CLM or something else (e.g. AOO). Several potential methods of screening for the presence or absence of CLM/SM have been evaluated in dogs, including ultrasound, brain-stem auditory evoked response (BAER) testing, and thermography.

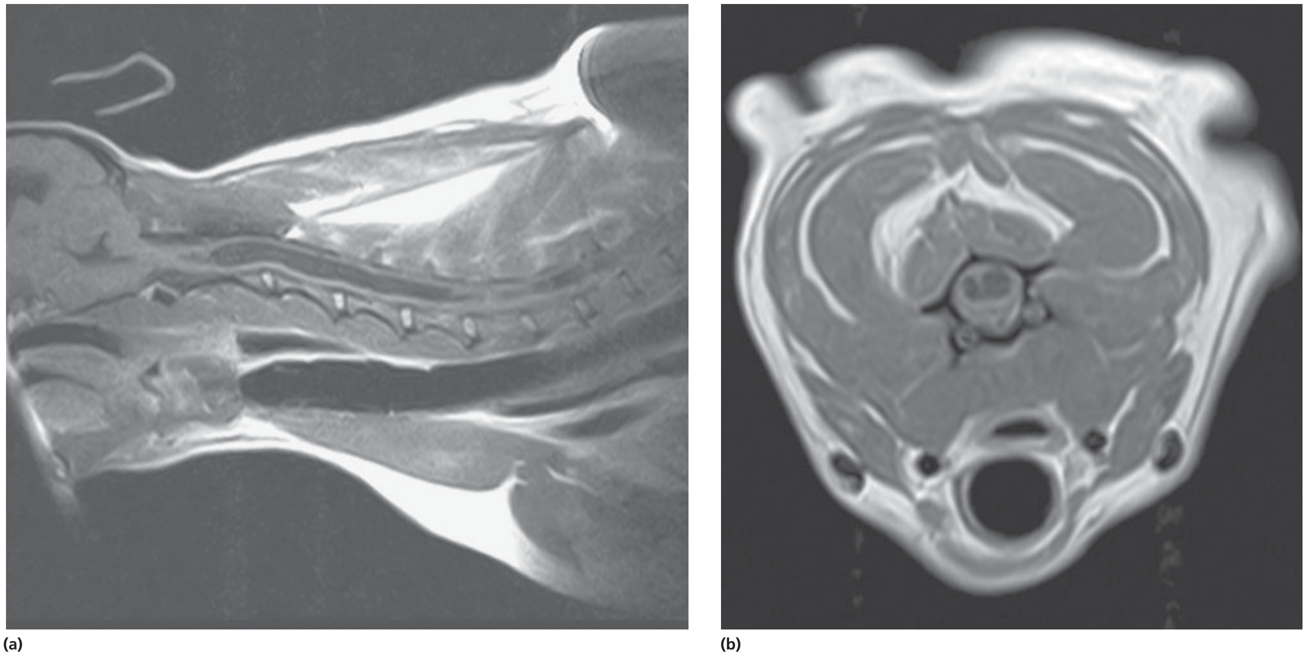


Figure 7.19 Sagittal (A) and transaxial (B) cervical spinal cord MR images demonstrating a large syrinx cavity in a dog with Chiari-like malformation.

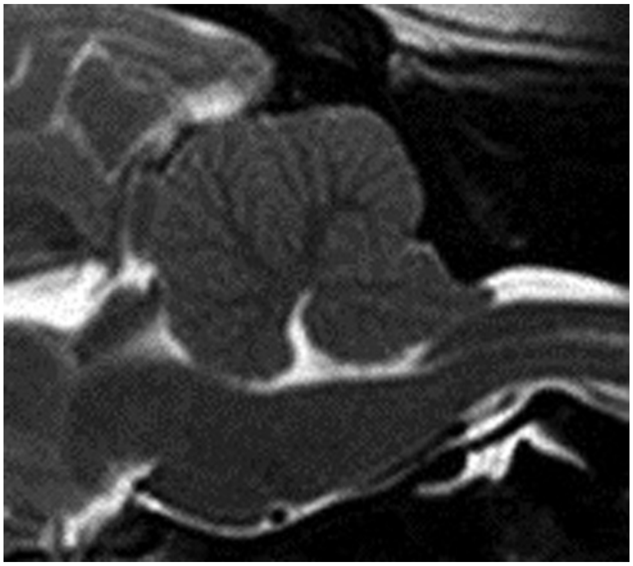


Figure 7.20 Midsagittal T2-weighted MR image of a dog with Chiari-like malformation, demonstrating cerebellar herniation through the foramen magnum.

None of these methods has emerged yet as a reliable screening tool; in addition, screening for a breed such as the CKCS that has such a high prevalence of the CLM/SM disorder with a high proportion of asymptomatic dogs may be of limited value. In the Brussels Griffon breed, one study demonstrated that a specific ratio based upon measurements from skull radiographs was 87% sensitive and 78% specific for predicting the presence of CLM (as diagnosed on MR images). In the absence of concurrent disease processes, CSF analysis is usually normal in CLM/SM; occasionally, a mild mononuclear pleocytosis will be apparent, however. In one study of CKCS dogs with CLM with or without SM, it was found that total nucleated cell counts (TNCC) and protein concentrations in CSF were significantly higher in dogs with SM versus dogs without SM. In that study, there was also a positive association between TNCC and syrinx size.

d. Treatment of CLM and other CJAs can be divided into medical and surgical therapy. In people with symptomatic Chiari type I malformation, surgical therapy is considered the treatment of choice, with foramen magnum decompression (FMD) being the preferred surgical procedure. Adjunctive surgical procedures are occasionally performed in people who have had a suboptimal response to FMD; such procedures usually involve placement of a shunt to divert SM fluid from the spinal cord region to another location for absorption (e.g. pleural or peritoneal cavity, subarachnoid space). Although there is a high degree of success in the surgical management of Chiari type I malformation in people, there is a re-operative rate varying from 8 to 30% for FMD; the most common problem necessitating re-operation is excessive scar tissue formation at the FMD site causing compression at the cervicomedullary junction, effectively recreating the original disease state.

Medical therapy for dogs with CLM generally falls into three categories: analgesic drugs (implies relief of dysesthesia/paresthesia also), drugs that decrease CSF production, and corticosteroid therapy. By far the most useful drug available for the relief of scratching activity associated with SM has been gabapentin (10 mg/kg body weight PO, q 8 hrs). It has been shown that neuropathic pain is accentuated over time due to up regulation of the α2δ-1 subunit of voltage-gated calcium channels in dorsal root ganglion neurons and dorsal horn nociceptive neurons of the spinal cord. Gabapentin, and the newer gabapentin analog, pregabalin, are believed to exert their antinociceptive effects by selectively binding to the α2δ-1 subunit and inhibiting calcium influx in these neurons. Side effects of gabapentin are minimal, usually restricted to mild sedation, pelvic limb ataxia, and weight gain. Pregabalin is the "next generation" of gabapentin with a higher affinity for the α2δ-1 subunit; the elimination half-life in dogs is about 7 hrs vs. 3–4 hrs for gabapentin. In the author's experience, oral pregabalin dosed at 2.0 mg/kg q 12 hrs is more effective in treating dogs with CLM/SM than gabapentin. Side effects of pregabalin have been limited to sedation and weight gain. Orally administered opiate drugs are sometimes helpful in alleviating neck and head pain in CLM dogs. The author has had success using oral tramadol (2–4 mg/kg, q 8–12 hrs). A number of drugs aimed at decreasing CSF production have been used in CLM patients, in an effort to diminish the CSF pulse pressure. All information regarding efficacy of these drugs is anecdotal. They include omeprazole (a proton pump inhibitor), acetazolamide (a carbonic anhydrase inhibitor), and furosemide (a loop diuretic). More specific information regarding these drugs is covered in the congenital hydrocephalus discussion. Corticosteroids are often used in the medical management of CLM. Potential benefits include anti-inflammatory effects, decreased CSF production, and decreased substance P (a nociceptive neurotransmitter) expression in spinal cord dorsal horn neurons. An initial anti-inflammatory dose of 0.5 mg/kg PO, q 12 hrs is often effective in controlling clinical signs. This dose should be tapered, if at all possible, to an every-other-day schedule within the first month of therapy. In most cases of CLM, medical therapy will diminish the severity of clinical signs, but resolution is unlikely.

The preferred surgical procedure for the treatment of CLM in dogs is FMD. Based on two similar reports, short-term surgical success rates with FMD in dogs with CLM are approximately 80%. One report found an inverse relationship between the length of time clinical signs were present prior to surgical intervention and the extent of postoperative improvement. Unfortunately, there appears to be a disease relapse rate ranging from 25 to 47% of cases; most of these relapses are suspected to be due to excessive postoperative scar tissue formation at the FMD site. In most cases, clinical signs of pain are routinely relieved with surgery, but scratching activity tends to persist. The author and colleagues have adapted a cranioplasty procedure used in human FMD surgery to discourage excessive postoperative scar tissue from recompressing the operative site (Fig. 7.21). Based on over 300 cases, the titanium mesh/PMMA plate procedure has

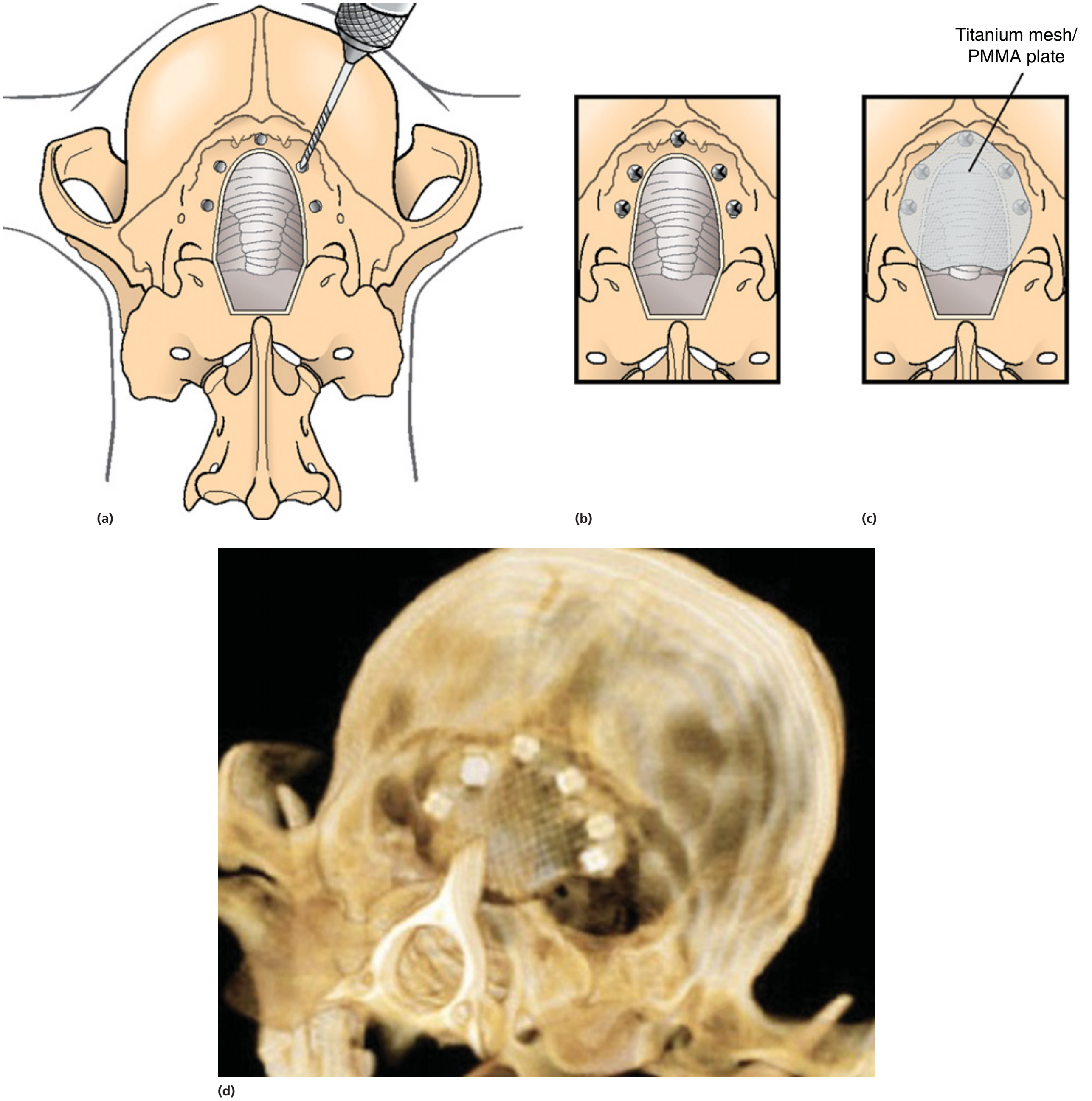


Figure 7.21 Schematic illustration of foramen magnum decompression/cranioplasty procedure for Chiari-like malformation (A–C), and postoperative three-dimensional CT reconstruction (D) demonstrating the plate in place. (Dewey, 2013. Reproduced with permission from Elsevier.)[132]

reduced the re-operative rate to less than 1% (unpublished data). Syringosubarachnoid shunting has been evaluated retrospectively in a small cohort of dogs (11 dogs) with CLM/SM; nine dogs were judged as neurologically improved at 6 mos follow-up, and seven dogs were still alive a mean of 2.6 yrs post surgery.

There is sparse information regarding the prognosis for CLM in dogs with both surgical and nonsurgical management. Most dogs with CLM will respond favorably to medical therapy, although in many cases this response is temporary. In one group of 10 CLM dogs treated medically, five dogs were euthanized within 2 yrs due to disease progression and diminished responsiveness to therapy. In another study, 36% of CLM dogs treated medically were euthanized due to clinical signs of their disease at mean of 1.7 yrs from the time of diagnosis. In one longer-term study evaluating the response to nonsurgical management, 48 CKCS dogs with CLM (+/−SM) were prospectively followed for a mean of 39 mos; despite the fact that the majority (75%) of these dogs continued to deteriorate clinically over time (25% remained static or improved), 75% of the total (36 dogs) were still alive at the end of the study period. Although the surgical success rate is generally favorable for CLM in dogs, many dogs still require some degree of medical management and some dogs do not improve—even in the absence of postoperative scar tissue compression of the FMD site. It is hoped that future modifications of surgical procedures (e.g. larger decompressions to account for intracranial cavity volume/parenchyma mismatch) or combinations of procedures (e.g. FMD with syrinx shunting) will ameliorate this problem. In general, the overall prognosis for CLM and related disorders in dogs is guarded to good for sustained improvement in clinical signs.

3. Intracranial arachnoid cyst (IAC)[134, 140, 141, 169, 358, 446, 476, 553, 611, 750, 751]
   a. Intracranial arachnoid cyst (also termed intra-arachnoid cyst and quadrigeminal cyst) is a developmental brain disorder in which CSF is thought to accumulate within a split of the arachnoid membrane during embryogenesis. The developing neural tube is surrounded by a loose layer of mesenchymal tissue called the perimedullary mesh; this tissue eventually becomes the pia and arachnoid layers of the meninges. In normal development, pulsatile CSF flow from the choroid plexuses is thought to divide the perimedullary mesh into pia and arachnoid layers, effectively creating the subarachnoid space. It is postulated that some aberration of CSF flow from the choroid plexuses during this stage of development forces a separation within the forming arachnoid layer, eventually leading to the creation of an IAC. The intra-arachnoid location of IACs has been demonstrated via light and electron microscopy in people. The mechanisms by which an IAC continues to expand with fluid are unknown, but several theories have been proposed. Fluid may be secreted by the arachnoid cells lining the cyst cavity. There is evidence that cells lining the IAC may have secretory capacity. There may also be fluid movement into the cyst via an osmotic pressure gradient. Considering that the fluid within the IAC is nearly identical to CSF, this theory is unlikely. In addition, there have been documented cases in people in which small slits exist between the IAC and the subarachnoid space; these slits act as one-way valves, diverting CSF into the cyst during systole which cannot return to the subarachnoid space during diastole.

      Although IAC has been reported to occur in several locations in humans, all reported canine cases have been in the caudal fossa. Because IAC is typically associated with the quadrigeminal cistern in dogs, these accumulations of fluid are often called quadrigeminal cysts in this species. A similar structure was reported in a 1-yr-old cat, based upon MR imaging of the patient. The author has also observed a similar cystic condition in a kitten. Also termed intracranial intra-arachnoid cyst, IAC accounts for 1% of all intracranial masses in people, and has been sporadically reported in dogs. IAC is often an incidental finding in humans; it has recently been suggested that this may also be the case for IAC in dogs. In the veterinary literature, there have been nine clinical reports of IAC in dogs, with a total of 53 cases. The IAC was suspected to be an incidental finding in approximately one-third to over one-half of the reported cases. The vast majority of reported IAC cases in dogs have been small breeds, with a predominance of brachycephalic dogs. The breeds reported to date include Shih Tzu (12), Maltese (4), Pug (4), CKCS (4), Yorkshire Terrier (4), Lhasa Apso (4), Chihuahua (3), Staffordshire Bull Terrier (3), Bulldog (3), Pekingese (2), West Highland White Terrier (2), and one each of Bichon Frise, Pomeranian, Cairn Terrier, Jack Russell Terrier, Terrier mix, Beagle, Miniature Schnauzer, and German Shorthaired Pointer.
   b. There is a wide age range at clinical presentation for dogs with IAC (2 mos–10 yrs), with an approximate average age of 4 yrs. The most common clinical signs seen with IAC are forebrain (including seizure activity) and/or central vestibular (cerebellovestibular) dysfunction. Dogs may also present with a primary complaint of neck pain.
   c. Diagnosis of IAC is typically made via CT or (preferably) MRI. IACs can also be visualized using ultrasound imaging (via foramen magnum, temporal

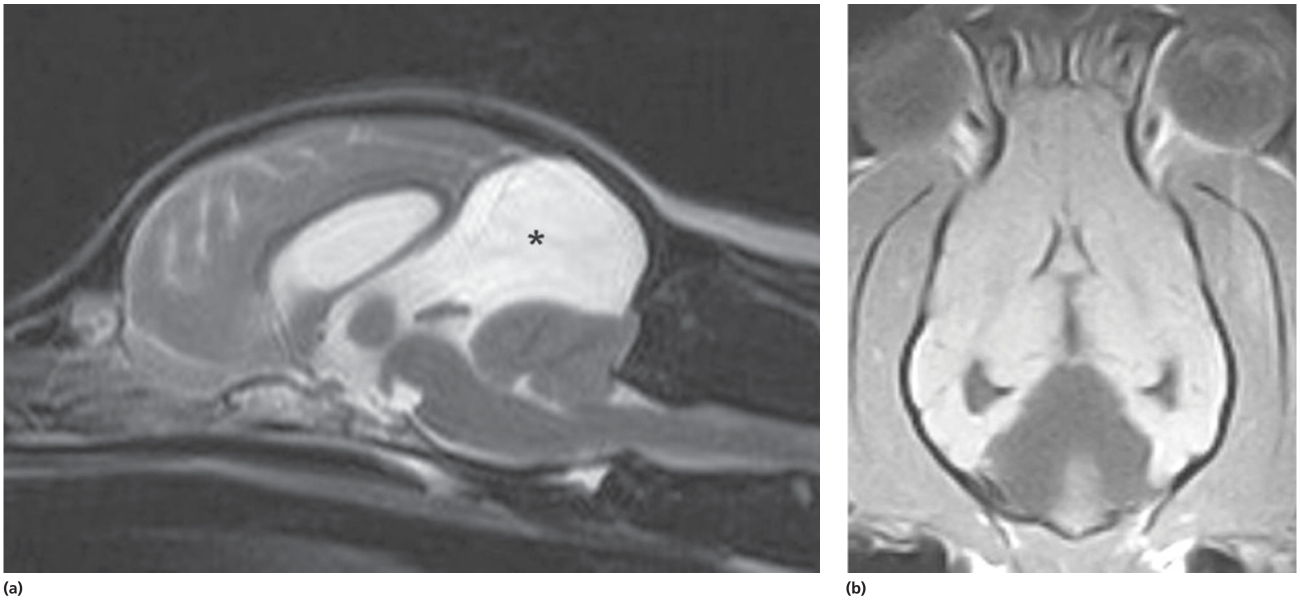


Figure 7.22 T2-weighted midsagittal (A) and dorsal T1-weighted (B) MR images of an intracranial arachnoid cyst.

window, and/or persistent bregmatic fontanelle), especially in younger dogs. The characteristic appearance of IAC is a large, well-demarcated fluid-filled structure, isointense with the CSF spaces and located between the caudal cerebrum and rostral cerebellum (Fig. 7.22). Because IAC may be an incidental finding, it is important to rule out concurrent inflammatory disease (i.e. CSF examination). In the author's opinion, it is often difficult or impossible to discern whether IAC in the presence of another brain disorder is purely an incidental finding. Since the presence of a large, fluid-filled structure within the cranial vault likely decreases intracranial compliance, some of these IACs may be contributory, rather than an incidental finding. As this disorder is believed to represent a developmental abnormality of the intracranial ventricular CSF system, it may occur concurrently with other fluid abnormalities (e.g. congenital hydrocephalus). The cyst may or may not communicate with the remainder of the ventricular system. When faced with evidence of IAC and another disease (e.g. GME) in the same patient, the optimal response to treatment may entail treating both conditions.

d. Medical treatment for IAC is identical to that described for congenital hydrocephalus (e.g. corticosteroids, diuretics, anticonvulsants if indicated). Dogs with IAC tend to respond initially to medical therapy, but the response is often temporary. The surgical management of IAC in people is typically either achieved via cyst fenestration or cystoperitoneal shunt placement (Fig. 7.23). Both procedures have been reported in dogs with IAC. There have been five reported fenestration cases in which IAC was considered the primary disease. Three were re-imaged post surgery; two of the three dogs had evidence of cyst persistence on MR imaging. However, only one of these two dogs required re-operation. The author has reported successful cystoperitoneal shunting of four dogs with IAC. The success rate for the surgical management of IAC appears to be high in humans and dogs, and whether fenestration or cystoperitoneal shunting is the preferred procedure remains controversial for both species.

4. Neuronal migration disorders—lissencephaly/pachygyria and polymicrogyria[99, 152, 694, 745]
   a. These are uncommon, probably heritable disorders thought to be due to abnormal cerebral cortical neuronal migration during fetal development. Lissencephaly/pachygyria is characterized by reduced numbers or the absence of gyri on the surface of the cerebral hemispheres and an abnormally thickened, histologically disorganized (loss of the normal laminar arrangement) cerebral cortex. This disorder is most commonly encountered in the Lhasa Apso breed, but has also been described in the Wire-haired Fox Terrier, Irish Setter, and Korat cat. In Irish Setters, cerebellar hypoplasia and dysplasia occur concurrently. Polymicrogyria is characterized by excessive, small gyri on the cerebral cortex. This condition was described in a group of four related standard Poodles that also displayed asymmetric dilation of the lateral ventricles. Disorganization of the cerebral cortex was also evident histologically in these standard Poodles.

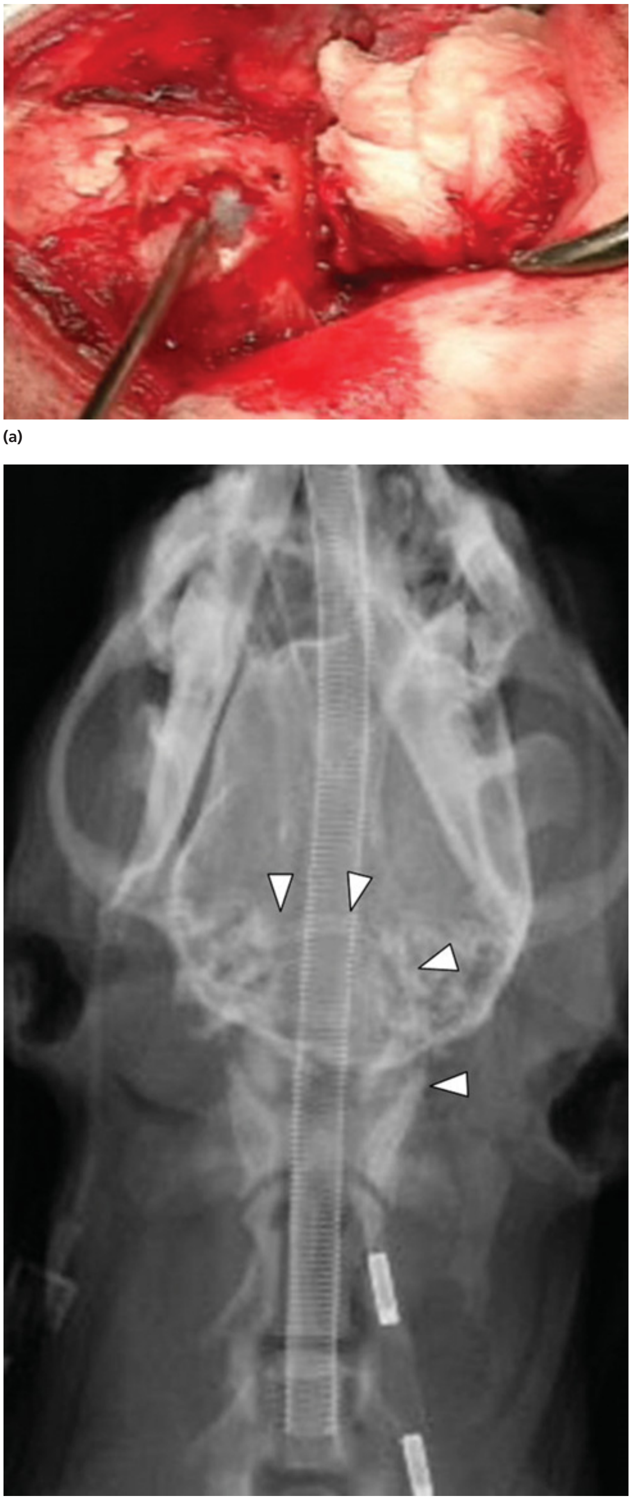


Figure 7.23 Intraoperative view (A) of the exposed wall of an intracranial arachnoid cyst and postoperative ventrodorsal radiograph (B) demonstrating placement of a cystoperitoneal shunt in a dog with an intracranial arachnoid cyst. (Dewey *et al.*, 2007. Reproduced with permission from Wiley.)[140]

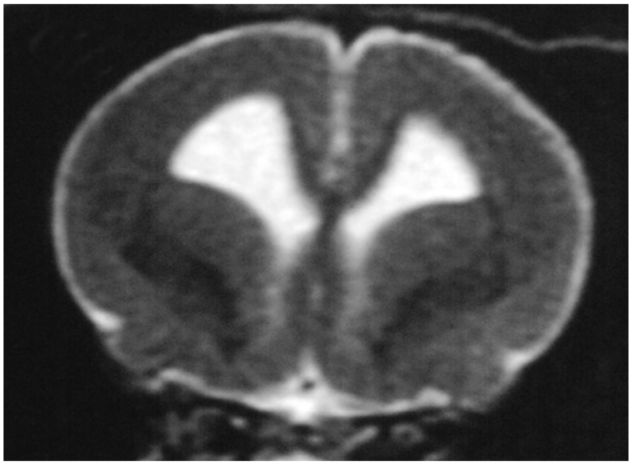


Figure 7.24 T2-weighted MR image (transaxial view) of a lissencephalic dog's brain. Note the absence of sulci on the cerebral surface. (Dr. G. Kort, 2014. Reproduced with permission from Dr. G. Kortz.)

b. Clinical signs associated with these neuronal migration disorders are typically evident within the first several months of life. Animals with lissencephaly/pachygyria may have behavioral abnormalities and seizure activity, and may be difficult to train. The dogs reported with polymicrogyria and ventriculomegaly exhibited blindness as the major clinical abnormality. Other clinical signs included a hypermetric gait in three of four dogs, and seizures in one dog.

c. The diagnosis of these disorders is tentatively based upon characteristic clinical signs in a susceptible breed. Diagnosis may be aided by advanced imaging (Fig. 7.24). Although it has not yet been investigated thoroughly in dogs and cats, MR imaging is used to diagnose children with these disorders, and would be preferable to CT in demonstrating abnormal gyral architecture of the cerebral cortex. CT and MRI revealed asymmetric ventricular dilation in three of four standard Poodles with polymicrogyria. A definitive diagnosis of neuronal migration disorders depends upon gross and histopathologic findings of the brain via biopsy or at necropsy.

d. Neuronal migration disorders are nonprogressive, nonfatal diseases. While there are no treatments for these disorders, animals with lissencephaly/pachygyria may be acceptable pets, if provided the appropriate home environment. Seizures can be controlled with anticonvulsant medication (see Chapter 9). The same may be true for animals with polymicrogyria; however, the only dogs reported to date with this disorder were euthanized at an early age.

5. Dandy–Walker syndrome (DWS)[92, 580, 631, 694]
   a. This is a developmental malformation described in dogs and one cat. The most striking abnormality is the partial or complete lack of a cerebellar vermis. Cystic dilation of the fourth ventricle, hydrocephalus, and other malformations of the brain and spinal cord often accompany the vermal defects. In humans, three separate developmental disorders involving cerebellar vermal hypoplasia are described: Dandy–Walker syndrome, rhombencephalosynapsis, and Joubert's syndrome. A more inclusive term, such as cerebellar vermis hypoplasia (CVH), may be more correct to use in cases that do not entirely fit the category of DWS. This disorder leads primarily to cerebellar dysfunction and is discussed in more detail in Chapter 12.
6. Miscellaneous malformations[3, 99, 207, 307, 341, 374, 426, 450, 518, 554, 679, 690, 694, 706]
   a. There are a number of rarely reported malformations of the brain, most of which are not compatible with life. Exencephaly is the protrusion of brain tissue through a calvarial defect without a meningeal or skin covering. Meningoencephalocele refers to a similar protrusion that maintains both meningeal and skin coverings. Hydranencephaly describes the absence or near absence of cerebral cortical tissue, and may be difficult to discern from very severe hydrocephalus. Anencephaly is the total or partial absence of brain tissue and calvarium. Porencephaly is a condition characterized by cystic cavities in the cerebrum, which may communicate with the ventricular system. Holoprosencephaly describes a single, nondivided cerebrum. This disorder has been described in a Miniature Schnauzer and has been associated with hypodipsic hypernatremia in this breed. Cyclopian malformation refers to the development of a single, median-positioned eye. Numerous etiologies have been proposed for these disorders, including heritable defects, infectious agents, toxin exposure, and nutritional imbalances. Meningoencephaloceles have been described in Burmese kittens as part of a heritable craniofacial malformation syndrome. Feline parvovirus (panleukopenia virus) has been implicated as a cause of hydranencephaly and porencephaly in kittens. Agenesis of the corpus callosum and cyclopian malformation have been described in kittens exposed to griseofulvin during gestation. Exencephaly may occur when kittens are exposed to griseofulvin, methylmercury, or hydroxyurea during gestation.

      A number of cystic intracranial developmental lesions have been reported in the veterinary literature. The majority of these reports have been of epidermoid cysts; dermoid cysts, choroid plexus cyst, and epidural mucocele have also been reported. Epidermoid cysts (cholesteatomas) and dermoid cysts have been reported primarily in the cerebellomedullary angle region of dogs of various ages. Most of these dogs had clinical signs of cerebellovestibular dysfunction, though a few were incidental necropsy findings. Epidermoid and dermoid cysts are thought to be due to a failure of complete separation of neuroectoderm from non-neural (epithelial) ectoderm during embryogenesis (i.e. neural tube closure). Epithelial ectoderm with (dermoid cyst) or without (epidermoid cyst) adnexal structures (e.g. hair follicles, sebaceous glands) becomes entrapped within the CNS, and forms a slowly expanding cystic mass. The lumen of an epidermoid cyst contains a mixture of cholesterol, keratinocytes, and keratinaceous debris; dermoid cyst lumens contain combinations of fat, hair, and sweat secretion. Leakage of cyst contents into the surrounding tissue can lead to aseptic meningitis, termed Mollaret's meningitis in people.
   b. Dogs and cats with these miscellaneous brain malformations are usually either stillborn, die, or are euthanized shortly after birth. Epidermoid cysts are usually diagnosed in mature dogs, usually young adults. The reports of dermoid cysts in dogs have also been seen in adults. The CT and MRI appearance of epidermoid cysts has been described in dogs, as has the MRI appearance of dermoid cysts in dogs. These imaging findings are similar to what is reported in people for these disorders. Epidermoid cysts appear to be hypoattenuating on CT images, hypointense on T1-weighted (T1-W) MR images, and hyperintense on T2-W MR images; there is also peripheral or ring-type enhancement of the cyst wall with contrast administration. Sustained hyperintensity of the cyst lumen on FLAIR imaging for epidermoid cysts (due to a lack of free, unbound water protons within the cyst) helps to distinguish them from other cystic-appearing diseases like IACs (Fig. 7.25). Dermoid cysts tend to be hyperintense on T1- and T2-W MR images, due to the fat content within the cyst lumen. The majority of the histopathologic descriptions to date of epidermoid and dermoid cysts have been necropsy reports. Surgical removal of a caudal fossa epidermoid cyst has been described in a dog, but the dog died in the postoperative period. Successful removal of a choroid plexus cyst from the caudal fossa of a dog has also been reported. The successful surgical management of meningoencephalocele has also been described in both the dog and the cat.

      A cat with intracranial epidural mucocele recovered fully following the surgical removal of the cystic structure. There are no effective treatments for the majority of these disorders and the prognosis is often guarded to poor.

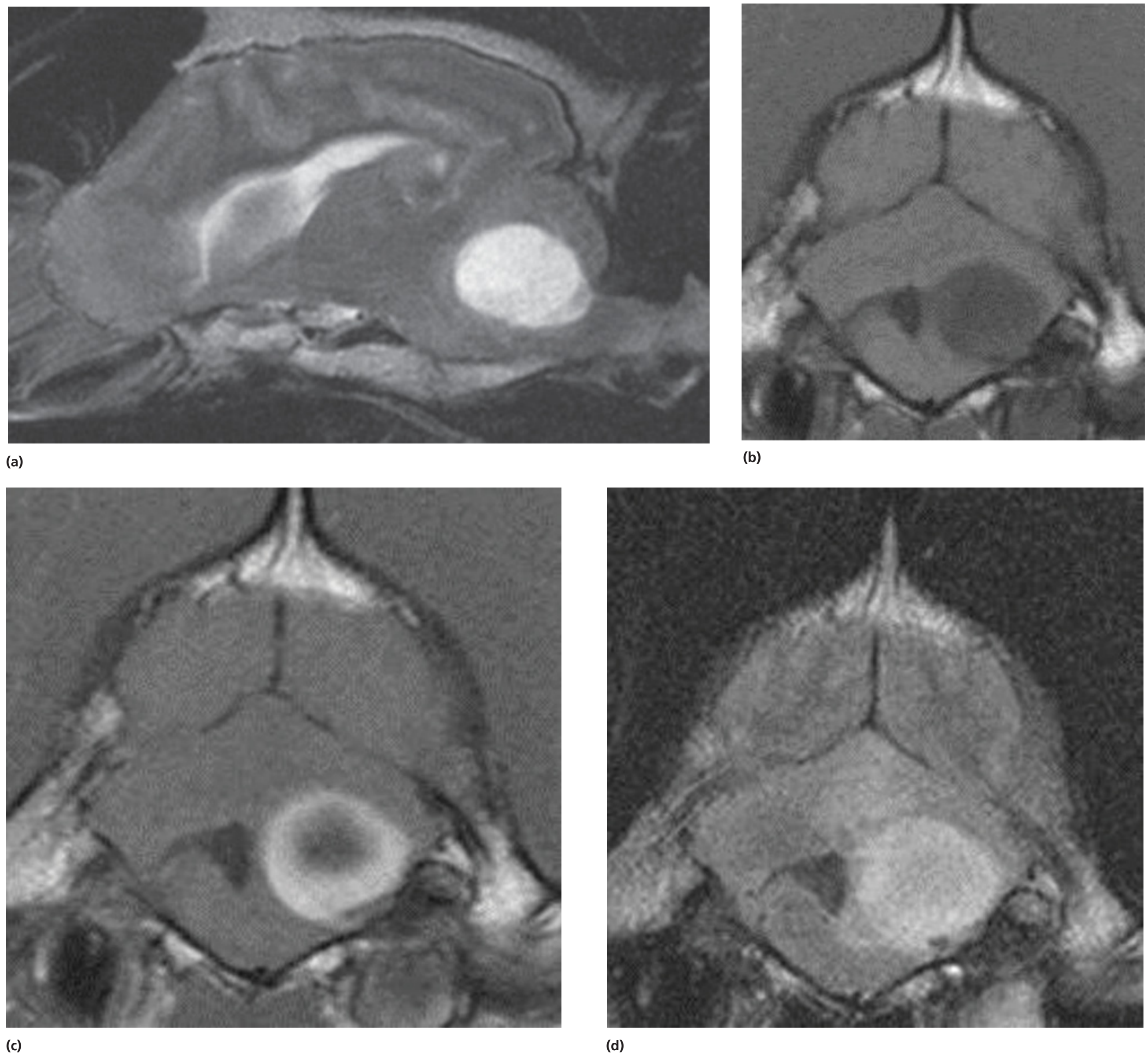


Figure 7.25 Sagittal T2-weighted (A), transaxial T1-weighted (B), T1-weighted with contrast (C), and FLAIR (D) images of an epidermoid cyst in a dog's brain. (Dr. Jennifer L. Bouma, DACVR, 2014. Reproduced with permission of Dr. Jennifer L. Bouma.)

C. Metabolic: Because the brain has extremely high metabolic demands, systemic abnormalities that interfere with normal energy metabolism of the CNS may result in clinical signs of encephalopathy. Since the cerebral cortical neurons are most susceptible to altered energy metabolism, most of these metabolic diseases lead to signs of forebrain dysfunction. If not corrected, however, brain-stem dysfunction and ultimately death of the patient can result from some metabolic diseases. Patients with metabolic encephalopathy tend to have symmetric clinical signs. In general, alleviating or eliminating clinical signs of encephalopathy in patients with the following disorders depends primarily on treatment of the underlying metabolic disease. The basic treatment strategies for these underlying diseases are discussed, but an in-depth discussion of specific therapies for these metabolic conditions is beyond the scope of this text.

1. Hepatic encephalopathy[8–11, 20, 65, 67, 118, 189, 200, 266, 269, 295, 305, 310, 320, 370, 383, 388, 407, 421, 422, 424, 428, 463, 465, 474, 475, 495, 519, 520, 549, 630, 640, 698, 700, 730–732, 734, 744, 757, 788]

   a. A major function of the liver is to filter out potentially toxic substances received from the gastrointestinal tract (via the portal venous system) so that these substances do not gain access to the general circulation. When this function is compromised due to either hepatic failure or portosystemic shunting, or both, clinical signs of encephalopathy may result. The pathogenesis of hepatic encephalopathy is complex. Proposed causative factors include gut-derived toxins—such as ammonia, skatoles, indoles, and short-chain fatty acids—that reach the systemic circulation and cause neurotoxicity; alteration in brain neurotransmitter balance and/or production of "false neurotransmitters" due to increased circulating levels of aromatic amino acids; and circulating benzodiazepine-like substances that act on brain GABA receptors. There are several documented neurotransmitter imbalances associated with hepatic encephalopathy, including decreased glutamatergic tone and increased GABA-ergic tone. Profound changes in brain serotonin metabolism have recently been described in hepatic encephalopathy. These aberrations involve increased serotonin production from tryptophan (probably related to hyperammonemia), increased serotonin turnover (metabolism by monoamine oxidase system), and decreased levels of serotonin transport proteins and neuronal binding sites. The overall effect is thought to be a reduction of serotonergic neurotransmission.

Most cases of hepatic encephalopathy are due to congenital portosystemic shunts (PSS), which are aberrant vascular communications between the portal and systemic venous systems (i.e. bypassing the liver). The majority of these shunts are extrahepatic (located outside the liver parenchyma) versus intrahepatic (within the liver parenchyma). Extrahepatic shunts typically occur in small- and toy-breeds of dogs (e.g. Yorkshire Terriers, Miniature Schnauzers) and less commonly in cats, whereas intrahepatic shunts are more common in larger dog breeds (e.g. Labrador Retrievers, Irish Wolfhounds). In one report, the median age for dogs with extrahepatic PSS was 12 mos, and over one-third of the cases were over 2 yrs of age at diagnosis. The Yorkshire Terrier is the most commonly reported breed with extrahepatic PSS. There are a number of breeds that are predisposed to PSS, including Havanese, Yorkshire Terrier, Maltese, Dandie Dinmont Terrier, Pug, and Miniature Schnauzer. There is probably a hereditary basis to PSS, and there is evidence to that effect for Yorkshire Terrier, Cairn Terrier, and Irish Wolfhound breeds. Multiple acquired extrahepatic shunts can form as a result of chronic portal hypertension in dogs and cats with long-standing hepatic disease.

A congenital disorder termed hepatic microvascular dysplasia (HMD) has been described in which there are suspected to be multiple microscopic shunting vessels within the liver that bypass the hepatic sinusoidal system, rather than a grossly visible anomalous vessel. This appears to be most common in small and toy breeds of dogs (e.g. Cairn Terriers may be predisposed) and cats. Animals with PSS may also have HMD concurrently. Other causes of hepatic encephalopathy include congenital arteriovenous fistulas, and acquired hepatic disorders (e.g. toxin-induced, infectious, chronic active hepatitis, neoplasia).

b. Clinical signs of hepatic encephalopathy include obtunded mental status, abnormal behavior, compulsive pacing, head-pressing, visual deficits, and seizure activity. Other clinical signs consistent with hepatic failure (e.g. weight loss or failure to gain weight, anorexia, vomiting, diarrhea, PU/PD) are often present. Cats with PSS are more likely to seizure than dogs, and often exhibit ptyalism as a characteristic clinical sign. Patients with PSS usually develop clinical signs associated with hepatic insufficiency within the first year of life, but adult animals are occasionally encountered. Dogs and cats with HMD (without PSS) and acquired hepatic disorders are more likely to develop clinical signs as adults (over 1 yr).

Although seizure activity may be a component of the hepatic encephalopathy displayed by PSS dogs, it is infrequent. In one large retrospective study of 168 dogs with single extrahepatic shunts, only one dog had evidence of seizure activity. However, an uncommon (approximately 5% of cases) yet often fatal postoperative complication of PSS attenuation in dogs is seizure activity, which is often severe (i.e. clusters, status epilepticus). Most of these patients do not have seizure histories prior to surgery, typically begin seizuring within the first few days postoperatively, and usually are profoundly encephalopathic. A similar phenomenon has been described in a small number of cats following PSS surgery. Following shunt ligation in some dogs, abrupt changes in brain serotonin levels may also be involved in the development of seizures.

c. Diagnosis of hepatic encephalopathy is based upon documenting hepatic dysfunction in a patient with neurologic deficits typical of a metabolic encephalopathy. Bloodwork abnormalities (microcytic red blood cells, low blood urea nitrogen [BUN], low albumin, etc.) often point to a liver problem. Liver enzymes (e.g. alanine aminotransferase [ALT], serum alkaline phosphatase [SAP]) are typically normal to slightly elevated in PSS and HMD patients but are often elevated in acquired hepatic disorders. Ammonium biurate crystals may be evident on urinalysis in PSS patients. Liver function tests, such as serum bile acid and ammonia levels, are often abnormally elevated.

There are multiple methods (e.g. mesenteric portography, abdominal ultrasound) available to

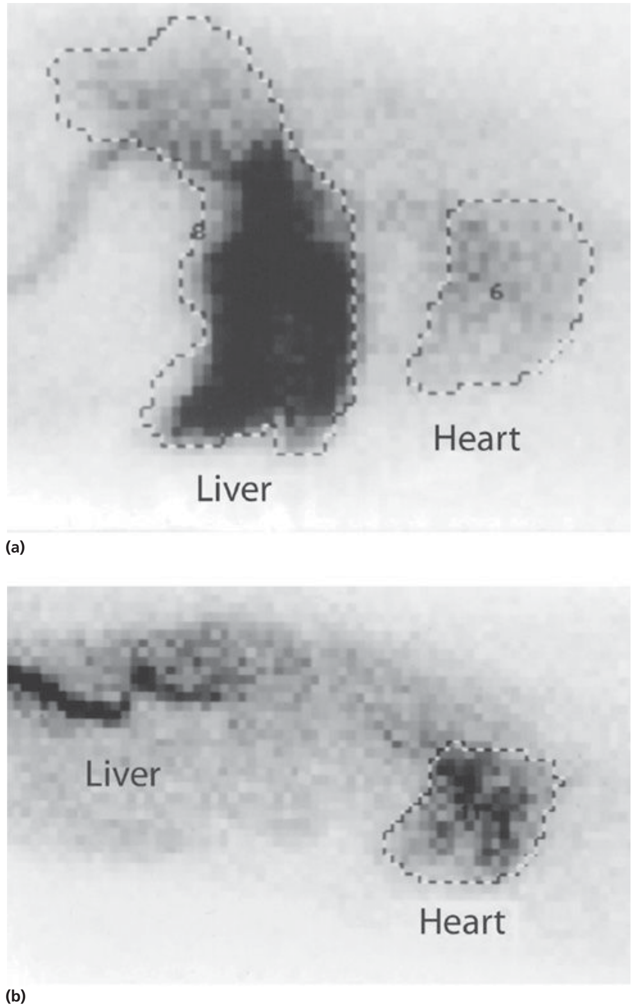


Figure 7.26 Normal (A) and abnormal (B) per-rectal scintigraphy studies in dogs. Note the lack of radioactivity in the liver of the dog with a PSS (B) compared to the liver of a normal dog (A). (Dr. Anne Bahr, 2014. Reproduced with permission from Dr. Anne Bahr.)

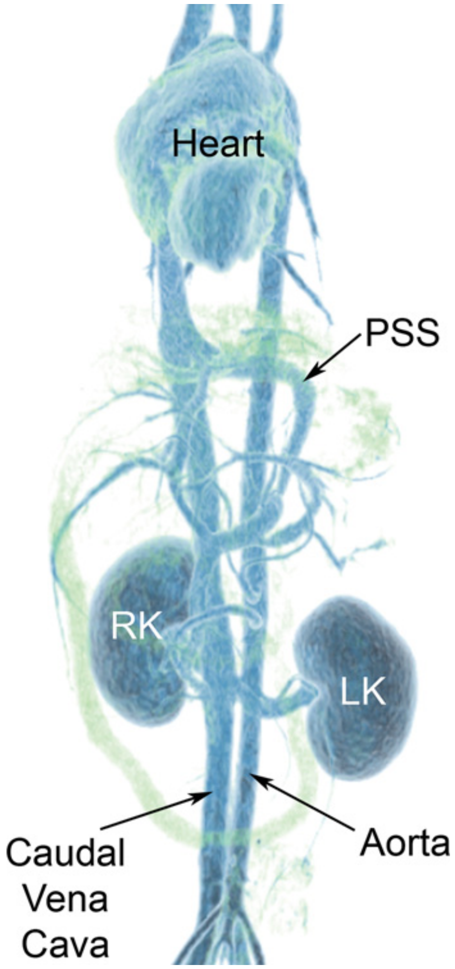


Figure 7.27 Three-dimensional CT angiography study of a dog with a PSS. (Dr. P. Scrivani, Cornell University, 2014. Reproduced with permission from Dr. P. Scrivani.)

demonstrate the existence of PSS, but a more commonly used method is per-rectal scintigraphy. A radioactive compound called technetium (^{99m}Tc) is administered rectally, and the patient is placed under a gamma camera to measure radiation activity as the substance is absorbed from the colon. If the radioactivity is first detected in the heart and lungs, rather than the liver, this indicates the presence of PSS (Fig. 7.26). Three-dimensional CT angiography (Fig. 7.27) is also useful in identifying PSS vessels as well as providing useful structural information for surgical planning. Hyperintense lesions in the basal nuclei (particularly the pallidum and putamen—the lentiform nuclei) on T1-W MR images are well described in humans with hepatic encephalopathy. The hyperintense regions are believed to be due to manganese deposition in these regions of the brain. Similar MRI lesions have been described in dogs and cats with PSS (Fig. 7.28), in addition to widened sulci.

Animals with HMD may be difficult, if not impossible, to diagnose without a liver biopsy. These patients tend to have normal or slightly abnormal bloodwork abnormalities compared to PSS patients (e.g. serum albumin and cholesterol levels, mean corpuscular volume). Also, serum bile acid concentrations in HMD patients, especially postprandial, tend to be lower than in patients with PSS. Per-rectal scintigraphy results are also normal in animals with HMD. Other hepatic disorders also typically require liver biopsy for a diagnosis.

d. Treatment for hepatic encephalopathy is directed at reducing the level of gut-derived toxins and controlling seizures, if present. A diet with a low amount of high-quality protein (e.g. K/D diet) is usually instituted to minimize ammonia production by gut

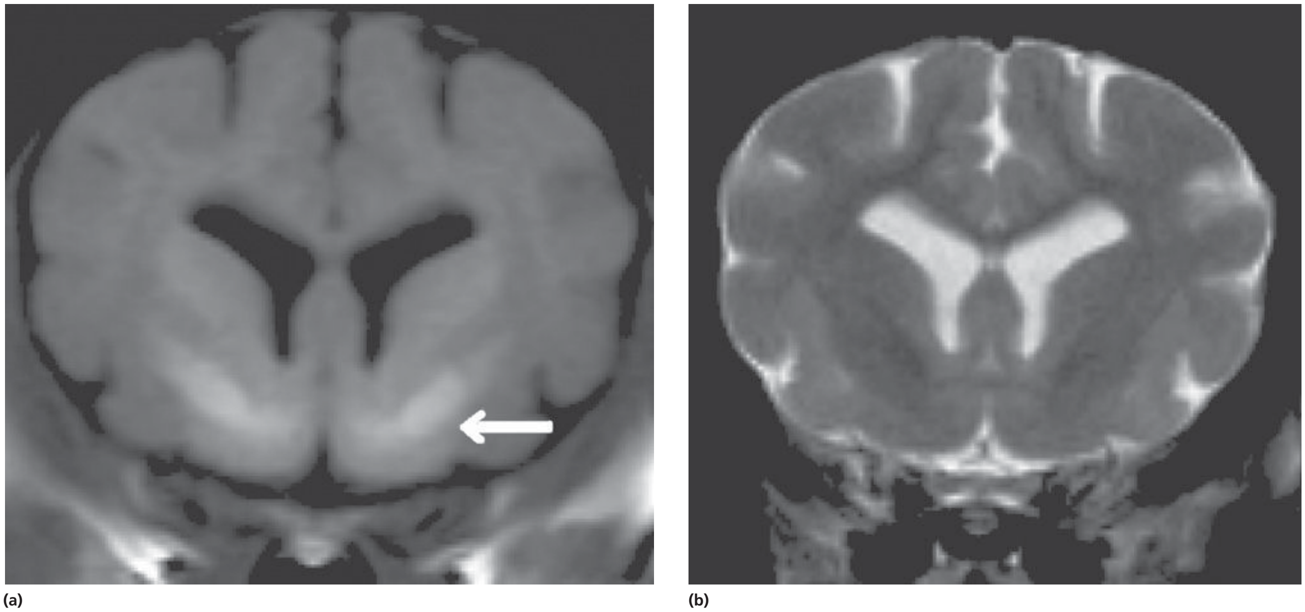


Figure 7.28 Transaxial T1-weighted (A) and T2-weighted (B) brain images of a dog with encephalopathy due to PSS. Note the hyperintense lesions in the lentiform nuclei evident on the T1-weighted images. (Torisu *et al.*, 2005. Reproduced with permission from Wiley.)[734]

bacteria. Oral medications such as lactulose, a synthetic disaccharide, with or without oral antibiotics (e.g. aminoglycosides), are administered, to decrease colonic bacterial production of volatile fatty acids and other potentially neurotoxic substances. Lactulose is hydrolyzed by colonic bacteria to produce organic acids (e.g. lactic, acetic, formic acid) and carbon dioxide. The organic acids lower the pH of the colon, trapping colonic ammonia in the form of nonabsorbable ammonium. Lactulose may also lead to a favorable alteration of the colonic flora, accelerated intestinal transit time, and may exert some antiendotoxin activity. Lactulose is administered at an initial dose of 0.5–1.0 ml/kg body weight, every 8 hrs. The dose is adjusted, if necessary, to result in two to three soft stools per day. Neomycin sulfate is poorly absorbed when administered orally, but is active against urea-splitting bacteria in the colon. The dose of neomycin is 20 mg/kg body weight, every 8 hrs. Oral ampicillin (22 mg/kg body weight, q 8 hrs) and metronidazole (7.5 mg/kg body weight, q 8 hrs) are also commonly administered to hepatic encephalopathy patients, for their effects on colonic flora, and as protection against sepsis.

In severely encephalopathic patients, dilute betadine, and/or lactulose enemas have been recommended. Because of its caustic nature, the author prefers not to use betadine enemas in these patients. A lactulose enema is prepared using three parts lactulose to seven parts water. The enema is administered at a dose of 20 ml/kg and retained in the colon for 15–20 min. This is repeated every 4–6 hrs, if necessary. Some patients with hepatic insufficiency may be hypoglycemic and need supplemental parenteral glucose. It is important to prevent or reverse conditions that may exacerbate hepatic encephalopathy, such as alkalosis, hypokalemia, and gastrointestinal hemorrhage.

In cases of postsurgical PSS intractable seizure activity, the author believes that brain swelling should be assumed, and mannitol therapy should be instituted. In addition, although bromide is a sound anticonvulsant choice in the PSS dog (no hepatic metabolism), it does contribute to the often obtunded mental state in these patients. The author has had success using intravenous levetiracetam (also no hepatic metabolism) in a limited number of PSS dogs with seizure activity. Anticonvulsant medication needs to be tapered to the individual patient, and generally administered at lower-than-standard dosages if metabolized by the liver.

Treatment of the underlying disorder in hepatic encephalopathy cases is the key to controlling signs of neurologic dysfunction. In HMD and most acquired hepatic disorders, medical management involving dietary modification, lactulose, and other medications (e.g. prednisone, anticholestatic, and antifibrotic drugs for chronic active hepatitis) form the basis of treatment. For PSS, surgical attenuation of the shunting vessel(s) is usually recommended. Shunt attenuation using a device called an ameroid constrictor is commonly practiced; the ameroid constrictor allows for the progressive attenuation of the shunting vessel following placement. Some PSS patients will develop refractory generalized seizures after shunt ligation/attenuation, which can be fatal. This phenomenon has been suspected to be due, in part, to an abrupt decrease in brain benzodiazepine-like substances following shunt ligation; however, this phenomenon likely involves a more complicated constellation of neurochemical aberrations.

Clinical signs of hepatic encephalopathy can often be reversed with appropriate medical therapy. The prognosis for each patient depends on the specific underlying disease responsible for the encephalopathy. Most extrahepatic PSS dogs are successfully treated surgically with partial or complete shunt attenuation. In addition to the ameroid constrictor, cellophane banding and intravascular thrombogenic coils have also been used in attempts to achieve a gradual closure of portosystemic shunts. Most recently, a percutaneously controlled hydraulic occluder device has been developed to provide the gradual postoperative occlusion of shunt vessels; preliminary data from this device are encouraging. In general, postoperative complications of PSS surgery are higher for cats than dogs, and surgical success rates are higher for dogs compared with cats with PSS. The prognosis for cats with extrahepatic PSS and both dogs and cats with intrahepatic PSS is guarded. HMD patients can be well controlled long term with medical therapy. The prognosis for dogs and cats with other hepatic disorders is highly variable.

2. Renal-associated encephalopathy[111, 179, 197, 256, 387, 771]
   a. This category of metabolic encephalopathy encompasses uremic encephalopathy (UE), dialysis disequilibrium syndrome (DDS), and posttransplantation encephalopathy (PTE). Similar to hepatic encephalopathy, there are numerous proposed mechanisms to explain UE, which include the following: circulating neurotoxins, such as high levels of parathyroid hormone (PTH), which may have a direct toxic effect on neurons in addition to secondary effects from increased extracellular calcium levels; ionic imbalances, particularly hypercalcemia, which can lead to neuronal mineralization; hyperosmolality, causing cerebral neuronal dehydration; hypertension, which may lead to tortuosity, intimal proliferation, and necrosis of cerebral vasculature; uremic vasculitis affecting cerebral blood vessels; acid-base imbalance, specifically acidosis depressing cerebral function; and uremia-induced neurotransmitter imbalance in the brain. Low-grade anemia in some renal-failure patients may contribute to these aforementioned processes in producing encephalopathy.

      DDS is thought to be caused by an osmotic gradient between the brain and the extracellular fluid environment, due to overly rapid hemodialysis. The brain remains relatively hyperosmotic to the blood, perhaps due to the production of intraneuronal idiogenic osmoles during the uremic state. The gradient causes the neurons to imbibe water, leading to cerebral edema.

      In PTE, described in cats after renal transplantation, uncontrolled hypertension is thought to play a major causative role.
   b. Clinical signs of renal-associated encephalopathy are similar, whether due to UE, DDS, or PTE, although they tend to be most severe with the latter disorder. Abnormal mentation—ranging from obtundation (with or without signs of dementia) to coma—and seizure activity are typical abnormalities. Other clinical signs may include muscle tremors, generalized weakness, and irregular respiration. The abnormal respiratory activity is thought to be due to decreased brain-stem receptivity to chemoreceptor stimulation. Other clinical signs (dehydration, nausea/vomiting, PU/PD, etc.) are reflective of renal failure.
   c. Diagnosis of renal-associated encephalopathy is based upon typical clinical signs of neurologic dysfunction in a patient with renal failure, with no other obvious cause of brain disease. Development of encephalopathic signs soon after hemodialysis or renal transplantation provides compelling evidence for DDS and PTE, respectively.
   d. Treatment of renal-associated encephalopathy depends primarily upon the management of the underlying kidney disease. Electrolyte and acid-base imbalances should be corrected, if indicated, and seizures should be controlled with anticonvulsant drugs. Managing arterial hypertension in cats before and after renal transplantation with propranolol, hydralazine, and/or acepromazine may help prevent the development of PTE.

      The prognosis of renal-associated encephalopathy is variable, and depends mainly on the specific renal abnormality. In most cases, the encephalopathy can be ameliorated or resolved with the control of uremia. The development of PTE is best avoided, as these cats tend to have severe signs of neurologic dysfunction, and a high mortality rate.
3. Hypoglycemic encephalopathy[31, 45, 118, 308, 519, 520, 565, 680, 766, 799]
   a. The brain has an absolute requirement for glucose. Glucose enters the brain via a noninsulin-dependent facilitated transport mechanism. This transport mechanism requires a minimum blood glucose level to operate effectively. There are limited glycogen stores in the brain, and the neuronal energy depletion associated with severe (usually less than 45 mg/dl)

hypoglycemia often results in clinical signs of encephalopathy.

There are multiple causes of hypoglycemia, including overproduction of endogenous insulin or insulin-like substances (e.g. insulin-like growth factors) by pancreatic insulinomas or other neoplasms, glycogen depletion in neonatal/juvenile puppies (usually of toy/miniature breeds) and kittens, sepsis, and exogenous insulin overdose (i.e. diabetes mellitus patients, especially feline). Other less-common causes of clinically significant hypoglycemia include hypoadrenocorticism, liver failure, glycogen storage diseases, and the so-called hunting dog hypoglycemia syndrome, the latter of which may represent the combined effects of strenuous exercise with inadequate caloric intake.

b. The nature and severity of clinical signs produced by severe hypoglycemia depend upon the rate of decline of blood glucose, the absolute degree of hypoglycemia, and the duration of hypoglycemia. Rapid decreases of blood glucose result in a systemic adrenergic response, with typical clinical signs such as pupillary dilation, tremors, irritability, vocalization, and extreme hunger. Slower decreases in blood glucose levels, as is common with insulinomas, typically result in signs of encephalopathy, such as behavior changes, altered mental status (typically obtundation, but coma can result if hypoglycemia is untreated), seizure activity, and visual dysfunction. Generalized weakness is also a common characteristic feature of dogs and cats with progressive hypoglycemia.

c. The diagnosis of hypoglycemic encephalopathy is based on documenting hypoglycemia in an encephalopathic patient whose clinical signs of neurologic dysfunction improve or resolve with normalization of blood glucose levels. Specific diagnostic tests (e.g. insulin/glucose ratio for insulinoma, identifying circulating insulin-like growth factor II for other neoplasms) for the various causes of hypoglycemia are not covered in this text (consult the appropriate references listed).

d. Symptomatic therapy for hypoglycemic encephalopathy involves the intravenous administration of 0.5–1 ml/kg of 50% dextrose, diluted 1:2 with sterile water. This may need to be repeated and/or the patient may require a continuous infusion of 5% dextrose. Concentrated dextrose solutions should be given through large-bore veins like the jugular, especially if repeated administrations are performed. Specific therapies for individual causes of hypoglycemia are covered in the references provided. The prognosis for the short-term correction of hypoglycemic encephalopathy is usually excellent. The long-term prognosis varies with the underlying disease process, but is generally guarded to good. Pancreatic insulinoma, probably the most common cause of hypoglycemic encephalopathy in dogs, is associated with mean and/or median survival times of 12–18 mos with combination surgical/medical management. In one report of 28 dogs with pancreatic insulinoma, survival times appeared to be substantially higher than previously described, especially for dogs treated surgically. The median survival time for the 19 surgically treated dogs was 785 days (approximately 26 mos).

4. Electrolyte-associated encephalopathy (EAE)[29, 94, 118, 196, 398, 427, 491, 514, 519–523, 568]

a. Imbalances of sodium (Na^+) and calcium (Ca^{++}) may cause clinical signs of encephalopathy, the severity of which tends to correlate directly with the rapidity of development of the particular imbalance. There are numerous potential causes for these electrolyte disturbances. Hypernatremia and hyponatremia are, for all practical purposes, synonymous with hyper-osmolality and hypo-osmolality, respectively. Hypernatremia can lead to shrinkage of brain parenchymal cells. A potential secondary effect of this parenchymal shrinkage is stretching and tearing of small intracranial blood vessels with resultant hemorrhage. Both intracellular dehydration and intracranial hemorrhage may contribute to brain dysfunction in the hypernatremic state. With chronic hypernatremia (more than two or three days), brain parenchymal cells will produce osmotically active intracellular substances, called idiogenic osmoles, in an attempt to compensate for the increased extracellular osmolality. Hyponatremia can result in the swelling of brain parenchymal cells with subsequent brain edema. Brain parenchymal cells will compensate for chronic hyponatremia (more than two or three days) by actively extruding osmotically active intracellular components, such as potassium and amino acids. Overly rapid correction of either a chronic hypernatremic or a hyponatremic state may lead to severe encephalopathic signs. In the former scenario, the encephalopathy is due to brain edema (associated with the idiogenic osmoles), whereas in the second, it is likely due to axonal shrinkage (due to the relative lack of intracellular osmolality) and subsequent demyelination in the brain stem (particularly the thalamus), similar to central pontine myelinolysis in people.

Hypercalcemia can cause decreased excitability of neuronal cell membranes, as well as direct toxic damage to neuronal intracellular energy-producing systems. Hypocalcemia may lead to increased excitability of neuronal cell membranes, as well as abnormal neurotransmission.

b. Clinical signs of EAE typically indicate forebrain dysfunction, but can progress to involving the brain stem. Dementia, behavior changes, altered mental status

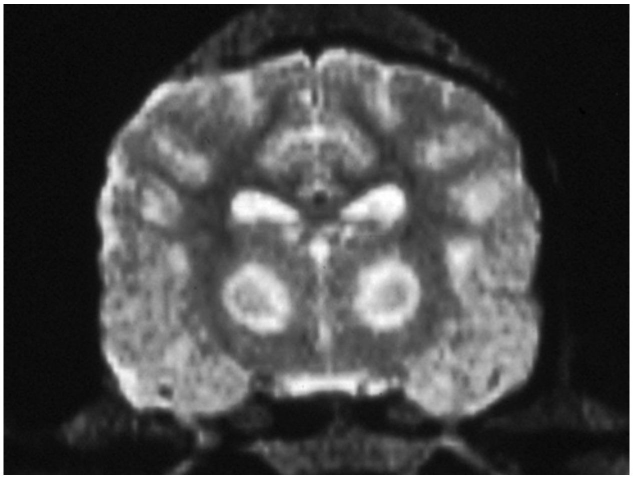


Figure 7.29 Transaxial T2-weighted brain MR image, demonstrating lesions associated with central myelinolysis after rapid correction of hyponatremia in a dog. (O'Brien *et al.*, 2004. Reproduced with permission from Wiley.)[521]

(obtundation that may progress to coma), seizures, and visual deficits are likely clinical signs of EAE. Patients with hypocalcemia may also exhibit muscular tetany.

c. Diagnosis of EAE is based upon demonstrating an abnormal electrolyte status in an encephalopathic patient that improves or normalizes upon correction of the abnormal electrolyte level. In overly rapid correction of hyponatremic states, bilaterally symmetric thalamic lesions may be evident on MR imaging (Fig. 7.29).

d. Treatment of EAE involves correction of the electrolyte disturbance, as well as investigation and potential treatment of the underlying cause for the electrolyte abnormality. Correction of hypernatremia is achieved by administering fluids that are hypo-osmolar to the patient. This can be achieved via using 5% dextrose (basically free water), half-strength or normal saline, depending upon the degree and chronicity of the hypernatremia. The amount of water to administer can be calculated according to the following formula:

$$\text{Water deficit (L)} = 0.6 \times \text{lean body weight (kg)} \times \text{patient's Na}^{+}/\text{normal Na}^{+} - 1$$

With relatively acute hypernatremia, the deficit can be corrected quickly using 5% dextrose. With chronic hypernatremia, the deficit should be corrected gradually over 48–72 hrs, starting with half-strength or normal saline, eventually switching to 5% dextrose. The chronically hypernatremic patient's sodium level should not be lowered faster than 0.5 mEq/L/hr. Hyponatremia is corrected by administering sodium-containing fluids such as normal or hypertonic saline (in acute, severe cases). The amount of sodium to be replenished can be calculated as follows:

$$\text{Sodium deficit (mEq/L)} = 0.6 \times \text{lean body weight (kg)} \times (\text{normal Na}^{+} - \text{patient's Na}^{+})$$

As with chronic hypernatremia, chronic hyponatremia should be corrected slowly over 48–72 hrs, raising the patient's sodium level by no more than 0.5 mEq/L/hr.

Hypocalcemia is corrected in the emergency situation by slow intravenous infusion of 10% calcium gluconate at a dosage of 5–15 mg/kg over 10–30 min; this should work out to be 0.5–1.5 ml/kg. It is extremely important not to confuse the two ways of expressing dosage of this drug, as overdosage can be fatal. While administering calcium gluconate, the patient's electrocardiogram (ECG) should be continuously recorded. The infusion should be stopped if premature ventricular contractions, shortening of the QT interval, or bradycardia are observed. Once the patient is stabilized, maintenance oral calcium and vitamin D supplementation can be initiated. Emergency therapy of the hypercalcemic patient usually involves diuresis with 0.9% saline (two to three times maintenance fluid rate) and furosemide (2–4 mg/kg intravenously, q 8–12 hrs, or a 5 mg/kg IV bolus, followed by 5 mg/kg/hr continuous infusion). Other therapies may include glucocorticoids and calcitonin administration. The prognosis for reversing encephalopathic signs due to electrolyte disturbances is generally favorable. The overall prognosis for the individual patient is highly variable and depends upon the specific disease process responsible for the electrolyte aberration.

5. Miscellaneous endocrine-related encephalopathies[88, 95, 118, 298, 300, 332, 344, 397, 416, 535, 797]

a. In addition to pancreatic insulinoma and disorders of the parathyroid glands, there are several endocrine disorders that can lead to brain dysfunction. Hyperthyroidism (in cats, rarely dogs), hypothyroidism (in dogs, rarely cats), diabetes mellitus, and hyperadrenocorticism may each occasionally lead to clinical signs of encephalopathy. Hyperthyroidism may cause encephalopathic signs by altering brain neurotransmitter balance; thyroid hormones may also directly increase membrane excitability of brain parenchymal cells. Systemic hypertension is a common feature of hyperthyroidism and may also contribute to encephalopathic signs. Low thyroid hormone levels in hypothyroidism may cause encephalopathy by a number of proposed mechanisms, including diminished neuronal oxygen consumption, the accumulation of water-retaining extracellular mucopolysaccharide substances in the brain (myxedema), and vascular compromise to the brain due to atherosclerosis of major blood vessels. Ketoacidotic and nonketotic hyperosmolar diabetes mellitus may both lead to encephalopathic signs. The pathogenesis of diabetic encephalopathy is thought to be due primarily to hyperosmolality in both forms of the disease. Excessive circulating glucocorticoid levels in hyperadrenocorticism may lead to brain neurotransmitter imbalance; the systemic hypertension commonly associated with hyperadrenocorticism may also lead to vascular compromise of the brain.

b. Dogs and cats with endocrine-related encephalopathy typically exhibit signs of forebrain dysfunction in addition to other clinical signs relating to the underlying endocrine disorder (e.g. PU/PD, polyphagia). An obtunded mental status is commonly appreciated with hypothyroidism and diabetes mellitus. Central vestibular dysfunction has recently been associated with hypothyroidism in dogs also; in that study, three of eight dogs imaged (five CT, three MRI) had evidence of brain infarction. Since ischemic lesions (especially in the caudal fossa) are difficult to detect on CT imaging, it was suggested that the role of vascular infarction may have been underestimated in these dogs. Hyperthyroid cats are more likely to appear restless and irritable, and may exhibit aggressive behavior. Hyperadrenocorticoid-related encephalopathy can manifest either as obtundation or hyperexcitability. Other clinical signs of encephalopathy—such as aimless pacing, focal and generalized seizure activity (rare with these endocrinopathies), and vocalization—may be appreciated in patients with these endocrine disorders. A rare yet life-threatening form of hypothyroid encephalopathy, called myxedema stupor or coma, produces severe alterations of consciousness, as the name implies. Doberman Pinschers appear to be predisposed to this syndrome.

c. Diagnosis of an endocrine-related encephalopathy is made by documenting clinical signs of brain dysfunction in a patient with an endocrinopathy, which improve or resolve with control of the endocrine disorder. The suggested references should be consulted for specifics pertaining to the diagnosis of endocrine disorders.

d. Treatment of endocrine-related encephalopathies involves successfully controlling the underlying endocrine disturbance. The specifics of treating each of the above-mentioned endocrinopathies is beyond the scope of this textbook. In general, severe ketoacidotic and nonketotic hyperosmolar diabetes mellitus are treated with fluid/electrolyte replacement and intravenous or intramuscular insulin administration. Hyperthyroidism is treated either by the surgical removal of the hyperfunctional thyroid gland(s) or via radioactive iodine therapy. Hypothyroidism is typically treated by the oral administration of thyroid replacement hormone at a dosage of 20 μg/kg every 12 hrs. Hypothyroid myxedema stupor/coma is treated via the intravenous administration of thyroid replacement hormone (0.066–0.11 mg/kg) and intensive supportive care, followed by maintenance oral thyroid hormone replacement therapy. Other less severe forms of hypothyroid-associated encephalopathy are treated with oral thyroid replacement therapy. Hyperadrenocorticism is usually treated with oral mitotane, the amount titrated based on the results of ACTH stimulation tests. The prognosis for endocrine-associated encephalopathies is quite variable, and depends on the underlying endocrine disorder. Except for the rare hypothyroid myxedema stupor/coma syndrome, the prognosis for both reversal of encephalopathic signs and control of the endocrine disease is typically good.

6. Encephalopathy associated with acid-base disturbances[118, 519, 520]

   a. Acid-base disturbances are uncommon causes of encephalopathy. There are multiple causes for the various acid-base disturbances, and the suggested references pertaining to this subject should be consulted. Of the four main types of acid-base disturbance (respiratory acidosis, metabolic acidosis, respiratory alkalosis, and metabolic alkalosis), respiratory acidosis is the most likely to cause signs of encephalopathy. Alkalosis is very unlikely to result in encephalopathic signs, and will not be discussed. Respiratory acidosis is usually due to poor ventilatory ability, but can also occur with severe pulmonary disease. Carbon dioxide diffuses readily across the blood–brain barrier (BBB) and can affect brain function in several ways. Carbon dioxide can affect the brain both directly and via decreasing brain pH levels. Carbon dioxide narcosis may occur via both alterations in brain neurotransmitter balance and increases in brain-blood volume (leading to increased ICP). The hypoxia that typically accompanies hypercapnia may exacerbate the effects of hypercapnia on the brain. Metabolic acidosis may also lead to mild encephalopathic signs, but this is less likely due to the patient's ability to compensate via hyperventilation.

   b. Encephalopathy from respiratory acidosis typically results in an alteration of level (obtundation to coma) and/or content (dementia/delirium) of consciousness. Such patients will also display obvious respiratory difficulty. When encephalopathic signs result from metabolic acidosis, they tend to be much less severe than those experienced with respiratory acidosis. These patients may be hyperventilating as a compensatory response, but are not usually in respiratory distress.

c. Diagnosis of acidosis as a cause of encephalopathy is based upon a reversal of clinical signs of brain dysfunction concomitant with correction of the acid-base disturbance. The nature of the acid-base disturbance is elucidated from arterial blood-gas analysis, as well as measurements of pH and bicarbonate levels. The underlying cause for the acid-base disturbance should be investigated.

d. The reader should refer to the suggested references for specific treatment of acidosis. In general, bicarbonate administration and fluid replacement therapy are titrated to the individual patient's needs. Overzealous administration of intravenous bicarbonate to a patient with encephalopathy due to acidosis may cause a transient worsening of brain dysfunction. The carbon dioxide produced after administering bicarbonate to an acidotic patient will rapidly cross the BBB, whereas the bicarbonate itself will not. This may lead to the so-called paradoxic CNS acidosis. If this phenomenon does occur, it is rarely of much clinical consequence. The prognosis for reversing encephalopathic signs due to acidosis is usually favorable in the short term. The overall prognosis for each patient depends upon which of the myriad possible diseases is responsible for the acid-base disturbance.

7. Mitochondrial encephalopathy (ME)[62–64, 251, 271, 412, 445, 449, 695, 759, 778]

a. Abnormal mitochondrial respiratory enzyme function, due to a number of potentially heritable defects, is believed to be the pathophysiologic basis for a number of recently described encephalopathies and encephalomyelopathies in dogs. Progressive or episodic signs of CNS dysfunction have been reported in several breeds, most notably Alaskan Huskies, Australian Cattle dogs, and Shetland Sheepdogs. It has been determined that the spongiform leukoencephalopathy of both the Australian Cattle dog and Shetland Sheepdog is due to a maternally inherited missense mutation of mitochondrial DNA. This disorder is now thought to be more similar to the human mitochondrial disorder called Kearns–Sayre syndrome than to Canavan's disease as previously described. A similar disorder has been reported in an English Springer Spaniel and was suspected (based on pathologic findings) in a Yorkshire Terrier and several kittens. Clinical and pathological features of six Yorkshire Terriers with a suspected mitochondrial encephalopathy were also recently described. A 10-mo-old female Jack Russell Terrier was reported with a progressive history of cerebellar dysfunction, blindness, and deafness beginning at 10 wks of age. At necropsy, lesions similar to human mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome were identified. In addition to severe, bilaterally symmetrical regions of neuronal degeneration in several areas of the brain, mineral deposits were found within the brain parenchyma and associated with vascular myocytes. Finally, some of the previously described idiopathic vacuolar or spongiform encephalopathies are currently suspected to be mitochondrial encephalopathies or organic acidurias (see next section). Clinical and pathologic findings in many of these animals (especially Alaskan Husky, Springer Spaniel, and Yorkshire Terrier breeds) are similar to a human disorder called Leigh's syndrome, or subacute necrotizing encephalopathy (SNE). Leigh's syndrome represents a group of heritable neurodegenerative diseases, the majority of which are due to defects in the mitochondrial respiratory enzyme chain.

b. The majority of reported dogs initially developed clinical signs of neurologic dysfunction in the first year of life (most between 6 and 12 mos). However, there appears to be a wide age range for the onset of clinical signs. The six reported Yorkshire Terriers developed clinical signs of neurologic dysfunction between 4 mos and 1 yr of age. One Alaskan Husky was 2.5 yrs of age at onset, and another was 6 yrs old. The English Springer Spaniel was approximately 15 mos old at the time of the onset of signs. Seizures and/or generalized ataxia of acute onset are typically the initial clinical signs. Clinical features supportive of a diffuse, symmetric encephalopathy (Alaskan Husky) or encephalomyelopathy (Australian Cattle dog, English Springer Spaniel) develop within weeks to months. Other signs of neurologic dysfunction in Alaskan Huskies with ME include behavioral abnormalities (e.g. anxiety, obtundation, propulsive exploratory behavior), difficulty prehending food, visual deficits, facial hypalgesia, head tremor, hypermetric gait with loss of balance, delayed proprioceptive placing, and varying degrees of tetraparesis. Clinical signs in both Australian Cattle dogs and Shetland Sheepdog puppies were indicative of multifocal CNS disease and were progressive in nature. In the Australian Cattle dogs, signs of progressive cerebellar dysfunction predominated, starting as a whole body tremor at about 3–4 wks of age. Other signs in severely affected pups included jaw drop, hypersalivation, hypoglossal nerve dysfunction, and dysphagia. Additional neurologic abnormalities in Australian Cattle dogs include progressive spastic

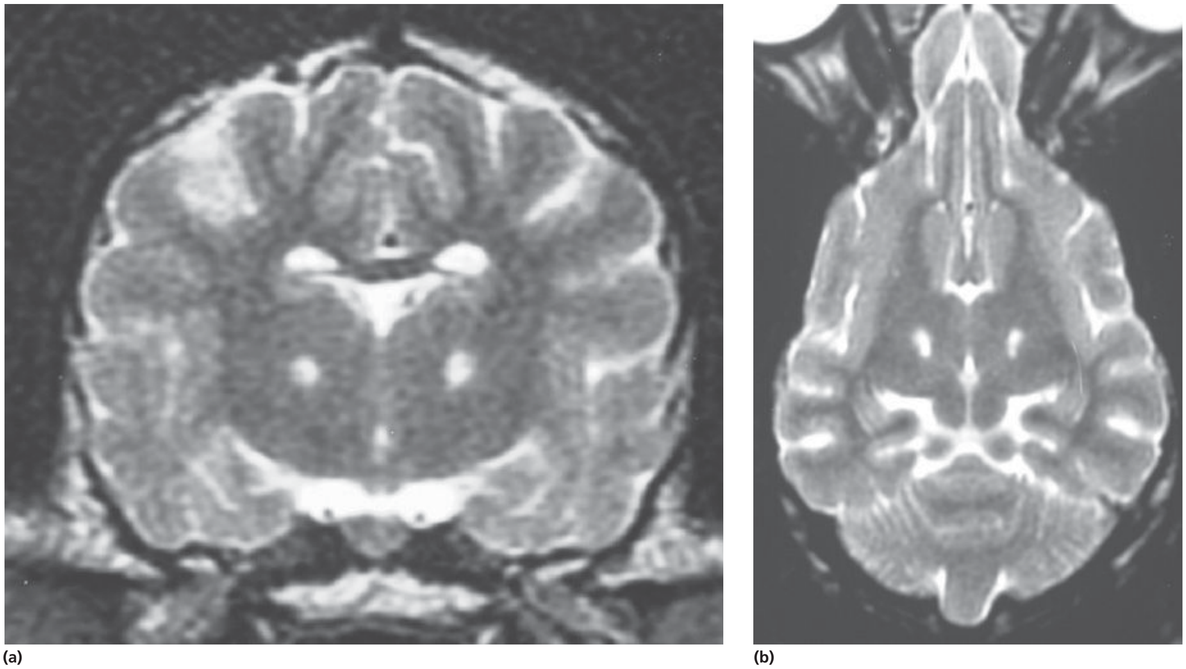


Figure 7.30 T2-weighted transaxial (A) and dorsal (B) brain images from of an Alaskan Husky dog with mitochondrial encephalopathy. Note the bilaterally symmetric, hyperintense lesions in the thalamus. (Dr. J. Wakshlag, 2014. Reproduced with permission from Dr. J. Wakshlag.)

tetraparesis with weakness and extensor rigidity of thoracic limbs (sometimes culminating in tetanic contraction), head tilt, and nystagmus. Progressive seizure activity was described in the Shetland Sheepdog pups, in addition to signs of cerebellar dysfunction. Clinical signs in these dogs developed between 1 and 3 wks of age. The English Springer Spaniel exhibited loss of menace response with some visual deficit, positional vertical nystagmus, and excitement-induced hypermetria and balance loss. The disease tends to be episodic in Alaskan Huskies, and slowly progressive in Australian Cattle dogs. Clinical signs in the Yorkshire Terriers included cerebellar dysfunction, blindness, seizures, deafness, and pharyngeal and laryngeal dysfunction.

c. Elevated levels of serum and CSF lactate and pyruvate are characteristic features in people with Leigh's syndrome; increased CSF levels of lactate and pyruvate were documented in the Australian Cattle dog puppies. With the exception of one Australian Cattle dog with a mild pleocytosis and elevated protein concentration, CSF evaluation has been normal in affected dogs. Advanced imaging (CT, MRI) has been performed in a limited number of dogs. Bilaterally symmetric, cavitary lesions in the brain and/or spinal cord were evident on imaging, which corresponded to lesions discovered at necropsy. Bilateral cavitary lesions were evident on CT imaging in the thalamus and medulla of the Yorkshire Terriers; electron microscopy of these lesions revealed abnormally shaped neuronal mitochondria. Similar to Leigh's syndrome of humans, MRI lesions associated with mitochondrial encephalopathy in dogs are characteristically hypointense on T1-W images, hyperintense on T2-W images, and noncontrast enhancing (Fig. 7.30).

Definitive diagnosis of these disorders is based on gross and histopathologic features of the CNS at necropsy. Bilaterally symmetric, spongiform/vacuolar lesions, primarily affecting gray matter, are the pathologic hallmark of these disorders. Histopathologically, multiple areas of the CNS are affected in ME dogs, but some regions are grossly abnormal on gross inspection. Spongiform brain-stem lesions from thalamus to medulla are prominent in Alaskan Huskies, the thalamic lesions being most conspicuous. Australian Cattle dogs tend to have cavitary lesions in cerebellar and brain-stem nuclei, as well as in both the cervical and lumbosacral intumescences. The English Springer Spaniel had similar lesions in the accessory olivary nuclei of the brain stem. Abnormal mitochondria in neurons and astrocytes have been demonstrated ultrastructurally in several cases of ME.

d. To date, all cases of ME have been euthanized due to either progression or recurrence of neurologic dysfunction. Most have been euthanized 2–7 mos from the onset of neurologic dysfunction. In people, therapies for mitochondrial encephalopathies are usually ineffective. There has been some small degree of success with dietary management and supplementation (e.g. B vitamins, vitamin E, coenzyme Q, succinate).

8. Organic acidurias[1, 93, 125, 128, 220, 238, 346, 440, 513, 515–517, 523, 529, 551, 563, 642, 695, 778, 794]
   a. The organic acidurias represent a number of diseases in which there is a defect (typically a deficiency in one or more enzymes) in cellular metabolism, leading to the accumulation of one or more organic acids; these organic acids accumulate and are often detectable in the serum, CSF, and/or urine. Most of these disorders are due to inherited (usually autosomal recessive) deficiencies of mitochondrial respiratory chain enzymes, although some involve cytosolic enzymes. In many ways, organic acidurias overlap with the previously described mitochondrial encephalopathies, differing primarily in the presence of identifiable accumulated organic acids in the urine and other body fluids. Since many of the previously reported cases of mitochondrial encephalopathy did not have organic acid screening of the urine performed, it is possible that some of these dogs had organic acidurias. As mentioned with the mitochondrial encephalopathies, some of the previously reported idiopathic spongiform/vacuolar encephalopathies may eventually be demonstrated to be organic acidurias. The deficiency for a specific organic aciduria may be due to a lack of an essential enzyme or a lack of function of an enzyme due to a cofactor insufficiency (e.g. cobalamin-vitamin B_{12} is required for the normal functioning of methylmalonyl CoA decarboxylase). Occasionally, an organic aciduria is an acquired disorder, due to either a malabsorptive problem (e.g. exocrine pancreatic insufficiency) or a toxin (e.g. propylene glycol toxicity). Clinical signs of encephalopathy are due to abnormal cellular energy metabolism, the toxic effects of the accumulated organic acid(s), or a combination of these two processes. In addition to these factors, altered oxidative cellular energy metabolism may lead to a shift toward anaerobic energy pathways. This may lead to other metabolic derangements such as ketoacidosis, hyperammonemia, hypoglycemia, and lactic acidosis, which may contribute to the encephalopathic state. The amino acid carnitine serves two vital roles in cellular metabolism. Carnitine transports fatty acids (conjugated with acyl-CoA) across the inner mitochondrial membrane for oxidation and cellular energy production. Carnitine also serves as a buffer for accumulated organic acids. Since the accumulation of organic acids interferes with mitochondrial function, carnitine will bind with the fatty acids and these conjugates are excreted in the urine. With organic acidurias, it is common for a secondary carnitine deficiency to develop, due to a loss of carnitine in the urine.

      A number of organic acidurias have been reported in people, including maple syrup urine disease (deficiency of oxo- or keto-acid dehydrogenase), methylmalonic aciduria (deficient methylmalonyl CoA mutase activity), malonic aciduria (malonyl CoA decarboxylase deficiency), propionic aciduria (propionyl CoA carboxylase deficiency), glutaric aciduria (glutaryl CoA dehydrogenase deficiency or electron transport flavoprotein dysfunction), and L-2-hydroxyglutaric aciduria (specific defect unknown, thought to involve lysine metabolism). Although classified as a leukodystrophy, Canavan's disease is an encephalopathy due to deficiency of aspartoacylase activity, which leads to the accumulation of N-acetylaspartic acid.

      Organic acidurias have been reported in a number of dogs. These include L-2-hydroxyglutaric aciduria in Staffordshire Bull Terriers and a West Highland White Terrier, malonic aciduria in Maltese dogs, a suspected primary organic aciduria in Standard Poodle dogs, a suspected acyl-CoA dehydrogenase deficiency in a CKCS, and a Labrador Retriever dog with combined methylmalonic and malonic aciduria. A Labrador Retriever with clinical signs, MR imaging findings, and histopathologic lesions similar to human Canavan's disease was described; it has been theorized that previously reported cases of leukodystrophy/spongy degeneration in Labradors may represent a canine form of Canavan's disease. The same was suspected for a previously reported leukodystrophy in Shetland Sheepdogs. More recently, however, it has been suggested that the Shetland Sheepdog disorder is more analogous to the human mitochondrial disorder called Kearns–Sayre syndrome than to Canavan's disease (see previous section, "Mitochondrial encephalopathy (ME)"). A cat with a suspected acquired organic aciduria has also been described. This cat developed D-lactic acidosis, presumably due to exocrine pancreatic insufficiency and subsequent intestinal bacterial overgrowth. Bacterial fermentation of undigested carbohydrates was thought to be the source of the D-lactic acid. Another cat was diagnosed with organic aciduria, which was associated with cobalamin (vitamin B_{12} deficiency). This latter cat was suspected of having some inborn error of cobalamin absorption, leading to an accumulation of methylmalonic acid and its precursors.
   b. Reported clinical signs of neurologic dysfunction with the organic acidurias are variable in their severity and progression, even within a specific disorder. In general these diseases tend to cause signs of multifocal or diffuse CNS dysfunction, and may be episodic in

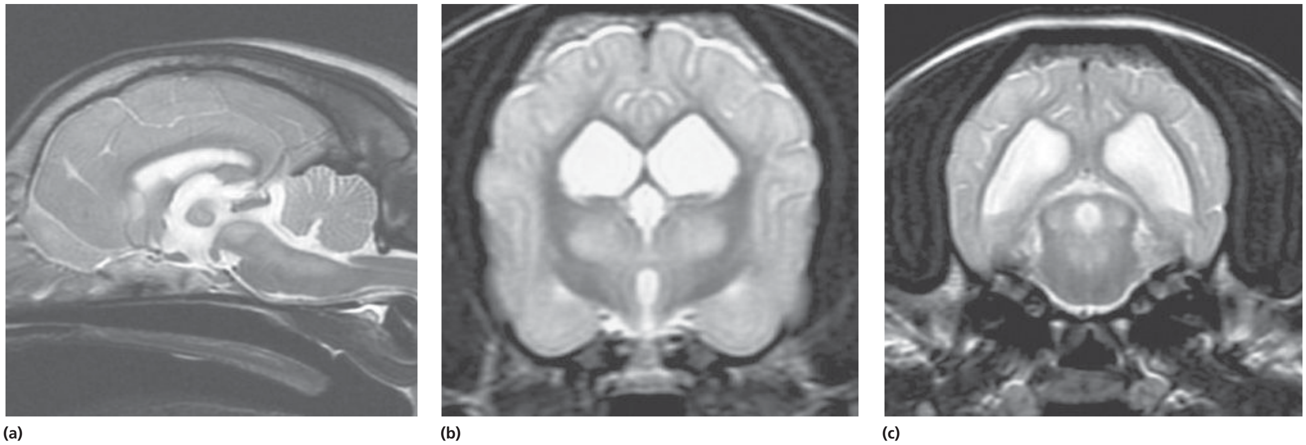


Figure 7.31 T2-weighted midsagittal (A) and transaxial MR images through the thalamus (B) and mesencephalon (C) from a dog with an organic aciduria. (Garosi *et al.*, 2005. Reproduced with permission from BMJ Publishing Group Ltd.)[220]

nature. The L-2-hydroxyglutaric aciduria described in Staffordshire Bull Terriers and one West Highland White Terrier was slowly progressive. In the former breed, six dogs presented between the ages of 4 mos and 7 yrs with clinical complaints of seizures, ataxia, dementia, and head/neck tremors. The West Highland White Terrier had visual impairment, dementia, episodic head tremors (stress-related), and an ataxic gait in all four limbs with thoracic limb hypermetria. The 6-mo-old CKCS with suspected acyl-CoA dehydrogenase deficiency displayed episodic ataxia with thoracic limb hypermetria, as well as altered mentation and seizure activity. The propositus case for the Maltese dogs with malonic aciduria exhibited seizure activity starting at 6 mos, and later exhibited progressive alteration of consciousness. Twenty-five Standard Poodle puppies with an unclassified organic aciduria had severe and progressive clinical signs which included generalized weakness, ataxia, obtunded mentation, neck muscle weakness with head ventroflexion, generalized tonic/clonic seizures, and tremors. Those puppies that survived longer than 4–5 wks progressed to lateral recumbency and opisthotonus. The 3-mo-old Labrador Retriever with combined methylmalonic/malonic aciduria exhibited signs of diffuse forebrain, brain-stem, and spinal cord dysfunction that progressed over a 5-mo period. This dog also had severe hydrocephalus and SM. The 7-mo-old Labrador Retriever with lesions similar to human Canavan's disease exhibited progressive tetraparesis and cerebellar dysfunction. The 2-yr-old cat with suspected acquired D-lactic acidosis displayed episodic weakness, ataxia, lethargy, and obtunded mentation over a 4-mo period. The 4-yr-old cat with suspected cobalamin malabsorption had displayed multiple episodes of forebrain dysfunction (e.g. obtunded mentation, blindness) and balance loss, supportive of multifocal/diffuse brain disease.

c. Diagnosis of organic acidurias is accomplished by demonstrating abnormally high levels of specific organic acids in urine, serum, and/or CSF using gas chromatography-mass spectroscopy. There are several reports of MRI lesions in patients with organic acidurias. Similar to the mitochondrial encephalopathies, these tend to be bilaterally symmetric lesions of white- or gray-matter structures (depending on the disorder) that are hyperintense on T2-W images (Fig. 7.31). These lesions tend to be slightly hypointense on T1-W images and are not contrast enhancing. CSF cytology and protein concentrations are normal.
d. Treatment of organic acidurias is based primarily on manipulating diet and adding vitamin supplementation to compensate for abnormal metabolic pathways. In addition, anticonvulsant therapy is necessary when seizure activity is part of the clinical picture. Although specific dietary manipulation should be tailored to the specific needs of a patient, general recommendations typically include a high-carbohydrate, low-fat (with the majority of fats being medium-chain triglycerides), low-protein diet, and supplementation with L-carnitine (50 mg/kg bid) and several B-vitamins (e.g. cobalamin, thiamine, riboflavin).

The prognosis for organic acidurias is variable, but is guarded overall. The dogs with L-2-hydroxyglutaric aciduria appear to have a slowly progressive disorder that may respond to dietary manipulation and supplements. Clinical signs of the propositus Maltese dog with malonic aciduria resolved with the institution of a low-fat diet high in medium-chain triglycerides. Neurologic dysfunction also resolved in the cat with D-lactic acidosis, following pancreatic enzyme replacement therapy. The prognosis for the remaining disorders, especially the neonatal Standard Poodle encephalopathy, appears to be poor.

D. Neoplastic

1. Primary brain tumors[4, 5, 18, 26, 30, 34, 48, 52–54, 56, 60, 61, 72, 73, 85–87, 90, 100, 112, 121, 134, 138, 146–148, 151, 171, 177, 190–192, 199, 201, 205, 206, 208–210, 218, 229, 232, 237, 239, 241, 257, 270, 277, 282, 293, 295, 301, 312, 318, 322, 359, 361, 365–369, 373, 376, 378, 380, 399–403, 414, 420, 439, 443, 444, 456–458, 465, 479, 481, 482, 486, 487, 496, 497, 507–509, 524, 530, 539, 540, 555–559, 564, 584, 585, 589, 591, 592, 613, 625, 637, 638, 641, 645, 647, 667, 670, 676, 682, 686, 692, 703, 709, 711, 712, 720, 733, 735, 736, 739, 742, 763, 764, 770, 772, 775, 791, 793, 798] (Video 1)

a. Primary brain tumors are commonly encountered in dogs and cats. Primary brain tumors include those neoplasms that originate from brain parenchymal tissue (glial cells and neurons), cells comprising the outer and inner lining of the brain (meninges and ependyma, respectively), as well as vascular elements (e.g. choroid plexus). In both species, meningioma is the most commonly reported tumor. Multiple histologic subtypes of meningiomas are encountered in dogs, whereas the spectrum of histologic subtypes of feline meningiomas is somewhat limited. Gliomas (e.g. astrocytoma, oligodendroglioma) are frequently reported in dogs, and occasionally reported in cats. A rare, diffusely infiltrative form of glioma, termed gliomatosis cerebri, has been described in dogs. There are two forms of gliomatosis cerebri: type I refers to the more common, diffusely infiltrative form that does not distort brain architecture (no mass effect), whereas type II includes evidence of an apparent mass lesion in addition to diffuse neoplastic infiltration. Gliomatosis cerebri is often bilateral and has been reported to involve the cerebellum, brain stem, and spinal cord, in addition to the cerebral hemispheres in dogs. Other primary brain tumors reported in dogs include choroid plexus tumors, primary CNS lymphosarcoma, primitive neuroectodermal tumors (PNET, which typically include neuroblastoma), primary CNS histiocytic sarcoma (also termed malignant histiocytosis), ependymoma, and vascular hamartoma. Other primary brain tumors occasionally encountered in cats include, in addition to gliomas, ependymomas, olfactory neuroblastomas, and choroid plexus tumors. In both dogs and cats, there are case reports of medulloblastomas, usually involving the cerebellum. Microglial tumors are also considered rare in dogs and cats. Meningioangiomatosis is a rare proliferative disorder, primarily of young dogs, involving the leptomeninges with invasion along parenchymal perivascular spaces. This enigmatic disorder tends to affect the brain stem and/or cranial cervical spinal cord. Although technically not a neoplasm, it is included here because it behaves as such. Similar to primary brain tumors in people, the causes of these neoplasms are uncertain. Brain tumors exert their pathologic effects both by directly encroaching upon and/or invading brain tissue and by secondary effects such as peritumoral edema, inflammation, obstructive hydrocephalus, and hemorrhage.

b. Primary brain tumors can occur in any breed of dog or cat of either sex. Dogs and cats with brain tumors are typically middle-aged to older (over 5 yrs), with the majority being greater than 9 yrs of age. The median age for dogs to develop brain tumors is 9 yrs, and for cats it is over 10 yrs. There appears to be a predilection for male cats to develop meningiomas, with no obvious breed predilection for this species. Dolichocephalic dog breeds (e.g. German Shepherd dogs, Collies) are more likely to develop meningiomas, whereas brachycephalic breeds (e.g. Boxers, Boston Terriers) seem more prone to gliomas. Golden Retrievers and Boxer dogs appear to be particularly predisposed to developing primary brain tumors. Golden Retrievers are prone to developing meningiomas, whereas Boxer dogs and other brachycephalic breeds are more likely to be diagnosed with gliomas. Golden Retrievers also appear to be predisposed to developing choroid plexus tumors. Pembroke Welsh Corgis may be predisposed to intracranial histiocytic sarcoma. In both dogs and cats, patients with meningiomas tend to be somewhat older at diagnosis than those with other brain tumor types. In dogs, astrocytomas are more likely to occur in the diencephalon and cerebellum than are other primary brain tumors. Choroid plexus tumors may occur in the lateral, third, or fourth ventricles. Choroid plexus tumors comprise choroid plexus papillomas (CPPs) and choroid plexus carcinomas (CPCs). Choroid plexus tumors, in general, tended to occur in the fourth ventricle in one report, and only CPCs occurred in the lateral ventricles. In this report, the two tumor subtypes were differentiated based upon the presence or absence of local or distant metastases, as well as on histopathologic features. Only CPCs exhibited intraventricular or subarachnoid metastasis on MR images. In one large study, it was found that half of canine primary brain tumors occupy more than one anatomic region of the brain; this could lead to the false conclusion based upon neurologic examination that a patient with a solitary brain mass has multifocal disease. Also in that study it was found that 23% of dogs with primary brain tumors had concurrent, unrelated neoplasia (e.g. pulmonary carcinoma, hemangiosarcoma), most of which involved the thoracic or abdominal cavity; this finding underscores the importance of screening for concurrent unrelated neoplasia (via thoracic radiography and abdominal ultrasonography) prior to pursuing advanced diagnostics and definitive therapy for the brain tumor. In cats with primary brain tumors, nonspecific presenting clinical signs (i.e. signs not obviously referable to neurologic dysfunction) are fairly common, occurring in over 20% of cats in one large case study. These clinical signs included lethargy, inappetence, and anorexia. Also in that study, it was found that approximately 19% of feline brain tumors were considered an incidental finding. Multiple intracranial meningiomas have been reported to occur in cats with some frequency (approximately 17%). In one study, 10% of cats were found to have two different types of intracranial neoplasia concurrently.

Historical and presenting clinical signs are variable and reflect both the location and the secondary effects (e.g. edema, hemorrhage) of the tumor. Seizures represent the most common presenting clinical sign of neurologic dysfunction in dogs with brain tumors, occurring in approximately half of the cases. In a retrospective study of dogs with brain tumors, MR imaging findings of marked gadolinium contrast enhancement, frontal lobe tumor location, and subfalcine or subtentorial herniation were all positively correlated with the likelihood of seizure activity. In one study of feline brain tumors, the overall incidence of seizure activity was 23%, occurring more commonly with glioma (26.7%) and lymphoma (26.3%), in comparison with meningioma (15%). Cats with brain tumors most commonly present to the veterinarian with a complaint of behavior change. Cats will occasionally have multiple meningiomas, so the clinical signs of dysfunction may reflect more than one intracranial mass lesion. Cerebral tumors are more common than tumors of the brain stem or cerebellum. Cerebral and diencephalic tumors tend to cause clinical signs of dysfunction such as seizure activity, behavior changes, circling, head-pressing, visual deficits, and hemi-inattention syndrome. Proprioceptive placing deficits and neck pain are often appreciable upon neurologic examination. Tumors of the brain stem from midbrain through medulla often cause alterations of consciousness, dysfunction of cranial nerves (other than CN I and CN II), and obvious gait/proprioceptive abnormalities. Cerebellar tumors may result in clinical signs of dysfunction such as ataxia, dysmetria, intention tremors, vestibular abnormalities, and menace reaction deficits with normal vision.

In most cases, clinical signs of neurologic dysfunction occur slowly and insidiously over time, especially with meningiomas. Owners of pets with meningiomas will often retrospectively realize that their pet had a behavior change for months to over a year prior to diagnosis. The subtle behavior changes are often attributed to "old age." However, brain-tumor patients can have subacute to acute development of neurologic dysfunction. These patients may experience sudden exhaustion of brain compensatory mechanisms, or may suffer hemorrhage or acute obstructive hydrocephalus due to the tumor.

c. The diagnosis of brain tumor should be highly suspected in an elderly dog or cat with slowly progressive signs of brain dysfunction. A brain tumor should also be suspected in animals that experience a recent onset of seizure activity after 5 yrs of age, especially in certain breeds (e.g. Golden Retriever). Depending upon the location and size of the tumor, such patients may appear neurologically normal interictally.

A definitive diagnosis of a brain tumor cannot be made without a biopsy sample; however, a very confident tentative diagnosis can often be made by imaging the brain tumor in a suspect patient. Before pursuing advanced imaging, basic bloodwork (complete blood count [CBC] and chemistry profile) and a urinalysis should be performed. Thoracic radiographs should be taken to help rule out the possibility of metastatic cancer. CT and MRI are commonly used in the diagnosis of brain tumors, with MRI being the preferred imaging modality. Although specific types of brain tumors can vary in their appearance with these imaging modalities, there are some characteristic features that help distinguish meningiomas from gliomas. Meningiomas tend to have a broad-based, extra-axial attachment (they arise from the periphery of the brain and move inward, or axially), exhibit distinct tumor margins, and uniformly contrast enhance (Fig. 7.32). Meningiomas tend to displace, rather than invade, parenchymal tissue. Some meningiomas will calcify, which can be appreciated on a noncontrast CT image (Fig. 7.33). The "dural tail" sign is an MRI feature typically associated with meningiomas, in which a contrast-enhancing meningeal-associated "tail" is seen extending from the main tumor mass (Fig. 7.34). Histiocytic sarcoma can appear similar to meningioma on MR images; the dural tail sign has also been reported with histiocytic sarcoma. Meningiomas also may occasionally have a cystic component (cystic meningioma) extending from the main tumor mass (Fig. 7.35). Gliomas tend to arise from an intra-axial location (from within the substance of the brain, moving outward), often lack distinct tumor margins (they tend to infiltrate, rather than displace normal tissue), and typically contrast enhance poorly and nonuniformly (Fig. 7.36). Hemorrhagic infarcts can be indistinguishable from gliomas on MR imaging, as they often have very similar imaging characteristics. Since gliomas can have areas of hemorrhage within the mass lesion, T2*-W imaging alone may not distinguish a tumor with hemorrhage from a hemorrhagic

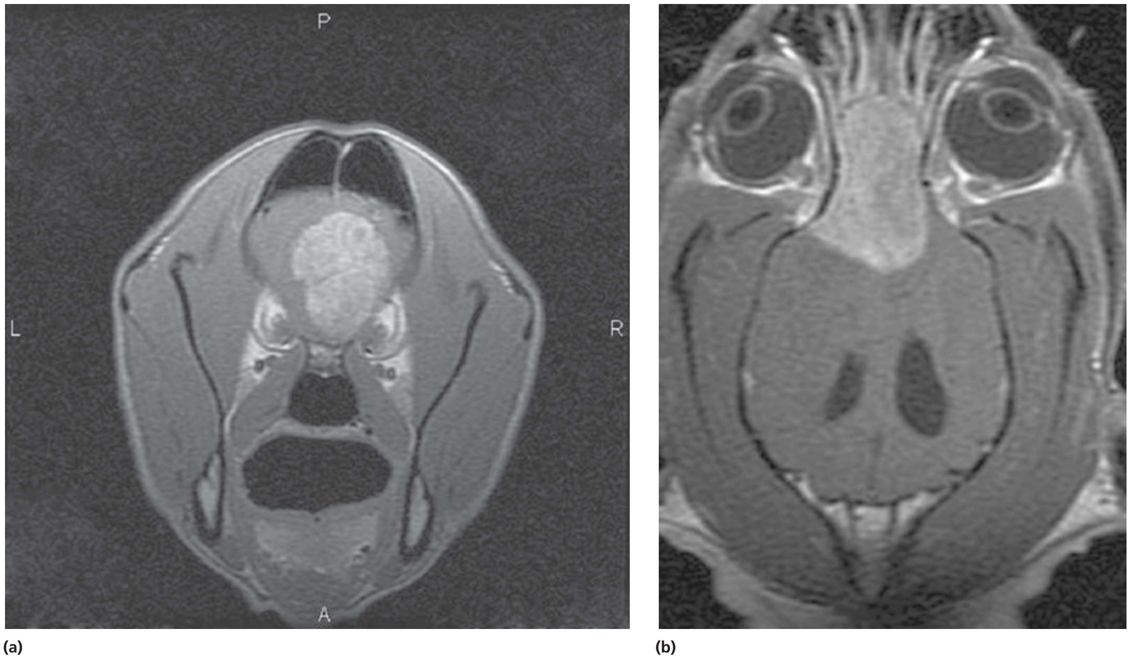


Figure 7.32 Brain MR images (T1-weighted with contrast) of dog with a large intracranial meningioma, transaxial (A) and dorsal (B) views.

infarct (Fig. 7.37). Gliomas tend to be located in the cerebral hemispheres more often than hemorrhagic infarcts (which tend to be in the brain stem and cerebellum) and they tend to be larger than hemorrhagic infarcts with more evidence of mass effect and perilesional edema. In addition, diffusion-weighted imaging sequences are more likely to be abnormal with infarcts versus gliomas. Whether a suspected glioma is an astrocytoma or an oligodendroglioma is difficult to ascertain on MR images; in one study, oligodendrogliomas were significantly more likely to extend to the meningeal surface than astrocytomas,

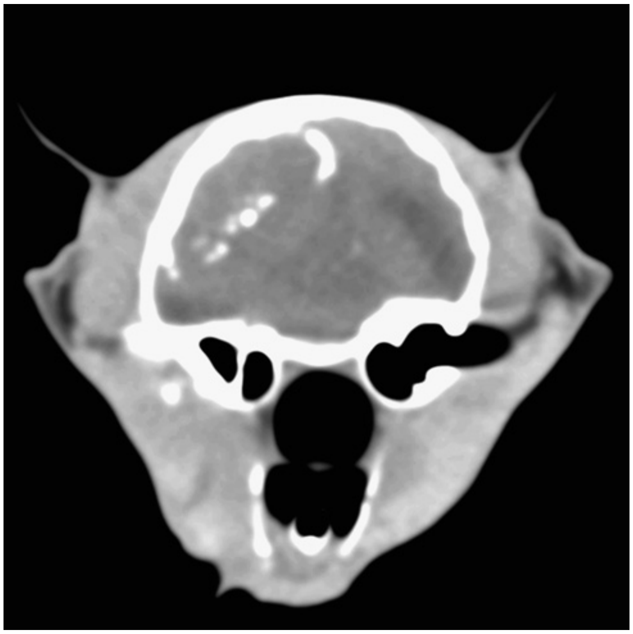


Figure 7.33 Noncontrast transaxial CT image of a meningioma in a cat, with areas of tumoral mineralization.

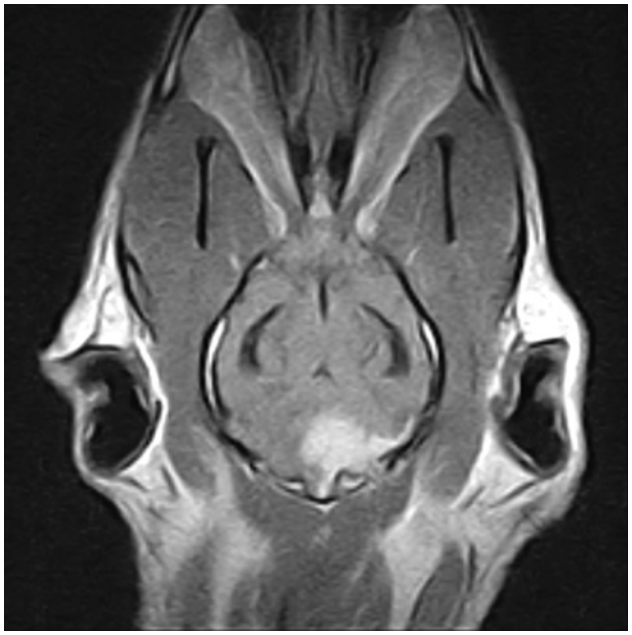


Figure 7.34 Dorsal MR brain image (T1-weighted with contrast) demonstrating the “dural tail” sign associated with meningiomas.

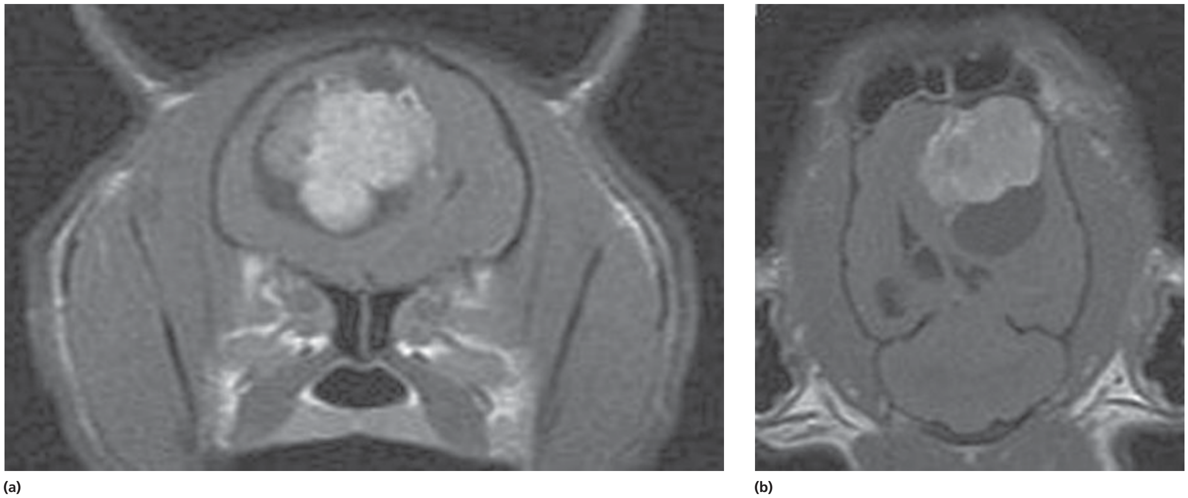


Figure 7.35 Transaxial (A) and dorsal (B) brain images (T1-weighted with contrast) of a cat with a cystic meningioma.

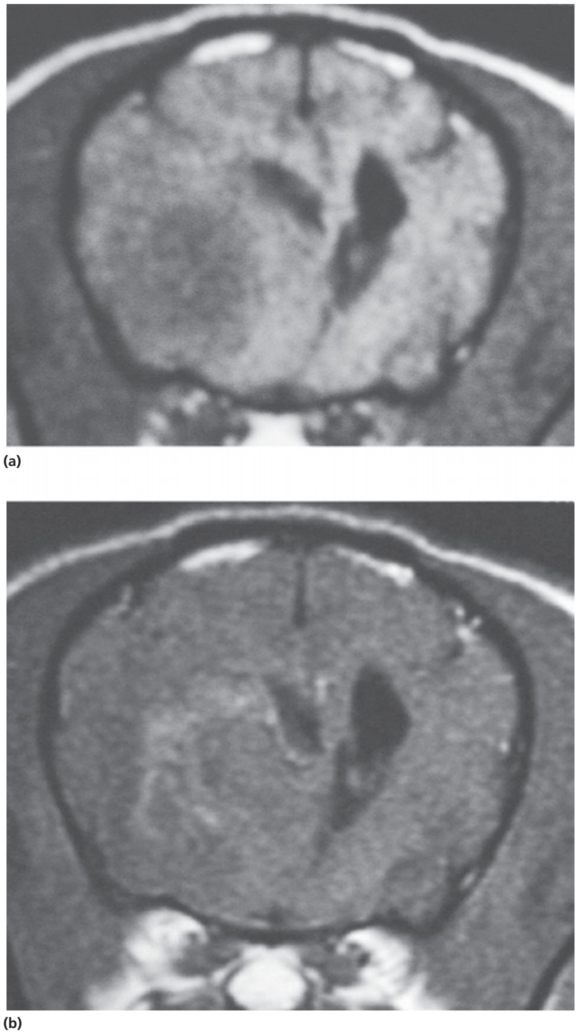


Figure 7.36 Transaxial MR brain images (T1-weighted) of a dog with an intracranial glioma, before (A) and after (B) contrast administration. Note the patchy contrast enhancement and indistinct tumor margins.

but there were no other consistent distinguishing MR imaging characteristics. Choroid plexus tumors and ependymomas tend to be intraventricular in location and often uniformly contrast-enhance (Fig. 7.38). The phenomenon of "ring enhancement," in which a circular ring of contrast enhancement surrounds nonenhancing tissue (Fig. 7.39), is nonspecific, and has been associated with several neoplastic and non-neoplastic brain diseases. However, ring enhancement is often associated with gliomas. Meningeal contrast enhancement evident on MR images of the brain has been described, but is not specific for brain tumors. These typical imaging features are guidelines only. Meningiomas can arise from the falx cerebri or the choroid plexus, and appear intra-axial. Gliomas can be peripherally located and contrast enhancing. In one study, the accuracy of predicting primary tumor type based on the MR images of 20 dogs was 65%. Stereotactic CT-guided biopsy of brain tumors is now available at several veterinary referral centers. With this new technology, a definitive diagnosis can be obtained at the time of imaging without the need for major intracranial surgery.

The utility of CSF evaluation for the suspected brain tumor patient is controversial. CSF is often abnormal in patients with brain tumors, but the white blood cell (WBC) counts and protein levels are variable and nonspecific for neoplasia. In fact, dogs and cats with meningiomas tend to have CSF with predominantly polymorphonuclear (neutrophilic) WBC counts. The author often does not pursue CSF analysis if the CT or MR image strongly suggests a brain neoplasm. Although the risk of CSF procurement in the face of elevated ICP in a brain-tumor patient is often not great, the potential benefit of a nonspecific CSF result may not outweigh even a small danger of harming

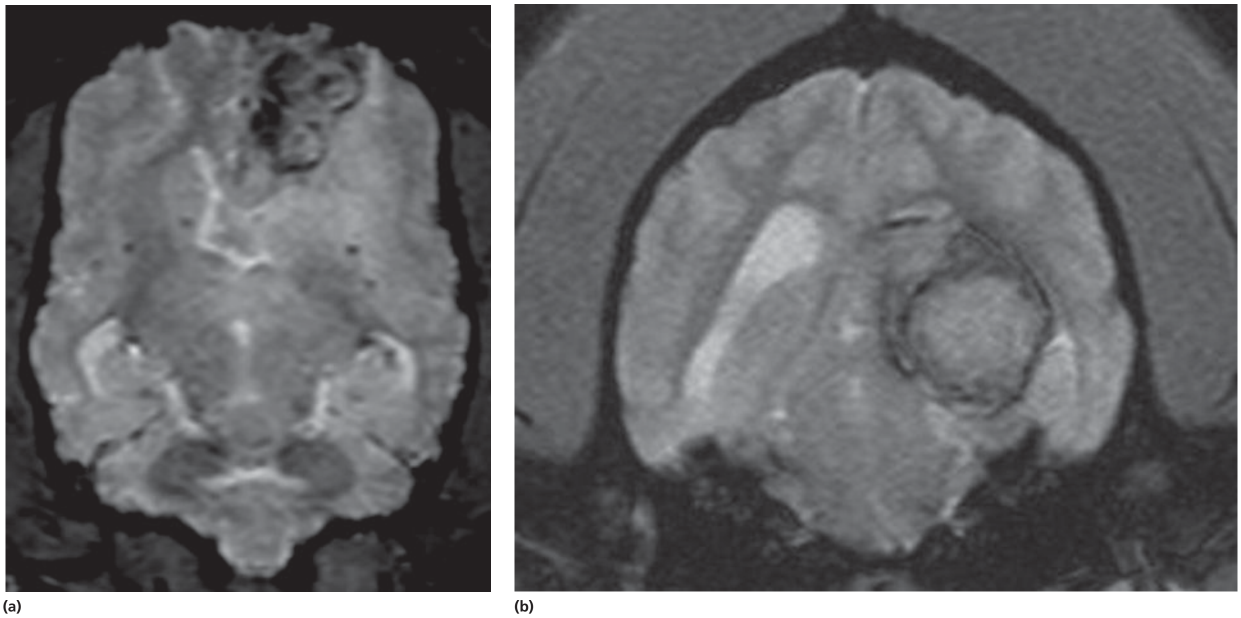


Figure 7.37 Dorsal (coronal) T2∗ MR image (A) of a dog with multiple brain hemorrhages and transaxial T2∗ MR image (B) of a dog with an intracranial glioma with hemorrhage around the mass periphery. (Dr. Jennifer L. Bouma, DACVR, 2014. Reproduced with permission of Dr. Jennifer L. Bouma.)

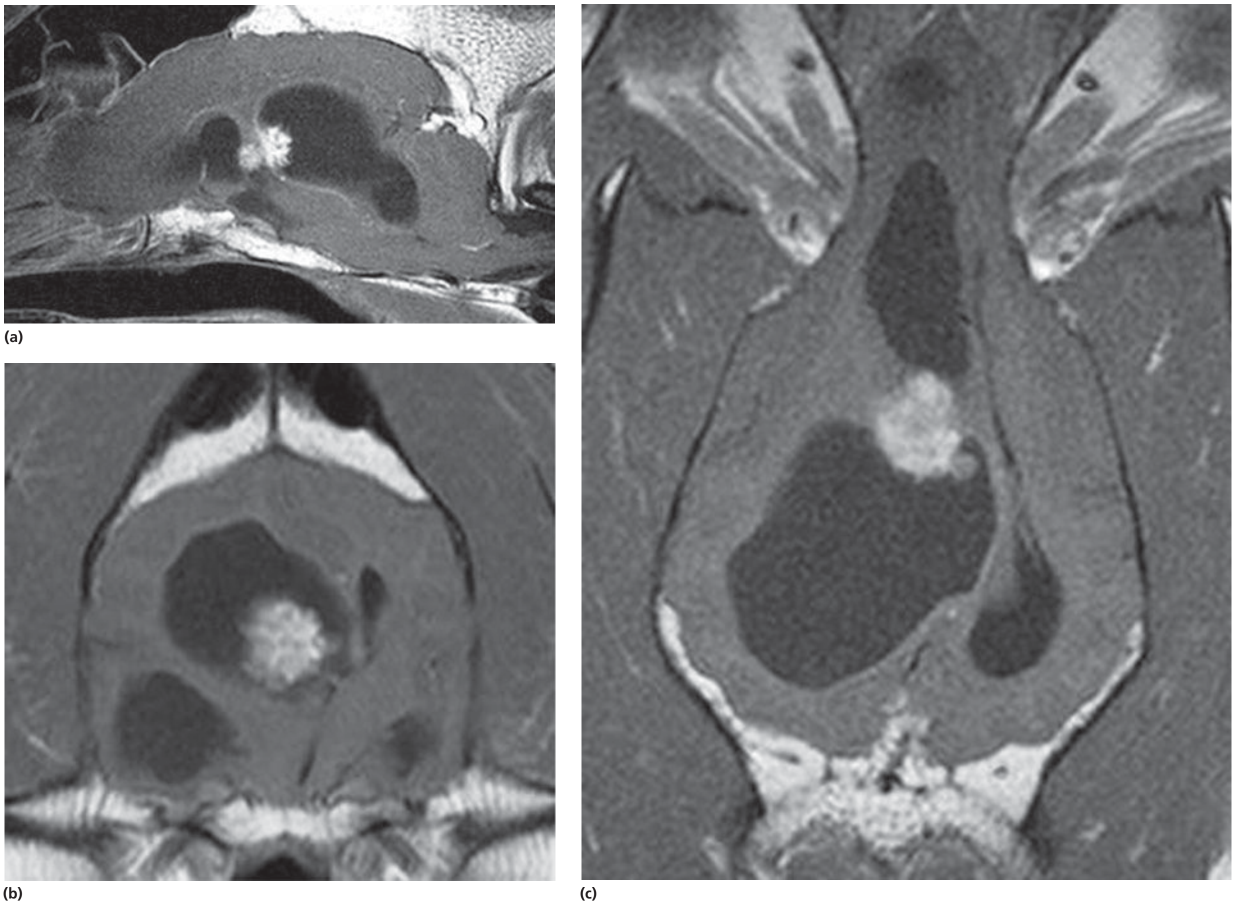


Figure 7.38 Sagittal (A), transaxial (B), and dorsal/coronal (C) T1-weighted MR images with contrast demonstrating a choroid plexus tumor in a dog, along with accompanying hydrocephalus. (Dr. Jennifer L. Bouma, DACVR, 2014. Reproduced with permission of Dr. Jennifer L. Bouma.)

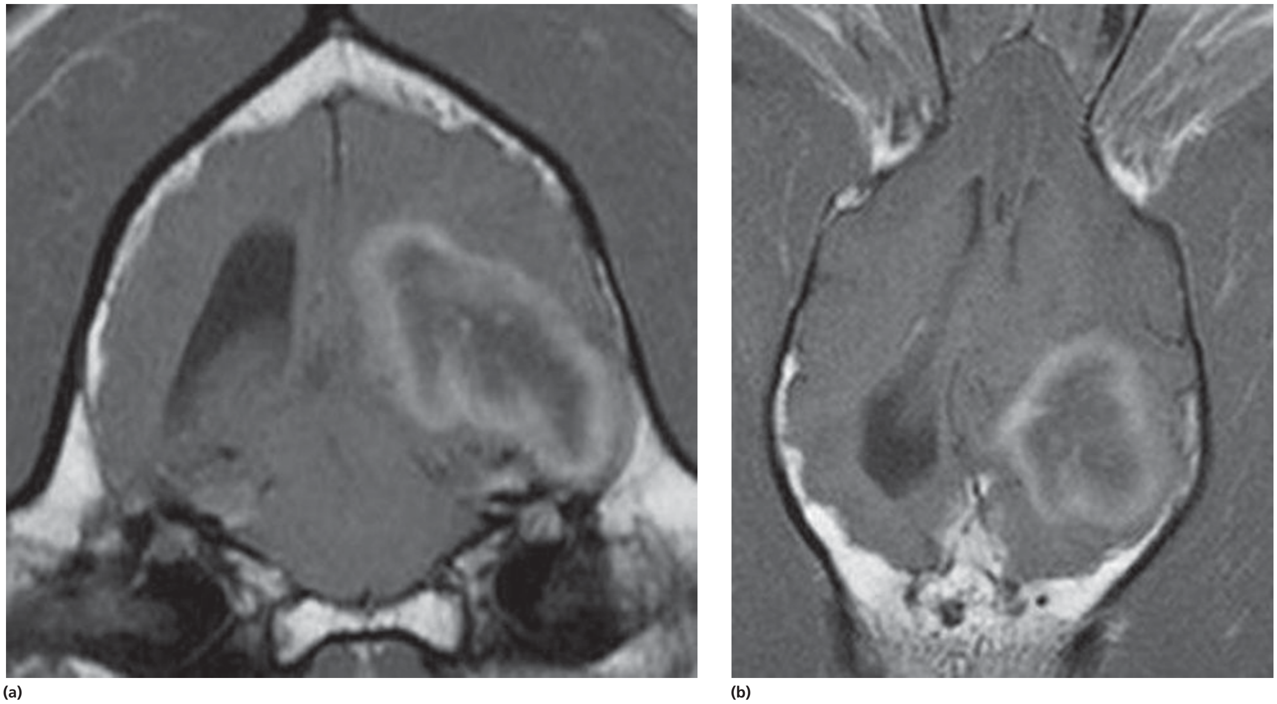


Figure 7.39 Transaxial (A) and dorsal/coronal (B) MR brain images (T1-weighted with contrast) of a dog with a suspected intracranial glioma. Note the characteristic "ring enhancement" around the tumor. (Dr. Jennifer L. Bouma, DACVR, 2014. Reproduced with permission of Dr. Jennifer L. Bouma.)

the patient with the procedure. Although CSF analysis tends to yield fairly nonspecific information in brain tumor cases, it may be helpful in helping to distinguish whether a choroid plexus tumor is a CPP or CPC. In one study, the more malignant CPC was significantly more likely to be associated with a CSF protein concentration > 80 mg/dl than the less malignant CPP tumor subtype. Regardless of whether or not CSF analysis is performed, imaging should always precede CSF analysis when a focal neoplasm is highly suspected. Anesthetizing a patient who is most likely to have a brain tumor solely for the purpose of obtaining CSF is generally contraindicated, as the resultant information is unlikely to assist in either planning treatment or estimating prognosis.

d. Treatment of primary brain tumors is divided into the categories of supportive and definitive. Supportive therapy is aimed at alleviation of the secondary effects of the tumor, whereas definitive therapy is directed toward diminishing tumor volume or eliminating the tumor. Supportive therapy typically consists of an anti-inflammatory dose of oral prednisone (0.5 mg/kg, q 12 hrs), that can be increased or decreased, dependent upon patient response. The prednisone should decrease ICP by relieving tumor-associated brain edema and decreasing CSF production. If the tumor results in seizure activity, anticonvulsant drugs are also prescribed. The author has found that administering standard doses of phenobarbital to dogs with rostral forebrain tumors tends to cause profound sedation. There are several relatively new and effective anticonvulsant drugs available for dogs that do not have appreciable sedative effects. The author preferentially chooses zonisamide, levetiracetam, felbamate or some combination of these for use in dogs with brain tumors, unless cost-prohibitive. Supportive therapy is usually recommended, whether or not the client opts to pursue definitive therapy for their pet.

There are numerous definitive treatment modalities available for canine and feline brain tumors, but surgical removal/debulking (Fig. 7.40), megavoltage radiation and oral chemotherapy are most commonly used. Several novel treatment modalities for canine brain tumors are being evaluated. These methods are aimed mainly at addressing intra-axial neoplasms, such as gliomas. They include brachytherapy, non-thermal irreversible electroporation (N-TIRE), and convection-enhanced delivery of liposomes containing chemotherapeutic drugs. Brachytherapy refers to the local application of radiation via a catheter inserted into the lesion to be irradiated. N-TIRE involves placing electrodes within the target and inducing a regional electric field with low-energy pulses that disrupts cell membranes. Convection-enhanced delivery utilizes infusion catheters inserted into the region to be treated; the chemotherapeutic agent is infused via

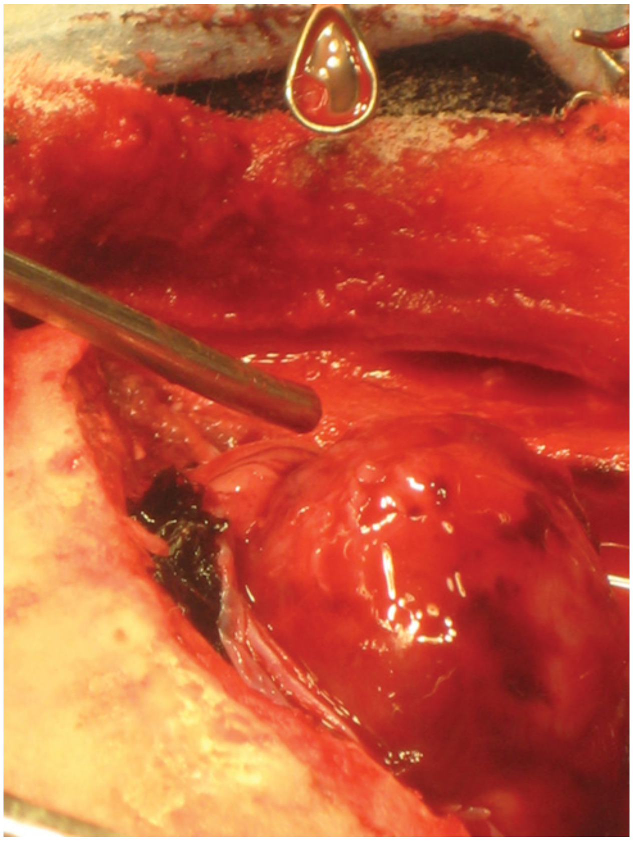


Figure 7.40 Surgical removal of an intracranial meningioma in a dog.

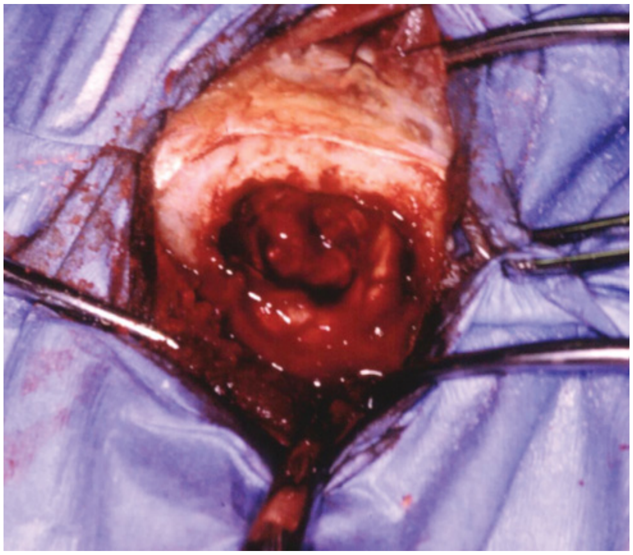


Figure 7.41 Intraoperative view of a cat's brain following meningioma removal. The tumor was removed en masse, leaving an indentation in the cerebrum. (Dewey *et al.*, 2000.)[138]

the catheter through the interstitial spaces under a pressure gradient. In addition to removing cancerous tissue, surgical debulking/removal allows for a histologic diagnosis as well as potentially providing an immediate decompressive effect (decreasing ICP). Feline meningiomas are typically located over the cerebral convexities, and tend to "peel away" from normal brain tissue at surgery (Fig. 7.41). In most cases, feline meningiomas can be relatively easily removed en masse. Although meningiomas are believed to be radiation sensitive in cats, information concerning radiation therapy for this tumor is lacking, probably due to the success of complete surgical removal. There are no reports describing definitive therapy of feline gliomas. The use of both surgery and radiation therapy have been described in a small number of cats with intracranial ependymoma. Descriptions of definitive therapy for canine brain tumors other than meningiomas and gliomas are largely anecdotal. Canine meningiomas are also often located over the cerebral cortical surface and are surgically accessible. However, meningiomas in the cerebellar and brain-stem regions are frequently encountered in dogs. Cerebellar meningiomas are often surgically accessible; meningiomas in the brain stem may not be accessible. Meningiomas in dogs are much less predictable than those in cats in terms of ease of surgical removal. There are typically more histologic subtypes of canine meningiomas encountered clinically than in cats, and nearly one-third of these tumors are invasive. The author has successfully used intraoperative ultrasound (Fig. 7.42) to assist in locating brain tumors and in judging completeness of removal. Canine meningiomas are generally thought to be radiation sensitive. A combination of surgical debulking and radiation therapy is often pursued for canine meningiomas. Surgically inaccessible meningiomas are often treated with radiation therapy alone. Some canine gliomas are surgically accessible, but surgical removal/debulking of gliomas is considerably more difficult than meningiomas. Gliomas tend to infiltrate normal brain parenchyma, and it is often difficult to discern tumor margin from brain tissue at surgery. Although gliomas are not thought to be as radiation sensitive as meningiomas, radiation therapy is often pursued as either a primary or adjunctive therapy for canine gliomas. The current standard protocol for definitive megavoltage radiation therapy of brain tumors is the administration of fractionated daily doses of 2.5–4 Gy on a Monday through Friday (once a day) schedule for 4 wks. Protocols vary, but most involve the administration of a total cumulative dose in the range of 40–50 Gy.

Chemotherapy has traditionally been regarded as ineffective for canine and feline brain tumors, mainly due to the poor ability of most drugs to cross the BBB, even when disturbed by the presence of a tumor. However, there are several reports of using nitrosourea

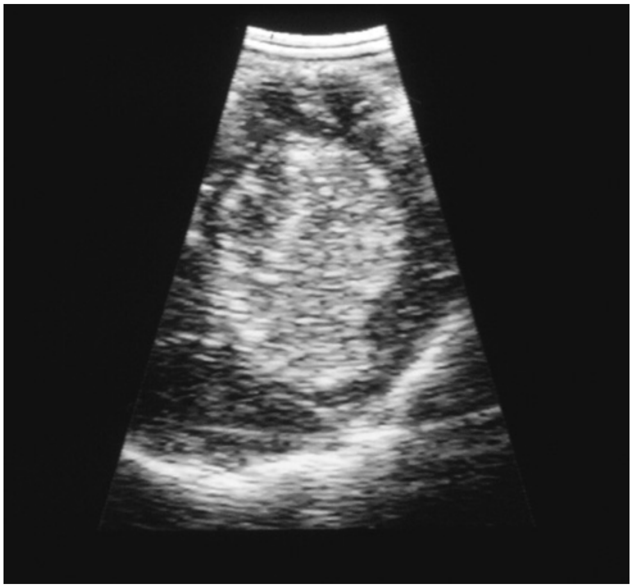


Figure 7.42 Intraoperative ultrasound image of the brain, revealing the presence of an intraparenchymal mass. (Dewey *et al.*, 2000.)[138]

compounds such as lomustine (CCNU) and carmustine (BCNU) for canine gliomas. These highly lipid-soluble alkylating agents cross the BBB readily and are used to treat human intracranial gliomas. Oral lomustine (CCNU), at a dosage of 60 mg/m^2 every 6–8 wk, is recommended for dogs. Since lomustine can cause severe neutropenia, weekly to biweekly CBCs should be checked during treatment, beginning 1 wk after drug administration. Broad-spectrum antibiotics are initiated if the neutrophil count drops below 1000 cells/ml. If myelosuppression is prolonged, administration of granulocyte colony stimulating factor (Neupogen) is recommended. The dose for Neupogen (filgrastim) is 5 mg/kg/day, subcutaneously for three to five days. The same hepatic microsomal enzymes necessary for generating antineoplastic metabolites from lomustine are also involved in the metabolism of phenobarbital. In order to minimize the possibility of reduced drug efficacy of lomustine, it is recommended that alternatives to phenobarbital be used in seizure patients receiving lomustine therapy. In addition to the potential for bone marrow suppression with oral lomustine use, delayed dose-related hepatotoxicity has also been reported to occur in approximately 6% of cases.

Hydroxyurea is an oral chemotherapeutic agent with efficacy against intracranial meningiomas in people. Proposed mechanisms of action of hydroxyurea include the induction of tumor cell apoptosis and the inhibition of ribonucleotide diphosphate reductase (with subsequent interference with DNA synthesis). The dose of hydroxyurea used in people is 20 mg/kg SID. The author and colleagues have adapted this protocol for dogs with intracranial meningiomas. In one study, dogs treated with only hydroxyurea and prednisone (i.e. no surgery or radiation therapy) had a significantly longer survival time (approximately 7–8 mos), compared with approximately 4 mos for dogs treated with prednisone alone. Mild to moderate bone marrow suppression is a potential side effect of hydroxyurea use in people. To date, this side effect has not been an issue in dogs at the recommended dose.

Chemotherapy and radiation therapy are often applied directly to the tumor in human brain-tumor treatment. Such focal therapy offers the advantage of administering a large dose of treatment to the tumor while minimizing toxicity to normal tissue. These focal therapies have not been extensively evaluated in dogs and cats. With the recent availability of stereotactic technology, focal therapies for canine and feline brain tumors may be pursued more commonly in the future.

In general, the prognosis for brain-tumor patients treated with supportive therapy alone is poor. The majority of these animals will die or be euthanized due to worsening neurologic dysfunction within 1–6 mos of initial presentation. In one prospective study investigating the survival times of dogs with primary brain tumors treated with supportive therapy alone, it was found that tumor location significantly impacted survival times following hospital discharge. Dogs with supratentorial masses had a median survival of 178 days, whereas those with infratentorial masses had a median survival of 28 days. Other than feline meningioma, prognostic information regarding individual primary brain tumors is highly variable and somewhat conflicting. This is probably due to the lack of controlled studies with large numbers of patients for each of these tumors, as well as the diverse biological behaviors of these tumors compared to feline meningiomas. The prognosis for long-term survival in cats with intracranial meningiomas is typically good to excellent with surgical removal. Median postoperative survival times have ranged from approximately 18 to 27 mos. In a more recent report of 121 cases, the median postoperative survival time was 58 mos; in this report it was found that cats with anaplastic and meningothelial subtypes had significantly shorter survival times compared with other subtypes. Considering the advanced age of some cats at the time of meningioma removal, it should be kept in mind that not all deaths are attributable to tumor regrowth. Tumor recurrence has been estimated to be somewhere between 20 and 25%. Regrowth of intracranial meningioma in cats is usually in the original tumor location. In the author's clinical experience, the success rate of re-operation of feline intracranial meningioma is similar to the reported success rate of first-time operation of these tumors. In other words, re-removal of recurrent feline intracranial meningiomas should be considered a logical therapeutic option. Simultaneous removal of multiple intracranial meningiomas in cats is also associated with prolonged survival times. Three cats with intracranial ependymoma were treated with radiation therapy, and one of these three also had surgery performed. One of the cats (treated with radiation alone) lived for approximately 4 mos; the other two survived for well over a year.

Survival rates reported for canine brain tumors with different modes of definitive therapy are quite variable. Part of the variability may be due to the inclusion of different tumor types and different variations of therapy within study populations. The tendency for these published rates to improve in general over time may reflect advancements in our ability to treat these tumors. In general, however, the prognosis for the definitive treatment of canine meningiomas is more guarded in comparison with the feline disease. In one large study, it was found that 43% of canine intracranial meningiomas had aggressive histologic grade tumors (atypical, Grade II), which differs from cats and humans, in which the vast majority of meningiomas are histologically benign (approximately 80% of human meningiomas are Grade I benign). This important finding may help explain the variable and often poor response to definitive therapy of canine intracranial meningiomas. The prognosis for readily resectable meningiomas in dogs is considered fair, but canine meningiomas are not commonly as easily resectable as feline meningiomas. In one report of four dogs with intracranial meningiomas, the median postoperative survival time was 4.6 mos. In another report of 14 dogs, the median postoperative survival time was 6.6 mos. In one small case series, three dogs with surgically excised intracranial meningiomas lived an average of 6.7 mos following surgery. A fourth dog was euthanized 2.5 mos after surgery, due to status epilepticus. In a report evaluating canine meningioma resection using an ultrasonic surgical aspirator, the median survival time was reported as 1,254 days. In a retrospective study evaluating the outcome of dogs whose meningiomas were removed using endoscopic guidance, the median survival time for dogs with forebrain tumors was 2,104 days and for dogs with caudally located tumors was 702 days. These results suggest that more complete tumor resection (due to better surgical visualization) may be associated with longer postsurgical survival times.

Results of the megavoltage radiation treatment of primary brain tumors are also variable. In one study, radiation therapy for canine meningiomas as a sole therapy resulted in median survival times of between 5 and 9 mos. In another report, hypofractionated radiation therapy was associated with median survival times of 12.5 mos and 10 mos for dogs with extra-axial (probable meningiomas) and intra-axial (probable gliomas) tumors, respectively. In one study of 29 dogs with primary brain tumors treated via megavoltage radiation therapy, the median survival time was 250 days. In a more recent study evaluating megavoltage radiation therapy as a sole definitive therapy for 46 dogs with brain tumors, the median survival time was 699 days (23.3 mos), and the median survival time attributed to neurologic deterioration was 1,174 days. In a study that evaluated stereotactic radiosurgery for delivering a single focused high dose of megavoltage radiation to a tumor using advanced imaging, the median survival was 426 days overall, and 584 days if corrected for patients dying from unrelated disorders. In this report, there was no significant effect of tumor type on survival time.

Survival times of dogs with meningiomas receiving surgical debulking/removal followed by megavoltage radiation therapy range from approximately 16 mos to 3 yrs. The limited information concerning definitive therapy of canine meningiomas suggests that combination surgery and radiation therapy may be necessary for prolonged survival in many cases. In a recent report of 21 dogs with olfactory bulb/frontal lobe meningiomas, mean/median survival times for supportive therapy (6.5/3.8 mos), surgery alone (8.3/6.7 mos), surgery plus hydroxyurea (18.3/18.4 mos), and surgery plus megavoltage radiation therapy (18.7/16.9 mos) were described. In a report of 10 dogs with choroid plexus tumors (eight CPP, two CPC), the median survival of eight treated dogs (six via supportive care, two via surgical debulking) was eight days. Four of the 10 dogs had megaesophagus and two of these four had aspiration pneumonia. The eight reported cases of meningioangiomatosis are all necropsy descriptions. Reported cases of primary brain histiocytic sarcoma (malignant histiocytosis) are also confined to pathological descriptions. The author removed a primary cerebral extra-axial histiocytic sarcoma from a Labrador Retriever, who subsequently received megavoltage radiation therapy; at last recheck examination, over 2 yrs following diagnosis, the dog was still alive and doing well.

Gliomas are associated with a poor prognosis. Data concerning surgical therapy for canine intracranial gliomas are almost nonexistent. Radiation therapy as a sole treatment in 10 dogs with gliomas resulted in a median survival time of approximately 6 mos.

Several reports on the use of nitrosourea compounds (carmustine, lomustine) suggest an important role for this form of chemotherapy in the treatment of gliomas; survival times ranging from 7 to 11 mos have been documented. In one case report of a dog with an anaplastic oligodendroglioma treated with combined radiation therapy and lomustine, a survival time of approximately 2.5 yrs was documented. There is no information available concerning the prognosis of other primary canine and feline brain tumors.

There have been several recent reports focusing on molecular aspects of canine brain tumors, for purposes of both predicting prognosis and devising novel therapeutic approaches. Tumor-specific genes have recently been identified for the dog, many of which are similar to those described in humans. Several types of receptors and cellular proteins have also been identified in canine brain tumors, including progesterone receptors, proliferating cell nuclear antigen (PCNA), vascular endothelial growth factor (VEGF), and a nuclear protein called MIB-1. The majority of canine and feline meningiomas appear to have progesterone receptors. There is a positive association with PCNA level and a likelihood of tumor recurrence, and a negative association with PCNA level and level of tumor progesterone receptors. There is also a documented association with the degree of malignancy and an increased expression of VEGF and MIB-1 in canine brain tumors. In addition, elevated CSF levels of uric acid (an indicator of oxidative injury and potential glutamate excitotoxicity) and glutamate have been demonstrated in dogs with primary brain tumors. There is currently work underway aimed at targeting brain tumors using viral vector-mediated gene transfer.

2. Secondary brain tumors[32, 69, 109, 129, 134, 154, 243, 267, 268, 313, 347, 354, 415, 419, 451, 464, 467, 481, 524, 525, 669, 692, 710, 777]
   a. Secondary brain tumors include metastatic neoplasia as well as tumors that affect the brain by local extension. Some examples of metastatic neoplasia include mammary, pulmonary, and prostatic carcinoma, hemangiosarcoma, malignant melanoma, and lymphosarcoma. Tumors that may extend into the brain from the periphery include nasal and frontal sinus carcinoma (adenocarcinoma, squamous cell carcinoma), calvarial tumors (e.g. osteosarcoma, chondrosarcoma, multilobular osteochondrosarcoma), pituitary tumors (e.g. pituitary macroadenomas in hyperadrenocorticism), and nerve sheath tumors (e.g. CN V tumors). In one large retrospective study of secondary brain tumors in dogs, the most common secondary brain tumor was hemangiosarcoma (29%), followed by pituitary tumors (25%), lymphosarcoma (12%), metastatic carcinoma (11%), and invasive nasal tumors (6%). In one recent report, secondary (multicentric) lymphoma and pituitary tumors were the second- and third-most-common intracranial neoplasms found in cats. Other reports suggest that lymphoma/lymphosarcoma is the most common secondary brain tumor type encountered in cats. An intracerebral (intraventricular) plasma cell tumor has been reported in a cat (necropsy report), but it was not determined whether this was a primary or secondary (i.e. multiple myeloma) tumor. A dog exhibiting clinical signs similar to human pituitary apoplexy (acute onset of headache, vomiting, altered mentation, and hormonal disturbance due to hemorrhage or infarction within a pituitary mass) was described. On necropsy, the dog was found to have a pituitary adenoma with intra- and peritumoral hemorrhage. Similar to primary brain tumors, secondary brain tumors produce clinical signs of neurologic dysfunction both by encroaching upon/invading brain tissue and by secondary effects such as hemorrhage, inflammation, and obstructive hydrocephalus.
   b. As with primary brain tumors, secondary brain tumors are primarily encountered in middle-aged to older dogs (usually) and cats. Medium-sized to large-breed dolichocephalic dogs are prone to developing nasal/frontal sinus carcinomas and calvarial tumors, whereas small and brachycephalic breeds of dogs are more likely to develop pituitary macroadenomas. In the large retrospective study mentioned earlier, the mean age of dogs with secondary brain tumors was similar to that of primary brain tumors (9.6 yrs). Mixed breeds were most common, followed by Golden Retrievers and Labrador Retrievers. On postmortem examination of these dogs, metastatic lesions were found in the lung (47%), kidney (35%), and heart (31%). Thoracic radiographs were abnormal in over half of the cases in which chest films were performed. Only 30% of secondary brain lesions were reported as multifocal in distribution. An additional, unrelated neoplasm was found in 18% of the dogs. This study also found that secondary brain tumors were slightly more common than primary brain tumors for the time period evaluated. Since all the evaluated cases were confirmed by postmortem examination, the higher number of secondary brain tumors may be more reflective of higher short-term mortality rates compared with primary brain tumors, rather than a truly higher incidence of secondary brain tumors in the dog population.

     Clinical signs of neurologic dysfunction reflect tumor location(s) within the brain as well as the degree of secondary effects of the tumor(s). Unlike primary brain tumors, secondary brain tumors are often associated with the rapid development of neurologic

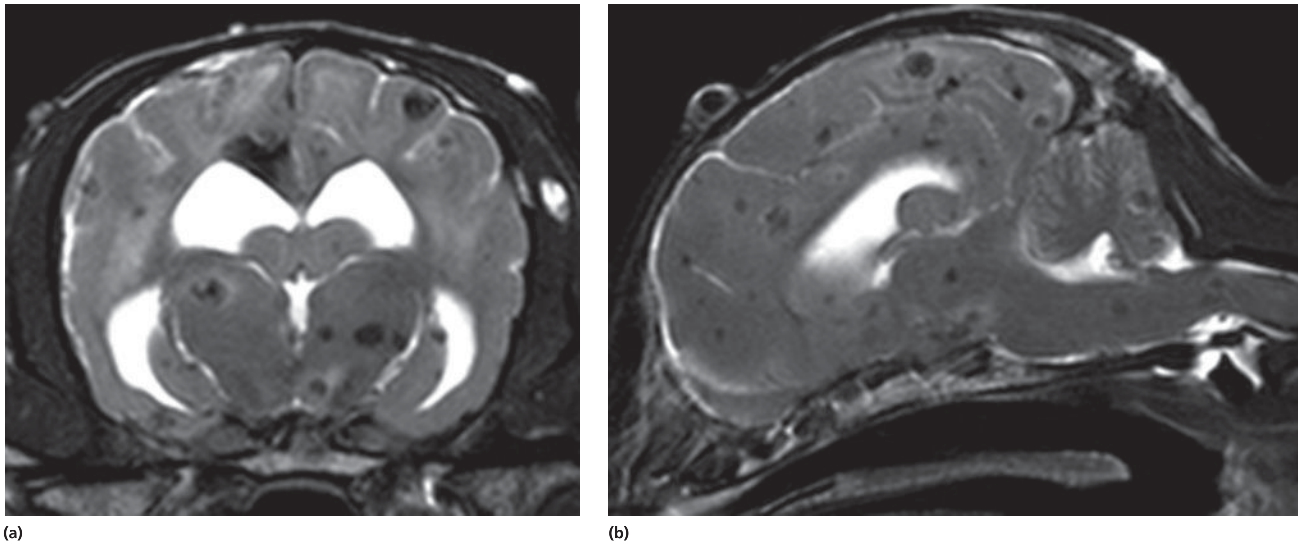

(a) (b)

Figure 7.43 Transaxial (A) and sagittal (B) T2*-weighted brain images in a dog with metastatic hemangiosarcoma.

dysfunction. Patients with metastatic disease may exhibit clinical signs of extraneural organ dysfunction due to neoplasia (e.g. collapse due to hemorrhage from a splenic hemangiosarcoma). Dogs with nasal carcinomas often, but not always, have historical/clinical evidence of epistaxis. Obvious skull deformities may be appreciable with nasal/frontal carcinomas and calvarial tumors. Most dogs with pituitary macroadenomas large enough to cause neurologic dysfunction display clinical signs of hyperadrenocorticism (e.g. PU/PD, polyphagia, pot-bellied appearance). In a large retrospective study of dogs with pituitary-dependent hyperadrenocorticism (PDH), however, no association was found between the development of neurologic dysfunction and the presence (on CT or MR imaging) or size (i.e. macrotumor vs. microtumor) of pituitary tumors. It was also found in that study that vague, nonspecific signs of forebrain dysfunction (e.g. mental obtundation, inappetence, lethargy) were more common in dogs with pituitary macrotumors than were more specific signs of brain disease such as circling, blindness, or seizures; such specific signs were more commonly encountered in dogs with pituitary tumors that were not detectable on imaging studies.

c. Similar to primary brain tumors, a definitive diagnosis of secondary brain tumors depends upon a histopathologic identification of the specific brain tumor. As with primary brain tumors, stereotactic biopsy may be potentially helpful in diagnosing some secondary brain tumors. In the case of metastatic neoplasia, identifying an extraneural neoplasia (e.g. pulmonary mass) in a patient with signs of encephalopathy is strong evidence for a secondary brain tumor. It must be kept in mind, however, that older animals may develop two or more primary tumors concurrently. A solitary pulmonary mass in a dog exhibiting signs of focal forebrain dysfunction does not necessarily equate to metastatic disease. Although rare, intracranial meningiomas have also been reported to metastasize to the lungs. The appearance of multiple intracranial masses on CT or MR imaging in a patient suspected of having metastatic disease is also strong confirmatory evidence for secondary brain neoplasia (Fig. 7.43). Metastatic carcinomas can, on occasion, appear as solitary, well-circumscribed brain tumors.

Nasal/frontal sinus carcinomas tend to cause bony destruction, which is readily visible on either skull films (procured with patient under general anesthesia) or CT/MR images (Fig. 7.44). Similarly, calvarial

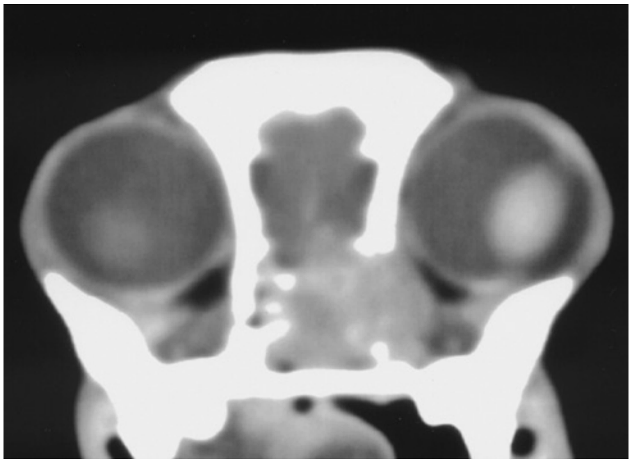


Figure 7.44 Transaxial, contrast-enhanced CT image of a dog with a nasal sinus carcinoma. Note the bony lysis associated with the tumor and invasion of the mass into the cranial vault.

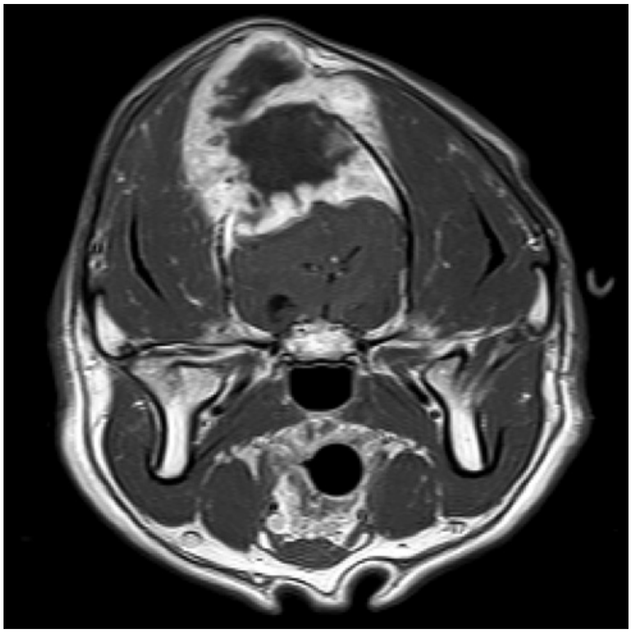


Figure 7.45 Transaxial MR brain image (T1-weighted with contrast) of a large multilobular osteochondrosarcoma causing severe brain compression in a dog.

tumors are often readily visualized with radiographs or CT/MR imaging (Fig. 7.45). In nasal/frontal sinus carcinomas, CT or MRI can provide confirmatory evidence of invasion into the cranial cavity (Fig. 7.46). Imaging a calvarial osteosarcoma, chondrosarcoma, or multilobular osteochondrosarcoma with CT can be invaluable in both diagnosis and treatment planning.

In addition to typical historical and clinical features of hyperadrenocorticism, the diagnosis of pituitary macroadenomas is based upon the results of endocrine testing (e.g. ACTH stimulation, dexamethasone suppression tests) and identifying a mass in the region of the pituitary on a CT (Fig. 7.47) or MR image.

Tentative diagnosis of a CN V-associated nerve sheath tumor invading the calvarium is based upon typical clinical signs of CN V dysfunction, clinical evidence of brain-stem involvement, and visualizing an intracranial mass on CT or MR imaging.

d. Supportive treatment of secondary brain tumors in dogs and cats is identical to that for primary brain tumors. Also, as with primary brain tumors, surgery and radiation therapy are the main definitive treatment modalities available for secondary brain tumors. Definitive treatment of metastatic secondary brain tumors is rarely attempted, due to the poor prognosis associated with these tumors, even in the absence of brain involvement. In some cases of single metastases (e.g. pulmonary carcinoma), definitive treatment

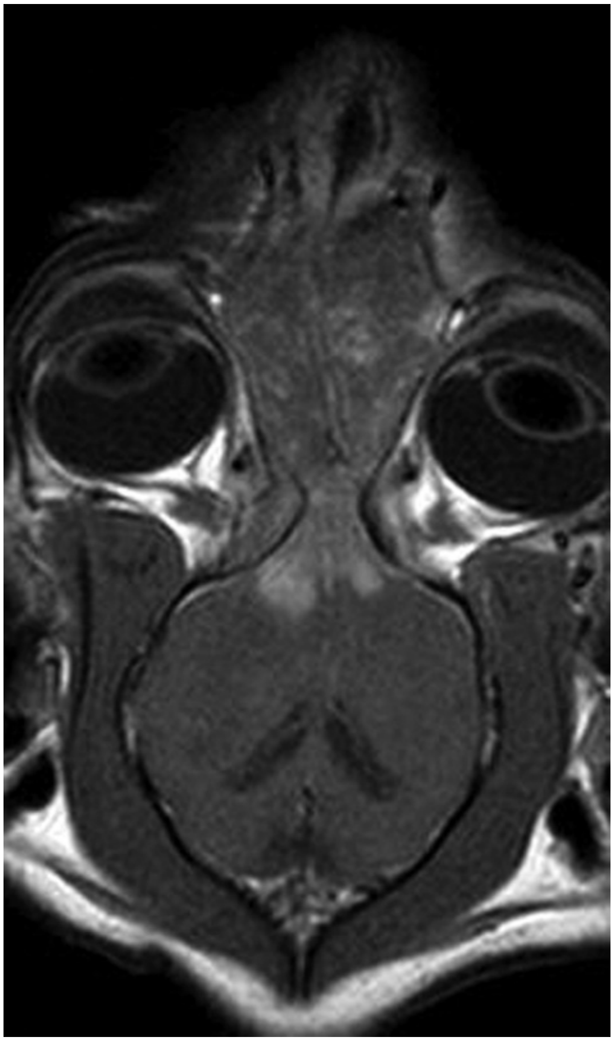


Figure 7.46 Dorsal T1-weighted with contrast brain image of a dog with a nasal frontal sinus carcinoma invading through the cribriform plate. (Dr. Jennifer L. Bouma, DACVR, 2014. Reproduced with permission of Dr. Jennifer L. Bouma.)

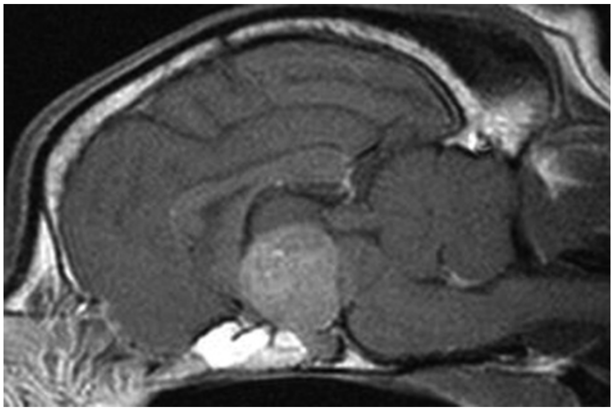


Figure 7.47 Midsagittal MR brain image (T1-weighted with contrast) of a dog with a pituitary macroadenoma. (Dr. Jennifer L. Bouma, DACVR, 2014. Reproduced with permission of Dr. Jennifer L. Bouma.)

of both the primary and secondary neoplasms may be indicated.

Nasal/frontal carcinomas with invasion into the cranial cavity are also rarely treated, as the prognosis for even short-term control of neurologic dysfunction is considered poor. Patients with calvarial tumors (e.g. multilobular osteochondrosarcoma), if aggressively treated with surgical resection, are likely to have prolonged survival times. These neoplasms are slow to recur and metastasize. In one report, the median survival time for multilobular osteochondrosarcoma of the skull was approximately 26 mos.

Pituitary adenomas are felt to be radiation sensitive, and median survival times after megavoltage irradiation are reported to be approximately 1–2 yrs in dogs. In one report of eight cats with pituitary tumors (six adenomas, two carcinomas), the median survival with megavoltage radiation therapy was 17.4 mos. Although traditionally rarely pursued due to technical complexity, excellent results of hypophysectomy via a transsphenoidal surgical approach have recently been documented in dogs with pituitary-dependent hyperadrenocorticism. This procedure is primarily intended for the removal of fairly small pituitary masses (i.e. as a treatment for hyperadrenocorticism), rather than as a mode of treatment for large pituitary tumors causing signs of encephalopathy.

In a report of trigeminal (CN V) nerve sheath tumors in dogs, the median survival time of nontreated cases was 12 mos. Two dogs treated with surgery were alive at the time of manuscript submission, 5 and 27 mos after surgery. One of the dogs that underwent surgery was euthanized due to progressive neurologic dysfunction 5 mos postoperatively.

E. Nutritional

1. Thiamine deficiency[118,217,286,431,519,658]

a. Thiamine deficiency is rarely a clinical problem in dogs and cats. Thiamine must be provided in the diet, as dogs and cats are unable to produce it endogenously. Thiamine (vitamin B_1) is a necessary cofactor for normal carbohydrate oxidation, and its deficiency results in insufficient ATP production in the brain with subsequent neuronal dysfunction and death (if not treated). Fish is high in thiaminase, and feeding an all-fish diet to cats can lead to thiamine deficiency. Overcooking canned food or meat, causing heat destruction of thiamine, has led to thiamine deficiency in dogs. Feeding meat preserved with sulfur dioxide to dogs and cats may also result in thiamine deficiency. There is a report of seven related Kuvasz puppies (from two litters) with a degenerative encephalomyelopathy that may have been due to amprolium-induced thiamine deficiency. Alternatively, these puppies may have suffered from a heritable metabolic neurodegenerative disorder.

b. Neurologic dysfunction due to thiamine deficiency tends to be acute and rapidly progressive. In both dogs and cats, signs of neurologic dysfunction due to thiamine deficiency typically include vestibular ataxia, decreased mentation (obtundation leading to coma, if not treated), ventroflexion of the head and neck, seizure activity, pupillary dilation with absent menace responses, and head tremors. Left untreated, affected animals progress to a comatose state with opisthotonus (decerebrate posture) and ultimately death.

c. Antemortem diagnosis of thiamine deficiency is typically based upon characteristic clinical signs of thiamine deficiency in a dog or cat receiving a thiamine-deficient diet. A positive response to thiamine administration also supports the diagnosis. Elevated blood pyruvate and lactate levels, and decreased erythrocyte transketolase activity are supportive of the diagnosis, but these tests are rarely done. There are reports of MR imaging in dogs with thiamine deficiency; similar to other metabolic encephalopathies, bilaterally symmetric brain lesions (hyperintense on T2-W images) were evident. In animals that die due to thiamine deficiency, characteristic bilaterally symmetric lesions (petechial hemorrhages) are appreciable throughout the brain at necropsy, especially in the caudal colliculi of the midbrain.

d. Treatment of suspected thiamine deficiency is thiamine hydrochloride via the intravenous, intramuscular, or subcutaneous route. The dosage for dogs is 5–50 mg/day and for cats is 1–20 mg/day. If recognized and treated early, the prognosis for survival of thiamine deficiency is good. If not treated rapidly in the early period of neurologic dysfunction, the prognosis for survival is guarded to poor.

F. Inflammatory/infectious

A wide variety of inflammatory brain conditions affect dogs and cats. For some of these conditions, an infectious agent is identifiable. For others, no infectious agent has been found. Some of the inflammatory brain diseases may have an autoimmune etiology. Diagnosis and treatment of inflammatory brain disorders can be frustrating. The “classic” description of a dog or cat with an inflammatory/infectious brain disease is a patient with a multifocal/diffuse encephalopathy, often with severe cervical spinal hyperesthesia. With infectious etiologies especially, fever and abnormal CBC results are often expected. In many cases, the affected patient will not follow the “classic” description of an inflammatory/infectious encephalopathy.

Historical, clinical, and laboratory data are typically combined in an effort to arrive at an antemortem diagnosis and institute appropriate therapy. CSF results may be particularly helpful when diagnosing diseases in this category.

In one report, a specific diagnosis was not ascribable to at least one-third of canine infectious/inflammatory disorders of the CNS. In the majority of canine and feline inflammatory brain diseases, especially those of confirmed infectious etiology, the prognosis for survival is poor. Prognostic data for many of these diseases are based mainly upon case reports and publications that focus on the pathologic aspects of the specific diseases. Considering the wide variety of potential clinical presentations for inflammatory/infectious brain disorders, and the frequent requirement of timely and aggressive treatment for successful outcomes, the clinician should maintain a high index of suspicion for these diseases. The pathophysiology of infectious meningoencephalitis is complex and is briefly reviewed below under bacterial meningoencephalitis. There are numerous treatment regimens for the various infectious agents discussed below, and this text is meant to provide an overview of these treatment options. The suggested references should be consulted for more detailed information.

1. Bacterial meningoencephalitis[42, 58, 103, 116, 134, 175, 182, 261, 316, 348, 406, 492, 522, 573, 576, 653, 672, 687, 726, 737, 779]
   a. In general, bacterial infections of the nervous system are felt to be uncommon. It is not clear whether these infections are truly rare or are rarely reported due to high early mortality. Bacteria can gain access to the brain via the hematogenous route or by extension of infection from a neighboring focus (e.g. extension of otitis interna into the brain stem). The BBB and absence of a lymphatic system in the CNS help protect it from microbial invasion. Once the BBB has been successfully breached by an infectious agent, the immunologically privileged nature of the CNS represents an advantage to the invading organism and a detriment to the host. The CNS is poorly endowed with immunologically active cells and complement, which provides a favorable environment for bacterial growth. Once cells from the systemic immune system are recruited into the CNS, the infection is often well established.

      Bacterial infections of the brain may result in neurologic dysfunction by producing a mass effect (i.e. organized abscess) or release of bacterial toxins. However, the main cause of neurologic deficits is the secondary inflammatory response induced by the bacteria. Inflammatory mediators, such as interferons, tumor necrosis factor (TNF), prostaglandins, and kinins are produced by WBCs in response to bacteria. These mediators result in edema, vasculitis, and infarction. By attracting additional WBCs to the infection focus or foci (chemotaxis), a self-perpetuation of tissue damage ensues. The most commonly implicated organisms in canine and feline bacterial meningoencephalitis have been *Staphylococcus* and *Streptococcus* species, *Pasteurella multocida* (especially cats), *Actinomyces* and *Nocardia* species, as well as anaerobes (e.g. *Bacteroides*, *Peptostreptococcus*, *Fusobacterium*, *Eubacterium*). In a recent report of canine bacterial meningoencephalitis, the most common causative organisms were *Escherichia coli*, *Streptococcus* species, and *Klebsiella* species. Gram-negative infections were most common, and single versus multiple organism infections were equally likely. *Bartonella* species have been implicated as potential causes of CNS disease in dogs and cats.
   b. Dogs and cats of any age, breed, or sex may develop bacterial meningoencephalitis, but it is more common in young to middle-aged animals (e.g. 1–7 yrs). In one study, most of the affected dogs were purebred, with a median age of 5 yrs at presentation. Clinical signs of neurologic dysfunction are often acute and rapidly progressive. Fever and cervical hyperesthesia are considered classic features of bacterial meningoencephalitis, but may not be evident. Fever and cervical hyperesthesia have been reported to occur in approximately 40 and 20% of canine bacterial meningoencephalitis cases, respectively. As with other diseases, clinical signs of neurologic dysfunction depend upon the location(s) and extent of the lesion(s). Both focal and multifocal encephalopathies are possibilities, involving the forebrain and/or brain stem. Some patients may appear generally ill due to systemic bacterial disease.
   c. A tentative diagnosis of bacterial meningoencephalitis is based upon historical and clinical data, as well as results of laboratory tests. A positive response to antibiotic drugs also supports the diagnosis. CBC results may indicate a systemic inflammatory response, but this is often not the case. Abnormalities such as leukocytosis, leukopenia, and thrombocytopenia have been reported to occur in approximately 57% of canine bacterial meningoencephalitis cases. Abnormalities on serum chemistry profiles (e.g. elevated ALT and SAP levels, hypoglycemia, hyperglycemia) are apparent in over 70% of such cases. Advanced imaging (CT, MRI) may be helpful in diagnosing mass lesions (Fig. 7.48) or obstructive hydrocephalus. The most valuable information is obtained from CSF analysis, which is abnormal in over 90% of cases. With acute bacterial meningoencephalitis, a suppurative CSF pattern, often with degenerate and toxic-appearing neutrophils, is typical. Protein levels are also often elevated. The presence of intracellular bacteria in the CSF sample confirms the diagnosis. Extracellular bacteria may represent causative agents but may also be contaminants. Positive CSF, blood, and/or urine culture results also support the diagnosis of bacterial meningoencephalitis. Since these culture results are often negative (approximately 80%) in

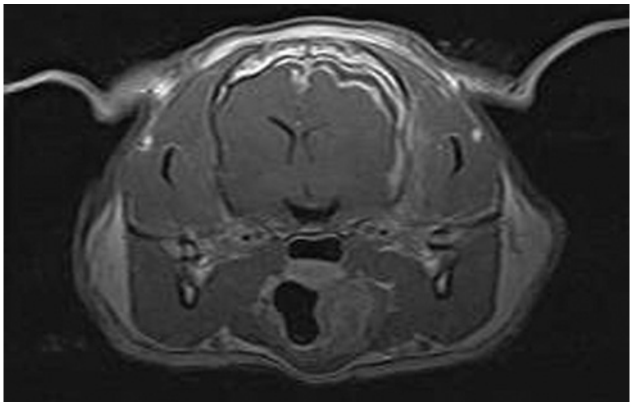


Figure 7.48 Transaxial brain image (T1-weighted with contrast) of a cat with an intracranial bacterial abscess (intracranial empyema) from a dog bite wound.

confirmed bacterial meningoencephalitis cases, a negative result should not be overinterpreted.

d. Ideally, an antibiotic treatment of bacterial meningoencephalitis is based upon culture/sensitivity results of the causative organism. As this is often not obtainable, antibiotic therapy is often based on gram-stain results of organisms seen on CSF analysis, or on the most likely pathogen(s), if organisms are not seen. Appropriate antibiotics for bacterial meningoencephalitis should ideally be bactericidal, have a low-level protein binding, and be able to cross the BBB. Intravenous therapy is recommended for at least the initial three to five days of therapy. High intravenous doses of ampicillin (e.g. 22 mg/kg, q 6 hrs) have been recommended as an appropriate therapeutic choice for most cases of canine and feline bacterial meningoencephalitis. Ampicillin crosses the inflamed BBB relatively well, and is bactericidal. If a gram-negative infection is suspected or confirmed, enrofloxacin (e.g. 10 mg/kg IV, q 12 hrs) or a third-generation cephalosporin (e.g. cefotaxime at 25–50 mg/kg IV q 8 hrs) is a good choice. Metronidazole (10 mg/kg IV slowly, q 8 hrs) is an excellent antibiotic choice for most anaerobic infections. Intravenous metronidazole should be administered over 30–40 min, as rapid infusion can lead to hypotension. In severe cases of bacterial meningoencephalitis, it may be prudent to institute combination antimicrobial therapy while awaiting CSF laboratory results (gram-stain, culture results). Based on information concerning causative agents in canine bacterial meningoencephalitis, inclusion of antibiotics with strong activity against gram-negative bacteria is highly recommended. Although chloramphenicol is broad spectrum and readily crosses the BBB, its use in human and experimental canine bacterial meningitis has been associated with a high relapse rate, presumably due to the bacteriostatic nature of this drug. Once a positive response to intravenous antibiotic therapy is achieved, the patient can be switched to oral therapy. Trimethoprim-sulfonamide (15 mg/kg PO, q 12 hrs) is broad and bactericidal, and it readily penetrates the BBB, even when the BBB is not inflamed. Oral formulations of enrofloxacin and metronidazole are also available. Recommendations for the length of oral antibiotic therapy vary. Discontinuation of antibiotic therapy is ideally based both on clinical signs as well as normal follow-up CSF tap results. However, the latter-mentioned information is often not available. In general, antibiotic therapy should be administered for 10–14 days after resolution of clinical signs of disease.

Although glucocorticoid use in the face of infection is usually contraindicated, there is abundant evidence that transient (maximum of 4 days), anti-inflammatory doses (e.g. 0.15 mg/kg dexamethasone, IV, q 6 hrs) of glucocorticoids improve outcomes in people with bacterial meningitis. Such therapy should be considered for dogs and cats with this disorder. If CT or MR imaging localizes a surgically accessible abscess, surgical intervention may play an important role in the management of bacterial meningoencephalitis.

Unfortunately, there are no reports describing large groups of dogs or cats treated appropriately for confirmed bacterial meningoencephalitis. The sparse information available suggests a poor prognosis overall. However, survival rates in people appropriately treated for bacterial meningitis are over 70%. There are isolated reports of successful outcomes in cases of canine and feline bacterial meningoencephalitis. Similar to human bacterial CNS infections, the key to the successful therapy of dogs and cats with bacterial meningoencephalitis is early diagnosis and rapid, aggressive therapy.

2. Fungal meningoencephalitis[50, 51, 102, 123, 124, 134, 186, 193, 224, 230, 244, 252, 261, 404, 430, 492, 528, 575, 610, 668, 693, 699, 726]

a. There is a wide variety of fungal organisms that may invade the CNS, including *Cryptococcus*, *Coccidioides*, *Blastomyces*, *Histoplasma*, *Aspergillus*, and the phaeohyphomycoses (e.g. *Cladosporium*). *Cryptococcus neoformans* is by far the most common fungal organism associated with meningoencephalitis in dogs and cats. Fungal disease is typically contracted by dogs and cats via inhalation of fungal spores. Infection of the CNS can occur via local extension (e.g. nasal/frontal sinus) or hematogenously. Similar to bacterial CNS infection, clinical signs of neurologic dysfunction may be due to a mass effect (e.g. gelatinous mass of fungal organisms, fungal granuloma) or to a more disseminated inflammatory response to the invading organisms. In people with fungal CNS infections, an underlying state of immunosuppression is usually present. While this may also be the case in some canine and feline CNS fungal infections, an underlying immunodeficiency state is often not identified in dogs and cats with fungal meningoencephalitis.

b. As with bacterial meningoencephalitis, dogs and cats with fungal meningoencephalitis are typically young to middle-aged (e.g. 1–7 yrs). American Cocker Spaniels and Siamese cats appear to be predisposed to developing CNS cryptococcosis. In one study, dogs with CNS cryptococcosis tended to exhibit pain localized to the cervical region, whereas pain was more often localized to the thoracolumbar spine or pelvic limbs in cats. Although clinical signs of neurologic dysfunction may be acute in onset and rapidly progressive, fungal meningoencephalitis is often characterized by slow progression (weeks to months) of neurologic dysfunction, often preceded by a period of nonspecific illness (e.g. lethargy, anorexia). Focal and multifocal encephalopathy are possible, affecting the forebrain and/or brain stem. Clinical evidence of extraneural fungal infection is common in cases of fungal meningoencephalitis. With cryptococcosis, extraneural infection around the head region (eyes, nasal and frontal sinuses) is most likely. With coccidioidomycosis, initial infection of the pulmonary system is typical.

c. The diagnosis of fungal meningoencephalitis is based upon identifying the presence of a fungal organism in a patient displaying signs of encephalopathy. Finding a fungal organism in an extraneural site in a patient with brain dysfunction is strong evidence for fungal meningoencephalitis. Brain imaging (preferably MRI) is likely to demonstrate intra-axial lesions that strongly contrast enhance (Fig. 7.49). A peripheral enhancement of intracranial cryptococcal granulomas has been demonstrated in cats. Fungal granulomas often have evidence of substantial perilesional edema. Identifying the organism in a CSF sample is the strongest evidence to support the diagnosis, and this is more likely to occur with *Cryptococcus* infections (93% in dogs) than with other fungal infections. Special stains are available to help identify specific fungi on cytology specimens. CNS fungal infections typically cause a mixed-cell pleocytosis with elevation of protein on CSF examination. The nature of the pleocytosis is highly variable, but usually includes a large proportion of both mononuclear cells as well as neutrophils, typical of a granulomatous disease. In a report of 36 dogs with intracranial coccidioidomycosis, mononuclear pleocytosis was most commonly demonstrated, followed by mixed-cell pleocytosis. Eosinophils may also comprise a large proportion of CSF WBCs in fungal meningoencephalitis patients. Testing of CSF and/or serum for antibodies to fungal antigens can also be performed. These tests are very reliable for *Cryptococcus*, *Coccidioides*, and *Blastomyces* infections, less so for *Aspergillus* infections, and unreliable for *Histoplasma* infections. No such tests are available for the phaeohyphomycoses. The various fungi can also be cultured from bodily fluids, using special growth media; this can be hazardous to human health in the case of coccidioidomycosis and histoplasmosis.

Bloodwork abnormalities are variable and nonspecific. Nonregenerative low-grade anemia, neutrophilia, and hypercalcemia (due to granulomatous disease) are examples of such abnormalities. Fungal elements may be identifiable in urine samples. Ophthalmic examination may reveal evidence of inflammatory disease (e.g. uveitis, chorioretinitis). Pulmonary lesions may be identifiable in some cases (e.g. *Histoplasma*, *Blastomyces*, *Coccidioides*) on thoracic radiographs. Cats with suspected or confirmed fungal meningoencephalitis should be tested for feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV).

d. The treatment and prognosis for canine and feline fungal meningoencephalitis are poorly defined. Although antifungal drugs constitute the mainstay of treatment for these cases, surgical removal/debulking of large intracranial granulomas may sometimes be indicated. Similar to bacterial meningoencephalitis, data describing large numbers of dogs and cats with CNS fungal disease treated with appropriate antifungal agents are lacking. Meningoencephalitis caused by *Aspergillus* or phaeohyphomycosis species is likely to be fatal. Few antifungal drugs are able to cross the BBB effectively, even when inflamed. However, flucytosine (5-fluorocytosine) and the triazole drug fluconazole are two antifungal drugs that readily cross the BBB. There are several reports of sustained remissions or cures in CNS cryptococcosis patients treated with drug combinations that included flucytosine and/or the newer triazole drugs (itraconazole and fluconazole). Flucytosine use alone may lead to the development of drug resistance. In a report of 36 dogs with intracranial coccidioidomycosis, 84% of dogs improved or resolved with fluconazole therapy. Once clinical signs of disease are controlled, most patients with fungal meningoencephalitis will require long-term antifungal therapy (months). In the author's experience, fluconazole therapy for fungal meningoencephalitis cases may need to be very prolonged, often exceeding a year. In the report of 36 dogs with coccidioidomycosis meningoencephalitis, the minimum treatment time was 1 yr. The decision of when to discontinue antifungal therapy should be based upon clinical signs, repeat CSF results, and CSF/serum

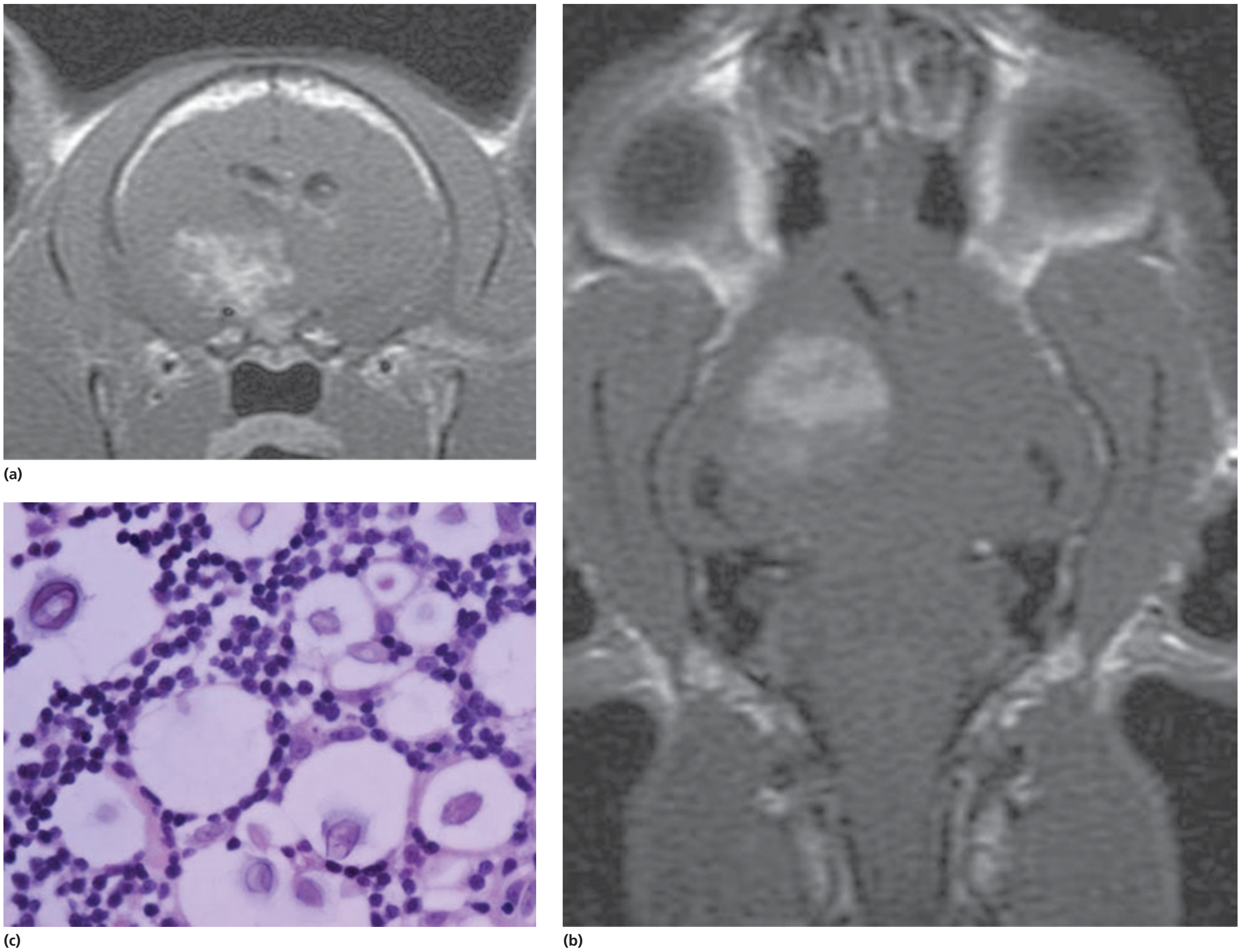


Figure 7.49 Transaxial (A) and dorsal (B) brain MR images (T1-weighted with contrast) and histopathology (C) from a cat with a cryptococcal granuloma.

titers for the organism (if appropriate). Since fluconazole penetrates the BBB well and itraconazole does not, fluconazole for CNS fungal infection is the preferred antifungal agent (5 mg/kg PO, q 12 hrs). The main drawback of fluconazole use is the high cost of the drug. Although controversial, it may be beneficial to administer low doses of oral prednisone (e.g. 0.5 mg/kg bid) in the early treatment period (1–2 wks), in order to combat perilesional edema. In one report of CNS cryptococcosis in dogs and cats, glucocorticoid use after diagnosis was associated with improved survival in the first 10 days. In this study, remission times were achieved for ≥ 1 yr in 32% of patients treated. Altered mentation on presentation was found to be a negative prognostic indicator for dogs and cats.

3. Viral meningoencephalitis[7, 40, 41, 55, 74, 108, 155, 185, 187, 188, 245, 247, 249, 251, 261, 262, 274, 275, 364, 377, 492, 503, 545–547, 550, 562, 578, 646, 649, 693, 719, 726, 746–748, 800]
   a. The most frequently encountered viral infections of the brain in dogs and cats in clinical practice are canine distemper (paramyxovirus) virus and feline infectious peritonitis (FIP, coronavirus) virus, respectively. Other, less-common causes of viral meningoencephalitides include rabies virus (dogs and cats), FIV (a lentivirus), canine herpesvirus, feline parvovirus (panleukopenia virus), feline Borna disease virus (BDV), pseudorabies (dogs and cats, caused by a porcine herpesvirus), and West Nile virus (a mosquito-borne flavivirus). CNS involvement is rarely reported in association with canine adenovirus (infectious canine hepatitis virus), canine parainfluenza virus (also a paramyxovirus), and canine parvovirus. Meningoencephalitis associated with these latter three canine viruses will not be discussed in this text.

   Canine herpesvirus infection typically affects neonatal puppies less than 3 wks of age and is associated with a high mortality rate due to severe systemic illness. Surviving dogs may have retinal and cerebellar dysplasia. There are multiple routes of viral infection, but inhalation is most common. Rabies is typically contracted via bite wounds from infected animals, and pseudorabies from ingestion of infected raw pork meat. FIV may also be spread via bite wounds. There are a number of reports of suspected vaccine-induced canine distemper CNS infections. Feline Borna disease may be transmitted by saliva or nasal secretions; ingesting rodents that carry the virus may also be a route of infection. Viruses can damage brain parenchyma via both direct (e.g. cytolytic) and indirect (e.g. immune-mediated) effects. Some viruses have a predilection for neuronal and glial cells, and are termed "neurotropic." Such viruses include the causative agents of canine distemper, rabies, pseudorabies, and feline Borna disease.

b. As with other CNS infectious diseases, affected animals are often young to middle-aged. Viral CNS infections typically run an acute to subacute course but may be peracute (e.g. pseudorabies) or insidious (FIP) in onset and progression. Clinical signs of multifocal encephalopathy are common, but evidence of focal brain dysfunction may also occur. Extraneural signs (e.g. fever, ophthalmic disease, respiratory disease) of viral infections may or may not be present.

In canine distemper meningoencephalitis, historical or clinical evidence of gastrointestinal and/or respiratory disease prior to or concurrent with neurologic dysfunction are classic findings supportive of the diagnosis. Hyperkeratosis, or "hard pad," affecting the footpads and/or planum nasale is another classic, yet inconsistent, indicator of canine distemper infection. Other extraneural manifestations of distemper virus infection in dogs include mucopurulent conjunctivitis, mucopurulent rhinitis, and chorioretinitis. Extraneural involvement can be either nonexistent or subclinical and therefore may not be appreciated. Young (1 yr or less) dogs with CNS distemper infections tend to develop noninflammatory, primarily gray-matter disease (polioencephalopathy), with predominant signs of forebrain dysfunction. Seizures are common with this form of canine distemper. Mature (more than 1 yrs old) dogs with CNS distemper infections tend to develop inflammatory demyelinating white-matter disease primarily affecting the brain stem, cerebellum, and spinal cord (leukoencephalomyelopathy). These latter patients tend to display predominant clinical signs of cerebellovestibular and/or spinal cord dysfunction. A form of canine distemper CNS infection called "old dog encephalitis" is characterized primarily by forebrain dysfunction (e.g. behavior changes, visual deficits, circling) in middle-aged to older dogs (5 yrs or older); this form of canine distemper is considered rare.

Myoclonus (repetitive, rhythmic muscular contraction) involving one or more limbs, and/or muscles of the head, is a relatively specific and common clinical finding in canine CNS distemper infection. Myoclonus is thought to be due to abnormal pacemaker activity in neurons damaged by the virus. "Chewing gum fits," rhythmic jaw movements displayed by some dogs with CNS distemper, may represent a form of myoclonus or focal seizure activity.

FIP (coronavirus) infection of the CSF is typically associated with the noneffusive form of the disease. Historical and clinical signs of systemic disease (e.g. fever, weight loss) are common in cats with coronavirus meningoencephalitis. Multifocal encephalopathy is common, often with brain-stem and cerebellar dysfunction.

A poor to nonexistent vaccination history in an acutely encephalopathic dog or cat with possible exposure to wildlife or other nonvaccinated dogs or cats should alert the clinician to consider rabies. The typical "furious" and "paralytic" forms of rabies have been described. The furious form is more common in cats and is characterized by apprehension and aggression, suggesting primarily forebrain dysfunction. The paralytic form, encountered more frequently in dogs, is characterized by LMN dysfunction of brain-stem nuclei, leading to a dropped jaw (CN V) and swallowing difficulty with attendant ptyalism (CN IX–XI). Respiratory difficulty and gait abnormalities may also be apparent. Focal and/or generalized seizure activity may occur with either form of rabies. Dogs and cats with rabies may present with a wide variety of clinical signs of neurologic dysfunction, and the above-mentioned forms of rabies should be viewed as very rough guidelines. It has been aptly stated that the only typical feature of the clinical signs of rabies is that they tend to be atypical. A young dog with rapidly progressive LMN paraplegia and a subsequent development of encephalopathy due to rabies virus was recently reported.

Pseudorabies is rarely encountered in dogs and cats. A peracute onset and rapid progression (24–48 hrs) of forebrain dysfunction (obtundation, seizures) is typically accompanied by hypersalivation, vomiting, diarrhea, fever, and hyperpnea. A characteristic feature of canine and feline pseudorabies is intense pruritus over the head, neck, and shoulder areas.

FIV-associated encephalopathy has recently been reported, and may be more common than previously thought. Encephalopathy may occur in as many as one-third of FIV-infected cats. Affected cats typically exhibit signs of forebrain dysfunction such as behavior change (e.g. aggression) and compulsive pacing. Delayed righting reflexes and PLRs, as well as anisocoria, have been observed in experimentally affected cats. Both experimentally and naturally infected cats tend to have minimally progressive or static signs of dysfunction for months; some cats even improve neurologically.

Clinical signs of feline Borna disease include progressive pelvic limb ataxia, sacral hyperesthesia, fever, loss of appetite, aggressiveness, staring activity, seizures, hypersensitivity to light and sound, inability to retract claws, and increased affection toward owners.

c. Definitive diagnosis of viral meningoencephalitis is usually accomplished at necropsy. Identification of causative virus in brain parenchyma through various methods (e.g. visualizing inclusion bodies, immunocytochemistry, viral isolation) and the appearance of characteristic histologic patterns (e.g. pyogranulomas in FIP, demyelinating brain-stem lesions in canine distemper), help to confirm a diagnosis of a specific viral-induced encephalopathy. In the case of an unvaccinated dog or cat that has died or was euthanized because of brain disease (of recent onset) and has had exposure to people (especially bite wounds), examination of the brain (e.g. direct fluorescent antibody test) for rabies is mandatory. The antemortem diagnosis of viral meningoencephalitis is often difficult and relies on combining characteristic historical and clinical findings with several diagnostic tests. Specific and reliable diagnostic tests for viral meningoencephalitis are lacking. Intuitively, identifying the presence of a viral agent in a patient displaying encephalopathic signs would support that virus's being the causative factor. However, identifying a virus or viral antigen in body tissues or fluids is usually unsuccessful.

The indirect fluorescent antibody test for canine distemper—usually performed on conjunctival scrapings, buffy coat smears, and/or urine sediment—may produce too many false negative and false positive results to be of much use. Identification of circulating antibody against various viruses in the blood and CSF can be readily accomplished. Since the patient may have been exposed naturally or intentionally (vaccination) to a suspect viral pathogen in the past, a positive serum antibody titer often has little clinical meaning. Similarly, in a patient previously immunized for a specific viral disease, demonstrating a positive titer in the CSF for that viral agent has little meaning. If the BBB is disrupted for any reason, the serum antibodies can passively move to the CSF. Demonstrating a gradient of titers (i.e. CSF titer for an antiviral antibody higher than the serum titer) is more definitive evidence of that virus as the causative agent. More recently, the use of a one-step, reverse transcriptase polymerase chain reaction (RT-PCR) test to amplify canine distemper virus-specific RNA products in serum and CSF has been described. This PCR procedure appears to be a specific antemortem test for canine distemper virus infection. The author has had a number of positive RT-PCR results for coronavirus from CSF procured from cats with suspected or proven neurologic FIP. In one study, RT-PCR results from brain tissue were positive for coronavirus in 13 of 17 cats (76%) with histopathologically confirmed neurologic FIP. The sensitivity and specificity of RT-PCR for CSF in neurologic FIP are currently unknown. However, it is likely that this test is sensitive but not specific for neurologic FIP.

Some basic laboratory tests may provide supportive evidence for specific viral infections, if abnormal. Lymphopenia may occur with canine distemper infections, and hyperglobulinemia is common with FIP infections. Ophthalmic examination may provide valuable clinical evidence in some diseases (e.g. hyperreflective retinal lesions in canine distemper). CSF values are often abnormal with viral meningoencephalitis. Immature dogs with distemper affecting primarily gray matter may have normal CSF results. The characteristic CSF tap of a patient with CNS viral disease consists of predominantly mononuclear (lymphocytic) pleocytosis with elevated protein. The exception to this rule is CSF from FIP patients. The coronavirus tends to induce an intense immune response in this disease, and the predominant cell type in FIP meningoencephalitis is usually the neutrophil, with variable numbers of lymphocytes and macrophages (a pyogranulomatous response). In one report, many cases of neurologic FIP had normal CSF results. A high CSF IgG titer to feline coronavirus (greater than 1:25) was predictive of FIP as the cause of neurologic dysfunction in that study. In a more recent study, however, coronavirus titers were not predictive of neurologic FIP; in this study, it was thought that CSF IgG against coronavirus was blood-derived and not reflective of local CNS antibody production.

Advanced imaging (CT/MRI) may demonstrate brain lesions (e.g. contrast-enhancing regions of inflammatory foci) in some cases of viral meningoencephalitis. Although brain imaging is unlikely to reveal specific characteristic abnormalities in most cases, it may be useful to rule out other diseases (e.g. intracranial intra-arachnoid cysts in young dogs and cats). Hydrocephalus may be a common sequela to FIP meningoencephalitis that can be appreciated on a CT or MR image. Periventricular contrast enhancement has also been described in MR brain images of cats with FIP meningoencephalitis (Fig. 7.50). In one small study of cats imaged via MRI, half of the cats with confirmed FIP meningoencephalitis had normal MR brain images.

d. There are no effective antiviral agents available for viral meningoencephalitis, and the prognosis for these

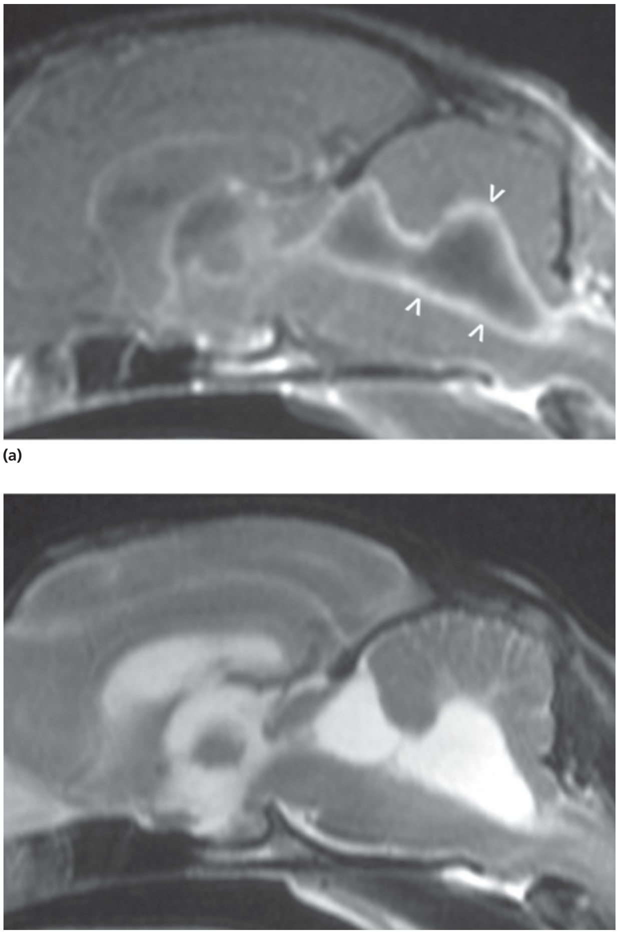


Figure 7.50 T1-weighted with contrast (A) and T2-weighted (B) sagittal brain MR images of a cat with FIP meningoencephalitis. (Negrin *et al.*, 2007. Reproduced with permission from Sage.)[503]

diseases is generally poor to grave for survival. Rabies and pseudorabies are rapidly progressive and invariably fatal (often from respiratory failure) within 1 wk and 48 hrs, respectively. FIP typically progresses over several weeks and is also invariably fatal. Most dogs with CNS distemper infections die or are euthanized due to progressive neurologic dysfunction. However, clinical signs of disease may remain static or improve in some dogs, and survival is possible with proper nursing care. Anti-inflammatory doses of prednisone are often prescribed to lessen the secondary effects of viral infection on CNS tissue in these cases. FIV-associated encephalopathy appears to have a chronic course without progression of clinical signs in many cases. Although not yet reported in clinical cases, the use of zidovudine (AZT) at a dose of 50 mg per os, every 12 hrs, has been recommended. Since this drug can cause myelosuppression, regular CBCs should be performed while a cat is receiving this therapy. Cats with feline Borna disease typically exhibit progressively worsening neurologic dysfunction, necessitating euthanasia within 6 mos of onset of clinical signs.

4. Protozoal meningoencephalitis[22, 158–166, 261, 283, 395, 413, 452, 492, 503, 548, 693, 707, 726, 740]
   a. *Toxoplasma gondii* and *Neospora caninum* are protozoal agents known to occasionally cause meningoencephalitis in dogs. *Toxoplasma* has also been reported to cause meningoencephalitis in cats. Experimental infection of cats with *Neospora* may lead to meningoencephalitis, but no naturally occurring cases have been reported. The life cycles of *Toxoplasma* and *Neospora* are similar, the definitive hosts being cats and dogs, respectively. These protozoans are similar in many respects. Host infection is believed to occur transplacentally (tachyzoites), via ingestion of fecally shed oocysts (cats are the definitive hosts and shed oocysts), and/or ingestion of intermediate hosts containing the organisms (tachyzoites and bradyzoites). Neurologic dysfunction is thought to be caused by the intracellular proliferation of tachyzoites. Canine and feline meningoencephalitis due to an organism that appears to be *Sarcocystis* has also been reported.
   b. Protozoal meningoencephalitis can occur at any age, but young animals seem more susceptible. The onset and progression of CNS dysfunction may be acute or chronic. Clinical signs reflecting either focal or multifocal encephalopathy are possible. A syndrome of cerebellar and brain-stem dysfunction due to neosporosis has been described in dogs; in these dogs, a necrotizing cerebellitis and symmetrical (on MR imaging) cerebellar atrophy was described (see Chapter 12 also). Although these protozoal organisms tend to affect multiple organ systems, clinical signs are often reflective only of CNS disease. However, clinical evidence of a concurrent myopathy may be present in dogs with protozoal meningoencephalitis.
   c. Diagnosis of protozoal meningoencephalitis is based upon providing evidence of active protozoal infection in a patient with signs of encephalopathy. Further support of the diagnosis is obtained if the patient responds favorably to antiprotozoal medication. Identifying protozoal organisms in the living patient is unlikely, but there are several reliable tests to identify IgG antibodies against both *Toxoplasma* and *Neospora* in dogs and cats. There is no cross-reactivity between the antibody tests for these two organisms. Since dogs and cats may be exposed to these organisms (and hence produce a titer against them) without developing clinical disease, a single positive antibody titer does not establish a causal relationship. A fourfold increase in serum antibody titers over several weeks is supportive of active infection. CSF titers can also be

performed and compared with serum titers. Also, IgM antibodies can be measured for *Toxoplasma* in addition to IgG. A positive IgM response with a negative IgG response suggests active infection.

Bloodwork may or may not reveal evidence of an inflammatory disease. Clinical evidence of ophthalmitis may be evident in some cases. Brain imaging should be performed (preferably MRI) and may reveal evidence of contrast-enhancing lesions (Fig. 7.51). CSF abnormalities are likely, and tend to be quite variable. Typically, a mixed-cell pleocytosis, primarily composed of neutrophils and mononuclear cells, with increased protein levels, is apparent. Predominantly mononuclear pleocytosis and normal CSF WBC counts with abnormal cellular distribution have also been reported with protozoal CNS infections.

d. Clindamycin, or sulfonamides in combination with trimethoprim or pyrimethamine, is recommended for treating suspected or confirmed cases of protozoal meningoencephalitis. Clindamycin is recommended as a first-choice therapy for toxoplasmosis. A suggested dosage for clindamycin is 10 mg/kg per os, every 8 hrs, for 2–4 wks. Trimethoprim-sulfa can be administered at a dosage of 15 mg/kg per os, every 12 hrs, for 2–4 wks. An oral combination of sulfonamide (30 mg/kg, q 12 hrs, for 2 wks) and pyrimethamine (0.25–0.5 mg/kg, q 12 hrs) for 2 wks can also be implemented. Pyrimethamine is thought to be more effective than trimethoprim against *Toxoplasma*. Cats may develop myelosuppression while receiving prolonged (more than 2 wks) trimethoprim, sulfonamide, and pyrimethamine therapy, and may require folinic or folic acid replacement therapy. The prognosis for protozoal meningoencephalitis is guarded. Dogs and cats may survive if diagnosed and treated early in the course of the disease.

5. Rickettsial meningoencephalitis[246, 261, 276, 396, 438, 468, 492, 501]
   a. Neurologic dysfunction from rickettsial meningoencephalitis may occur in as much as 43% of dogs with ehrlichiosis or Rocky Mountain spotted fever (RMSF), with the latter disorder being more commonly incriminated. The causative agents of these disorders are *Ehrlichia canis* and *Rickettsia rickettsii*, respectively. These organisms are obligate intracellular parasites transmitted to dogs via the bites of infected ticks. Clinical signs of neurologic dysfunction may be due to vasculitis and/or hemorrhage in the CNS. Intracranial hemorrhages may be due to the vasculitis, as well as thrombocytopenia and platelet dysfunction characteristic of rickettsial disease. Feline rickettsial meningoencephalitis has not been reported.
   b. Dogs of any age, sex, or breed can develop rickettsial meningoencephalitis, but German Shepherd dogs appear to be predisposed to rickettsial infection.

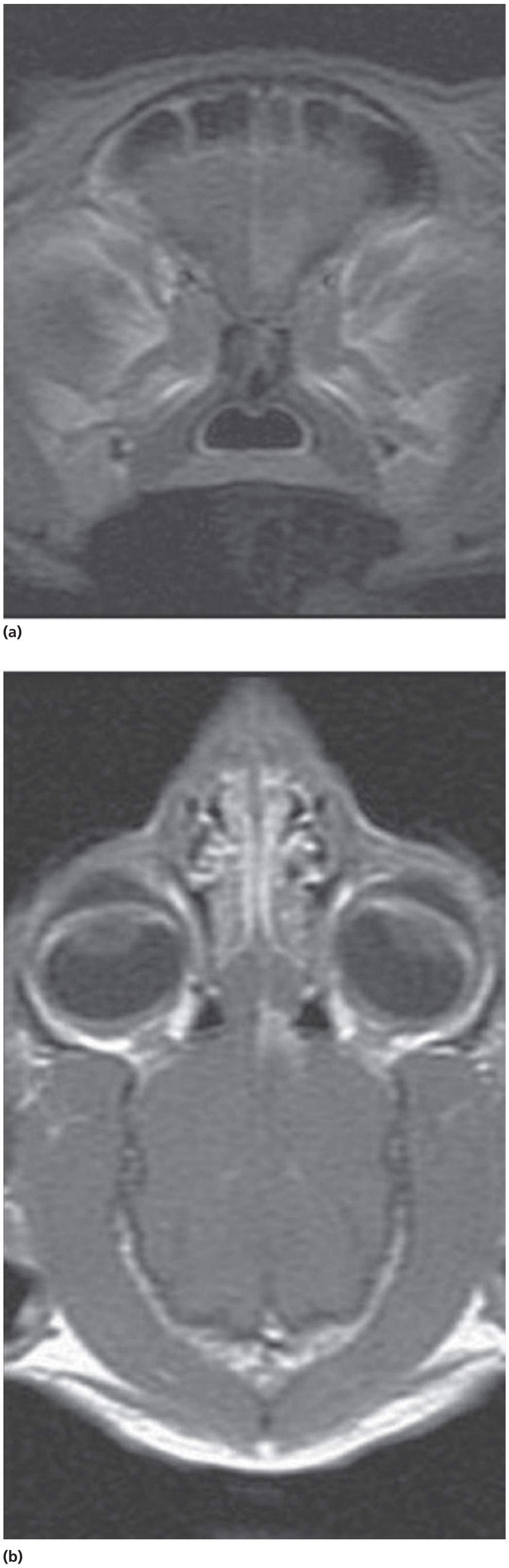


Figure 7.51 Transaxial (A) and dorsal (B) MR brain images (T1-weighted with contrast) of a cat with an intracranial toxoplasma granuloma. (Pfohl and Dewey, 2005. Reproduced with permission from Sage.)[548]

There is often a history of potential or confirmed tick exposure. Onset of neurologic dysfunction is often acute and rapidly progressive. Focal and multifocal signs of encephalopathy may occur. Central vestibular disease is a common presentation. Clinical signs of systemic illness (e.g. fever, anorexia, lethargy) are common with rickettsial meningoencephalitis.

- **c.** A tentative diagnosis of rickettsial meningoencephalitis is based on characteristic historical and clinical signs in a thrombocytopenic patient. Other bloodwork abnormalities may be appreciated, but thrombocytopenia is the most consistent. Antibodies to *E. canis* and *R. rickettsii* can be measured in the serum and/or CSF. There is little cross-reactivity between the two organisms. A single, markedly elevated serum titer, in association with other supportive data, is highly suggestive of active rickettsial infection. Demonstration of a rising titer after several weeks is recommended, especially for RMSF. Appropriate treatment of ehrlichiosis may result in a decreased convalescent titer. CSF titers can be compared with serum titers, as with other infectious diseases. CSF may reveal mainly mononuclear, mainly neutrophilic (suppurative), or a mixed pleocytosis. Because of the risk of hemorrhage in these patients, the procurement of CSF may not be advisable, especially if all other clinical evidence suggests rickettsial disease. A positive response to therapy also supports the diagnosis of rickettsial meningoencephalitis.
- **d.** Doxycycline, a tetracycline drug, is recommended for rickettsial meningoencephalitis, whether due to *E. canis* or *R. rickettsii*, at an oral dosage of 10 mg/kg, every 12 hrs, for 3 wks. Chloramphenicol is a viable alternative in very young (less than 6 mos; danger of teeth discoloration) dogs, or when doxycycline is ineffective. Enrofloxacin may be effective in RMSF cases, but appears to be ineffective in cases of ehrlichiosis. The prognosis for dogs with rickettsial meningoencephalitis is guarded to good, depending on the severity of neurologic dysfunction and the timeliness of therapeutic intervention.

6. Verminous meningoencephalitis[101, 223, 231, 261, 284, 285, 311, 460, 492, 542, 574, 594, 626, 662, 664, 693, 715, 723, 768]

- **a.** There are several reports describing aberrant parasitic migration to the brain of dogs and cats by organisms such as *Dirofilaria immitis*, *Baylisascaris procyonis* (raccoon roundworm), *Cuterebra*, and *Taenia serialis* (cystic coenurus formation in cats). Other parasites, such as *Ancylostoma*, *Toxascaris*, and *Angiostrongylus* also have potential for aberrant migration to the brain. The route of access to the host for most of these parasites is fecal–oral. In the case of *Cuterebra*, the small, first-stage larvae gain access through mucous-membrane-lined areas (e.g. the nose) or directly penetrate the skin. These parasites may cause neurologic dysfunction via a variety of mechanisms, including direct tissue damage and vascular compromise from migrating through brain parenchyma, inciting an intense inflammatory reaction by their presence, and the producing and releasing of neurotoxic and vasospastic substances. In general, these aberrant migrations are considered rare clinical phenomena. One potential exception is feline cuterebriasis. Recent data concerning *Cuterebra* migration in the brains of cats support this disease entity as the cause of feline ischemic encephalopathy (FIE), as well as a potential cause of other, poorly defined, feline seizure disorders.
- **b.** Although there are no age limits for verminous meningoencephalitis, it tends to occur in young to middle-aged animals that have access to the outdoors. Clinical signs of neurologic dysfunction tend to be acute to peracute in onset, and may reflect focal or multifocal encephalopathy. In cats with cuterebriasis, asymmetric signs of focal forebrain dysfunction (e.g. behavior change, seizures, visual deficits) predominate, but clinical signs of a multifocal encephalopathy were apparent in five of 11 cases. A history of upper-respiratory disease was also common in these cats, possibly reflecting the migration of the parasite through the nasal cavity toward the cribriform plate. These cats tend to present with signs of neurologic dysfunction between the months of July and September. Hyperthermia or hypothermia are common clinical findings in cats with CNS cuterebriasis. The rate of progression of feline cuterebriasis is not clear from the recently reported case series. Other case reports of verminous meningoencephalitis support a rapid progression of neurologic dysfunction.
- **c.** Definitive diagnosis of verminous meningoencephalitis depends upon identification of the causative parasite in the brain of an encephalopathic patient (Fig. 7.52). To date, this has been accomplished at necropsy in all reported cases of verminous meningoencephalitis. In one feline *Cuterebra* case, the organism was not found, but other histopathologic evidence of its presence (parasite track, gliosis, infarction, laminar cerebrocortical necrosis) was apparent in the brain. *Cuterebra* organisms are most commonly located in the olfactory area of the brain in cats. The antemortem diagnosis depends primarily on clinical suspicion. Bloodwork abnormalities are often nonexistent or nonspecific. CSF evaluation has been reported in only several cases; in two of three cats with CNS cuterebriasis, the CSF was abnormal, with mononuclear pleocytosis and elevated protein. One of these two cats had 8% eosinophils in the CSF WBC differential count. The use of advanced imaging (CT/MRI)

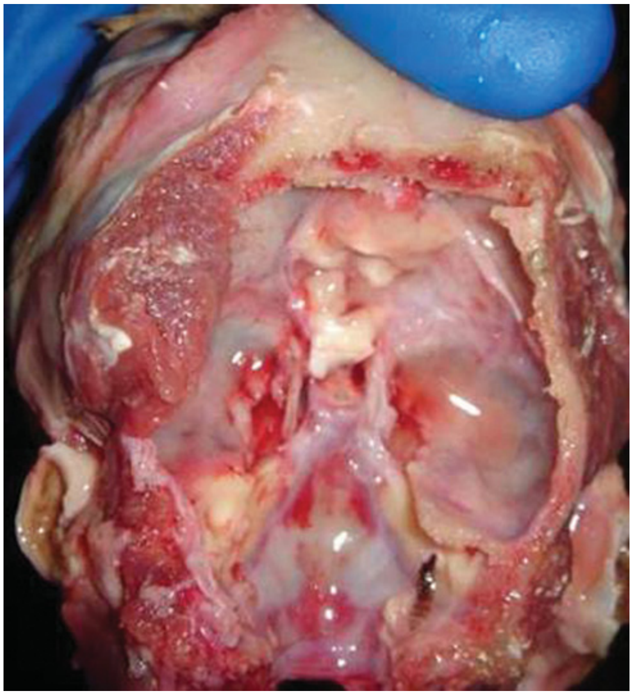


Figure 7.52 Necropsy specimen from a cat, demonstrating a *Cuterebra* larva in the right caudal fossa.

has been reported in one definitively diagnosed case of feline CNS cuterebriasis. The CT of this cat showed the brain to have a mottled appearance with no discrete mass lesions. Advanced imaging may become an important diagnostic tool in the antemortem diagnosis of verminous meningoencephalitis.

d. In general, treatment options for verminous meningoencephalitis are limited and the prognosis is grave. The prognosis for feline cuterebriasis is unknown, as antemortem diagnosis is difficult and reports of definitive treatment of tentatively diagnosed cases are limited. The recently reported case series was based on a retrospective evaluation of necropsy cases, so these cases may reflect the most severely affected cats. Cats with seizure disorders and CSF evidence of nonsuppurative meningoencephalitis generally respond favorably for long time periods to treatment with anticonvulsants and prednisone. *Cuterebra* larvae are thought to be susceptible to ivermectin, and a treatment protocol has been suggested for cats with suspected cuterebriasis (a single SQ ivermectin dose of 400 μg/kg). Pretreatment (1–2 hrs prior) with diphenhydramine (4 mg/kg), and intravenous dexamethasone (0.1 mg/kg) administered at the time of ivermectin injection are recommended to prevent or mitigate allergic/anaphylactic reactions to dead or dying larvae. A 2-wk course of prophylactic antibiotic therapy is also recommended to help prevent secondary bacterial meningoencephalitis. Although not yet reported, the surgical removal of intracranial *Cuterebra* in cats may be another viable therapeutic option for feline cuterebriasis-associated meningoencephalitis, alone or in addition to ivermectin therapy.

7. Miscellaneous infectious meningoencephalitides[27, 248, 250, 261, 262, 405, 410, 432, 480, 683, 714, 780]

a. There are a number of infectious agents that have been rarely reported to cause CNS disease in dogs and cats. Included among these are *Prototheca* (an algae), *Borrelia burgdorferi* (the spirochete responsible for Lyme disease) in dogs, and suspected scrapie infection in cats in the United Kingdom (feline spongiform encephalopathy). *Prototheca* is an environmental contaminant that may invade immunocompromised animals. *Borrelia* is transmitted via *Ixodid* ticks in endemic areas (e.g. New England). Feline spongiform encephalopathy (FSE) is thought to develop after cats ingest food contaminated with the bovine spongiform encephalopathy (BSE) agent.

b. Because of the paucity of reported cases, little is known about typical signalment and historical findings in dogs and cats with CNS protothecosis or borreliosis. Collies may be predisposed to disseminated protothecosis, and dogs with suspected borreliosis may have a history of tick exposure and/or having lived in or visited a Lyme-endemic area. Reports of cats with FSE have been primarily limited to Great Britain. These cats tend to start exhibiting clinical signs of neurologic dysfunction at about 5 yrs of age. As with other animals infected with scrapie, a long incubation period is suspected for FSE. Animals with protothecosis and borreliosis tend to exhibit clinical signs of extraneural disease. Bloody diarrhea and ocular abnormalities (e.g. chorioretinitis) are frequent findings in disseminated protothecosis, and arthritis involving one or more limbs is a hallmark of borreliosis. Focal and multifocal/diffuse, progressive encephalopathy can result from protothecosis, borreliosis, and FSE.

c. Antemortem diagnosis of these infectious diseases is uncommon and depends primarily on historical findings and clinical signs. *Prototheca* may cause a mixed-cell (neutrophils and lymphocytes) CSF pleocytosis. FSE is a noninflammatory disease, and CSF pleocytosis is unlikely. CSF findings in CNS borreliosis are poorly defined. In one reported dog with suspected CNS borreliosis, CSF values were within normal limits. Demonstration of CSF antibodies against *Borrelia* in excess of those found in the serum is highly suggestive of CNS borreliosis. *Prototheca* may be identified by examining body fluids or tissue aspirates/biopsies, and/or by culturing these samples for the organism. A definitive diagnosis of CNS protothecosis and FSE is typically made at necropsy.

d. There is no known effective treatment for FSE and the disease is uniformly fatal. Efforts to eliminate BSE in the United Kingdom will likely result in the disappearance of the feline disease. Although a number of antifungal agents have been advocated to treat disseminated protothecosis, this disease is typically fatal, despite therapy. Antibiotics such as doxycycline, amoxicillin, and third-generation cephalosporins have shown activity against *Borrelia*, but their efficacy in treating dogs with CNS borreliosis is currently unknown.

8. Granulomatous meningoencephalomyelitis (GME)[2,6,33,37,38,59,71,97,117,133,181,233,240,253,339,353,360,389,417,429,447,492,493,512,531,537,552,609,628,629,651,674,688,693,697,702,713,725,727,729,776,796]

a. A common idiopathic inflammatory disease of the CNS in dogs (extremely rare in cats), GME is characterized histologically by perivascular infiltrates of primarily mononuclear cells (lymphocytes, macrophages, and plasma cells) in the brain and/or spinal cord. The characteristic perivascular cellular infiltrates of GME both define the disease syndrome and account for the neurologic deficits. Although the underlying cause of this disease remains a mystery, there is evidence that GME represents an autoimmune disorder, specifically a delayed-type (T cell-mediated) hypersensitivity reaction. Lesions predominate in the white matter with GME. Autoantibodies directed against astrocytes have been demonstrated in GME cases, further supporting the suspicion that this is an autoimmune brain disorder. It remains unclear, however, whether these anti-astrocytic antibodies represent a primary or secondary immune response. Recent polymerase chain reaction (PCR) studies have failed to detect viral genetic material in brain tissue from dogs with GME. There are three recognized clinical forms of GME: focal, multifocal (disseminated), and ocular. The ocular form is the least commonly encountered. In the author's experience, multifocal GME is the most common form of the disorder.

b. GME can affect any breed of dog of any age and either sex. However, young to middle-aged (median age of 5 yrs) female dogs of small breeds (e.g. poodles, terriers) appear to be predisposed. Clinical signs of either focal or multifocal CNS dysfunction are possible. Multifocal GME is characterized by acute onset and rapid progression of CNS dysfunction, whereas dogs with focal GME tend to have a more insidious onset and slower progression of clinical signs. Whether alone (focal GME) or in combination (multifocal GME), seizures, cerebellovestibular dysfunction, and cervical hyperesthesia are common features of GME. Isolated spinal cord dysfunction and optic neuritis are relatively uncommon clinical presentations of GME. Patients with GME may occasionally be febrile upon presentation. A group of young (4- to 18-mo-old) Greyhound dogs from Ireland has been described with a nonsuppurative meningoencephalitis very similar to GME, but with more gray-matter involvement. These dogs exhibited a combination of forebrain (e.g. circling, blindness) and central vestibular (e.g. head tilt, ataxia) dysfunction. There is evidence that greyhounds with this disorder have altered gene expression in their brains compared with control greyhounds and that many of these genes are involved in immune function.

c. A definitive diagnosis of GME is based upon characteristic histopathologic features of affected brain and/or spinal cord tissue. Although there are reports of biopsy-confirmed cases of GME in dogs with focal cerebral lesions, the vast majority of confirmed GME cases have been diagnosed via necropsy. An antemortem diagnosis of GME is based upon characteristic signalment, historical and clinical findings, as well as results of diagnostic tests. CSF evaluation usually provides the most important information in the antemortem diagnosis of GME. A mainly mononuclear pleocytosis, with a variable percentage of neutrophils (mean of about 20%) and elevated protein level, is characteristic of GME. Uncommonly (10% or less), GME patients will have primarily neutrophilic or normal CSF results. Results of imaging studies are highly variable in dogs with GME. CT/MR images of the brain in GME patients may be normal, may show solitary (Fig. 7.53) or multiple (Fig. 7.54) circumscribed mass lesions, or may reveal areas of contrast enhancement with indistinct margins (Fig. 7.55). In one study evaluating MRI findings in dogs with intracranial disease and inflammatory CSF results, 24% of cases had

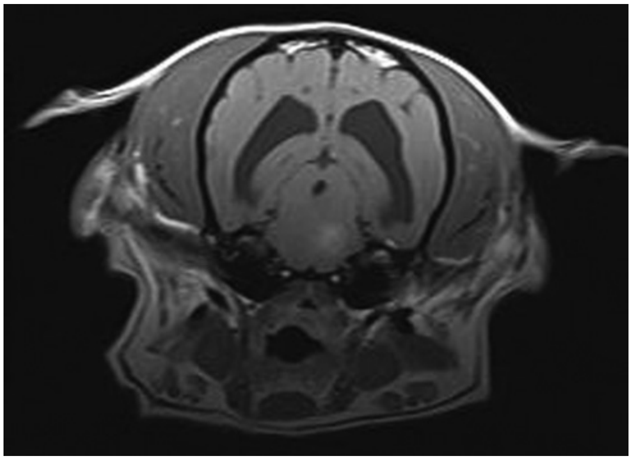


Figure 7.53 Transaxial brain MR image (T1-weighted with contrast) from a dog with GME, demonstrating a focal contrast-enhancing lesion at the level of the caudal midbrain and rostral pons.

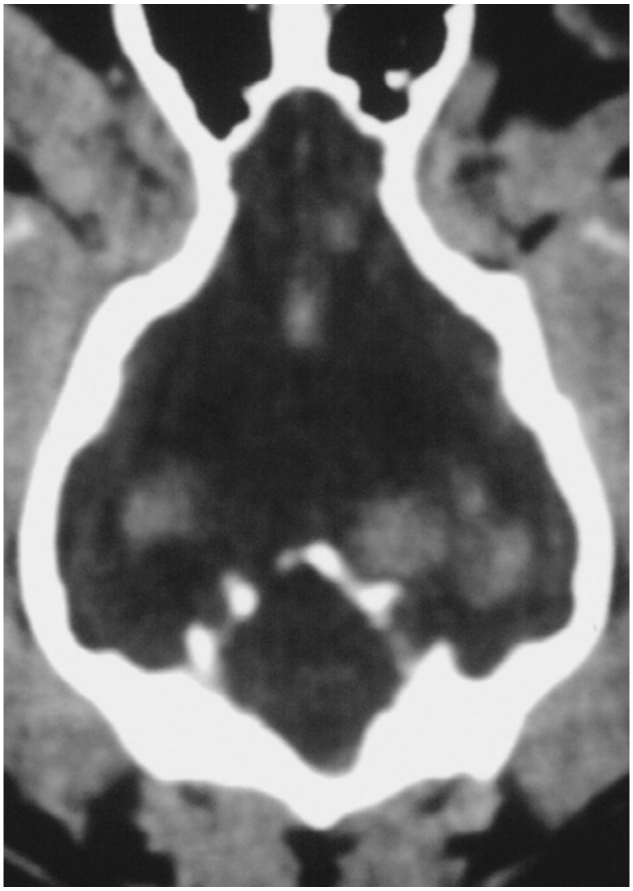
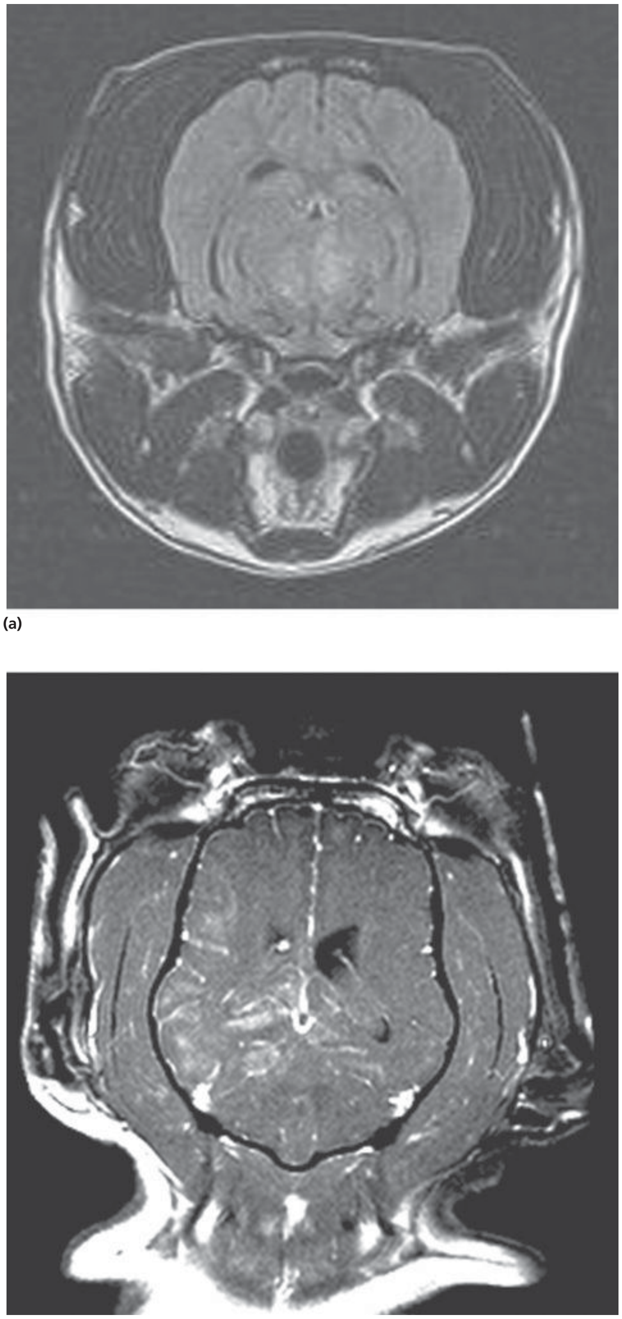


Figure 7.54 Dorsal contrast-enhanced CT brain image of a dog with multifocal GME. Note the multiple areas of circumscribed contrast enhancement.

brain images interpreted as normal. Conversely, dogs with multifocal contrast-enhancing brain lesions consistent with GME and normal CSF results have also been reported. Some dogs with GME have secondary hydrocephalus evident on CT/MR images of the brain.

d. The preferred treatment protocol for GME remains a matter of clinical preference, as there have been multiple reports of success with numerous treatment regimens (Table 7.7). Immunosuppressive glucocorticoid therapy (e.g. oral prednisone, 1–2 mg/kg, q 12 hrs) has long been the standard treatment protocol for GME. The dose may be slowly reduced over time if the patient exhibits a clinical response to treatment. However, GME patients typically require lifelong immunosuppressive therapy. Megavoltage radiation therapy has shown some efficacy in cases of focal GME.

The prognosis for GME is often guarded to poor, but has improved dramatically in recent years, ostensibly due to new treatment protocols for the disease. A report into the survival time of GME patients treated with glucocorticoid therapy gave a median survival time of 14 days. Dogs with focal GME had significantly longer survival times (median of 114 days) than those with multifocal GME (median of 8 days) in that study. Dogs with clinical signs of focal forebrain dysfunction had the longest survival times (more than 395 days). Although the prognosis for GME is still considered guarded, it is important to note that this study



(a)

(b)

Figure 7.55 Transaxial FLAIR brain MR image (A) and dorsal T1-weighted with contrast image (B) from a dog with GME. Note the multiple parenchymal lesions with indistinct margins.

Table 7.7 Drugs used to treat dogs with GME and NE.

Drug	Dosage
Prednisone	1–2 mg/kg PO, q 12 hrs
Azathioprine	2.0 mg/kg PO, q 24 hrs
Cyclosporine	3.0–5.0 mg/kg PO, q 12 hrs
Cytosine arabinoside	50 mg/m^2 SQ, q 12 hrs for 2 days; 400 mg/m^2 IV (as a CRI) over 24 hrs
Procarbazine	25 mg/m^2 PO, q 24 hrs
Leflunomide	2.0–4.0 mg/kg PO, q 24 hrs

PO = oral.

comprised GME cases that were confirmed postmortem. In one recent study, the survival of GME patients treated with prednisolone alone (median of 457 days) was not statistically different than those treated with a combination of prednisolone and lomustine (median of 329 days); in this study, most of the patients were diagnosed presumptively rather than via postmortem brain histopathology. Due to the variable and sometimes poor response to glucocorticoid therapy as well as frequent glucocorticoid-related side effects, a number of immunosuppressive drugs have been evaluated as adjunctive treatment options for GME patients. Some of the more promising drug options include azathioprine, procarbazine, cytosine arabinoside, and cyclosporine. Survival times exceeding 12 mos have been reported for each of these three drugs. In addition, the use of these drugs appears to allow for successive decreases in glucocorticoid dosages, thereby minimizing adverse side effects associated with corticosteroid use. Azathioprine is a cytotoxic antimetabolite drug that is relatively T-cell specific. In one study of dogs with meningoencephalitis of unknown etiology (MUE encompasses GME and NE) treated with azathioprine and prednisone, the median survival time was approximately 5 yrs. In that study, dogs that exhibited a complete response to therapy had significantly longer survival times than those with a partial response and dogs that did not relapse had significantly longer survival times than those that did relapse. The most common side effect of azathioprine is bone-marrow suppression, necessitating regular CBC examinations. Other potential side effects include gastrointestinal upset, pancreatitis, hepatotoxicity, and poor hair growth. Procarbazine is an antineoplastic drug that crosses the BBB and has some specificity for T-cells. The cytotoxic effects of procarbazine are thought to be primarily via the methylation of DNA bases. In one study of presumptive GME dogs, the use of procarbazine as an adjunct to prednisone was associated with a median survival time of 14 mos, regardless of the clinical form of GME (the majority were multifocal). The dose used by the author is 25 mg/m^2 PO, SID. Myelosuppression is the most likely adverse effect, although hemorrhagic gastroenteritis may also occur. A CBC should be checked weekly for the first month, then monthly thereafter to monitor for myelosuppression. Cytosine arabinoside is a synthetic nucleoside analog that crosses the BBB. This drug inserts itself into DNA molecules after enzymatic activation, causing premature chain termination in mitotically active cells. The protocol used for dogs with GME is a subcutaneous injection of 50 mg/m^2, q 12 hrs for two subsequent days, to be repeated initially every 3 wks. The drug should be diluted 2:1 with sterile saline (to prevent tissue irritation) prior to injection, and gloves should be worn when handling cytosine arabinoside. Because myelosuppression is a potential side effect of this drug, a CBC should be checked weekly for the first month or two, then every 2–3 mos thereafter. Myelosuppression appears to be very infrequent with this protocol. In one case report, a dog with presumptive multifocal GME treated with cytosine arabinoside was alive and doing well at a 12-mo follow-up. In another report of 10 dogs with noninfectious encephalitis of undetermined etiology, cytosine arabinoside treatment was associated with a median survival time of approximately 1.5 yrs. In two of these dogs, tertiary treatment (procarbazine, leflunomide) was also administered. Anecdotal reports of cytosine arabinoside use in suspected GME patients concur with the limited published material. Cyclosporine (cyclosporine A) is a lipophilic peptide that does not readily cross the BBB. Despite this, it is thought that the drug may become trapped in endothelial cells in the CNS, and that the inflammatory nature of GME may allow more cyclosporine to cross the BBB than would occur in the absence of inflammation. The mode of action of cyclosporine blocks the transcription of genes in activated T-cells that lead to the production of inflammatory cytokines. There are two clinical reports of three dogs, each describing the use of cyclosporine for presumptive GME. In one report, dogs were administered a dosage of 3–6 mg/kg body weight PO, q 12 hrs; in the other report, the initial dose was 10 mg/kg body weight PO, q 24 hrs. One dog did not respond, and necropsy confirmed the diagnosis of GME. The other five dogs improved on cyclosporine therapy. Two dogs in one report were doing well after 1 yr, and all three dogs were doing well at last follow-up, between 7 and 9 mos after diagnosis. Mild side effects (shedding with symmetric alopecia, two dogs; intermittent vomiting, one dog) were reported in association with cyclosporine administration in these dogs. Reported side effects attributable to cyclosporine use in dogs include vomiting, diarrhea, anorexia, weight loss, gingival hyperplasia, papillomatosis, hypertrichosis, and excessive shedding. In a follow-up study of 10 dogs with presumptive GME treated with cyclosporine with or without ketoconazole (given to decrease the systemic clearance of cyclosporine and reduce the cost of therapy), the median survival time was approximately 2.5 yrs. There has been one report describing the use of leflunomide, a pyrimidine analog, for noninfectious inflammatory brain disease in three dogs. The dogs responded favorably to leflunomide and were still alive more than 12 mos after starting therapy. It was not determined what specific inflammatory brain disease(s) the dogs had.

9. Necrotizing encephalitis (NE; necrotizing meningoencephalitis, necrotizing leukoencephalitis)[14,39,76,105,167,181,212,240,254,299,333–335,381,385,447,448,492,537,544,552,561,629,675,677,693,696,702,724,726,728,729,738,758,790] (Video 16 and 7)

    a. This category of noninfectious inflammatory encephalitides includes two pathologically distinct disorders referred to as necrotizing meningoencephalitis (NME) and necrotizing leukoencephalitis (NLE). These are thought to represent autoimmune disorders. Autoantibody directed against astrocytic antigens has been demonstrated for necrotizing meningoencephalitis. Both disorders are similar in that they are characterized by multiple cavitary necrotic nonsuppurative inflammatory brain lesions that involve both gray and white matter. In NME, the lesions are typically found in the cerebrum, with consistent involvement of the leptomeninges. Extensive cerebral cavitations with a loss of demarcation between gray and white matter are typical for NME. NLE is characterized by similar lesions that often involve the brain stem in addition to the cerebrum, with less consistent involvement of the leptomeninges and cerebral cortex (i.e. mainly white matter). Initial reports of these diseases in predisposed breeds led to the terms Pug encephalitis or Pug/Maltese encephalitis for NME and Yorkshire Terrier encephalitis for NLE. Although Pug and Maltese dogs are most commonly affected by NME, other breeds reported with this disorder include Chihuahua, Shih Tzu, Pekingese, and Papillon. The author has also encountered a necrotizing meningoencephalitis disorder in a Boston Terrier. Yorkshire Terriers appear to be the most common breed afflicted by NLE, but this disease may also affect other small-breed dogs. In one report, a Pug dog and a Maltese dog with lesions more typical of NLE than NME were described. In addition, in a report of five Chihuahua dogs with NME, two of the five dogs had small lesions in the medulla, a feature more typical of NLE. In addition, a disorder very similar to NLE was described in a 20-mo-old French Bulldog. It is very possible that NME and NLE represent variants of the same disease process. It is expected that more breeds will be reported with idiopathic necrotizing encephalitis. As with GME, the necrotic lesions observed on brain histopathology both account for the clinical signs of dysfunction and define the disease syndrome. Although the cause is unknown, the brain lesions are reminiscent of alpha herpes virus meningoencephalitis of people. However, as with GME, PCR tests have failed to identify viral DNA associated with these disorders.

    b. NE tends to occur in young, small-breed dogs, although a wide age range has been reported. In one report of 36 dogs with NE, the age ranged from 6.7 mos to 13 yrs (median, 2.5 yrs). Clinical signs reflect the distribution of brain lesions. Seizure activity is frequent with NE, representing the most common clinical complaint in one study. Pug and Maltese dogs with NME have varied in age at presentation between 6 mos and 7 yrs. The onset and progression of clinical signs of neurologic dysfunction may be acute (disease course of 2 wks or less) or chronic (disease course of 4–6 mos). Clinical signs of forebrain dysfunction (seizures, circling, obtundation, visual deficits with normal PLRs, head-pressing, etc.) predominate. Neck pain is also common and may be due to the meningitis and/or the forebrain disease.

    Yorkshire Terriers with NLE have been reported between the ages of 1 and 10 yrs. These dogs typically experience a chronic, progressive worsening of neurologic dysfunction over several months. In addition to clinical signs of forebrain dysfunction and neck pain, Yorkshire Terriers with NLE often display clinical signs of brain-stem dysfunction (e.g. central vestibular disease).

    In one report, it was found that dogs with NE tend to have clinical onset of disease most often during the summer months, between May and September.

    c. The definitive diagnosis of NE is based upon characteristic histopathologic brain lesions observed at necropsy. A tentative diagnosis is based primarily upon signalment, history, and the findings of the neurologic examination. Bloodwork results are typically normal. CSF findings are often abnormal; most commonly, a predominantly or exclusively mononuclear pleocytosis with elevated protein levels is evident. The mononuclear cells in NME are usually primarily lymphocytic, whereas a mixture of lymphocytes and monocytes is usually seen in the CSF of NLE patients. In one Maltese dog with NME, one-half of the cells in the CSF differential were neutrophils.

    CT/MR findings have been described in a number of cases of NE. Lesions on MRI are usually iso- or

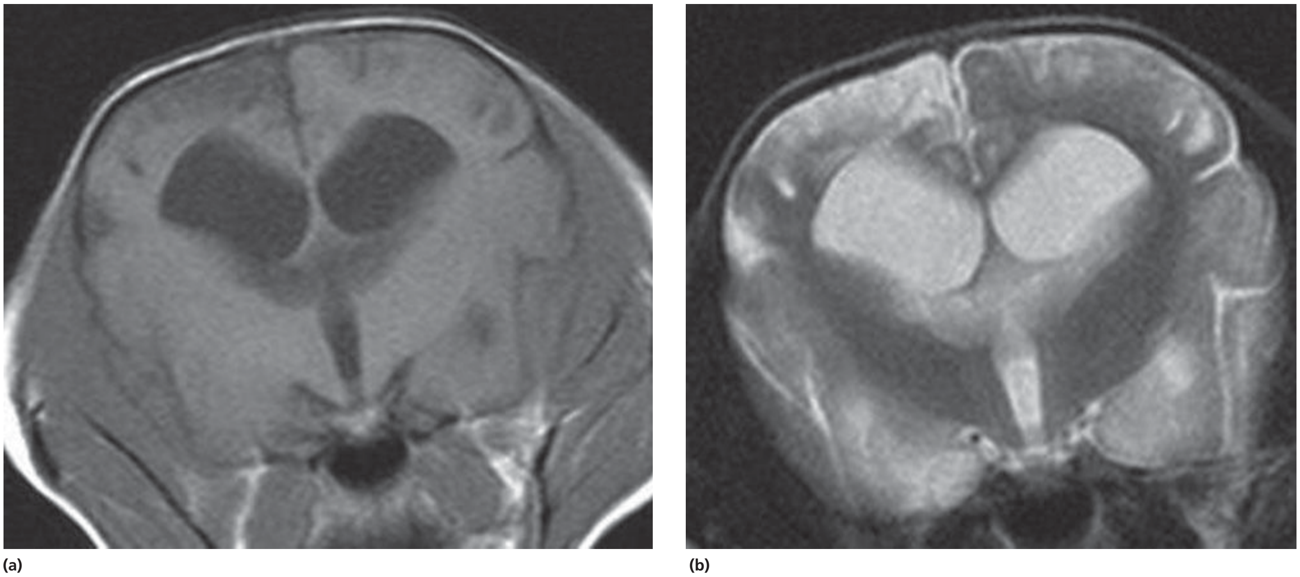


Figure 7.56 Transaxial T1- (A) and T2-weighted (B) MR images of a dog with necrotizing meningoencephalitis. (Dr. Jennifer L. Bouma, DACVR, 2014. Reproduced with permission of Dr. Jennifer L. Bouma.)

hypointense on T1-W images, hyperintense on T2-W and FLAIR images, and inconsistently and nonuniformly contrast enhancing. Asymmetric ventricular dilation, and areas of hypointensity in the brain (corresponding with malacic brain parenchyma), sometimes appearing continuous with the lateral ventricles, are consistent findings (Fig. 7.56).

d. Treatment of suspected NE patients with glucocorticoids and anticonvulsant drugs (if seizuring) should be attempted, but often has little to no appreciable clinical effect. The prognosis for necrotizing meningoencephalitis is poor to grave. Although one Yorkshire Terrier with NLE survived for 18 mos, the majority of dogs die or are euthanized due to progressive neurologic dysfunction within 6 mos of the onset of neurologic dysfunction. In the report of 36 dogs with NE, the median survival time was 11.5 days. The same drug protocols used in recent years for GME have been suggested for use in cases of NE. Due to lower case numbers compared with GME, as well as a lack of distinction in some reports between GME and NE, it is unclear whether these drugs are effective for NE. In the author's experience, procarbazine does not appear to be as effective in suspected NE cases, as compared with GME cases. The prognosis for this group of disorders remains poor. The author and colleagues have had anecdotal success treating several suspected NME patients with mycophenolate mofetil.

10. Eosinophilic meningoencephalitis (EME)[46, 297, 526, 614, 639, 666, 769]

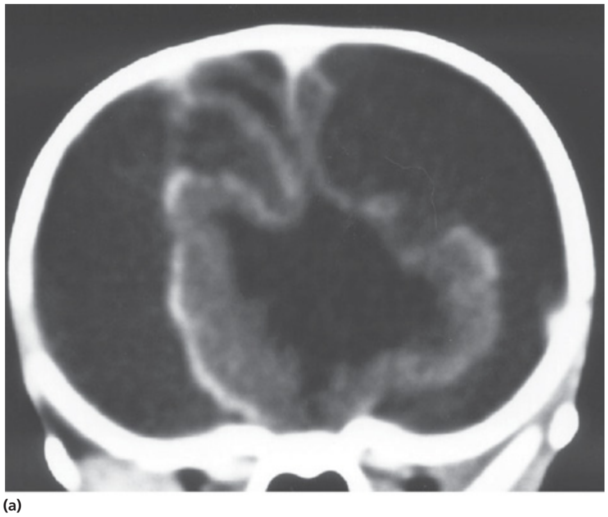
a. A rare, idiopathic meningoencephalitis, characterized by eosinophilic pleocytosis of the CSF has been described in 29 dogs (from multiple reports) and one cat. No infectious agents have been identified to account for the meningoencephalitis, and a type I hypersensitivity reaction is suspected. Eosinophils can release substances that are directly neurotoxic, which may explain some of the clinical signs of dysfunction in these patients, as well as the variable response to treatment.

b. The dogs reported with eosinophilic meningoencephalitis varied in age at onset of clinical signs from 4 mos to over 10 yrs, but most were young to middle-aged at onset. Large dogs appear to be predisposed to EME, with Golden Retrievers and Rottweilers being overrepresented. The reported cat (domestic shorthaired breed) was 6 yrs old at the time of clinical disease onset. Neurologic dysfunction developed over 1 to several wks in most of the animals, but a range of 1 wk to 12 mos of progression has been reported. Clinical signs may suggest forebrain dysfunction (e.g. circling, obtundation, seizure activity), brain-stem disease (gait deficits, facial paresis, diminished gag reflex), cerebellovestibular dysfunction (head tremors, hypermetric gait, head tilt), and/or spinal cord (diminished patellar reflex) dysfunction. The cat with EME exhibited signs of forebrain and brain-stem dysfunction.

c. The diagnosis of EME is based upon demonstrating an eosinophilic CSF pleocytosis in an encephalopathic patient, with no apparent inciting cause. In people, a CSF pleocytosis is considered eosinophilic if the eosinophils comprise more than 10% of the WBC differential. The eosinophil percentage in the reported veterinary cases varied between 22 and 100%. Since histopathologic lesions have been described for only a limited number of dogs with EME, there is no defined histopathologic pattern upon which to base a definitive diagnosis. Histopathologic findings have included leptomeningeal infiltrates with eosinophils and other inflammatory cells, perivascular cuffing, parenchymal granulomas, necrosis, malacia, axonal loss, and demyelination. Peripheral eosinophilia may be evident on a CBC evaluation. Magnetic resonance imaging results may be normal, or may be characterized by focal or multifocal lesions. In one report, seven of 13 dogs imaged had abnormal MRI results, two dogs had focal lesions, and five had multifocal lesions; the lesions consisted of patchy hyperintensities on T2-W images with contrast enhancement.

   d. The appropriate therapy for this enigmatic syndrome is unclear. As this is suspected to be an autoimmune disorder, prednisone is typically part of the treatment protocol. There are a number of case reports documenting the successful treatment of EME with prednisone. Prednisone combined with antibiotics has also been reported. The single cat reported with EME recovered with glucocorticoid therapy. In one report of 16 idiopathic EME dogs, 12 dogs (75%) resolved with prednisone treatment. From this limited information, it appears that the prognosis for survival is fair with EME.

11. Hydrocephalus with periventricular encephalitis (HPE)[71, 135, 302, 729]
   a. A rare form of meningoencephalitis has been described in puppies. This idiopathic disease is characterized by hydrocephalus and intense inflammatory and hemorrhagic lesions in the brain parenchyma, especially in subependymal locations. Although the etiology of this syndrome is unknown, a bacterial cause is suspected.
   b. This syndrome tends to occur in puppies 2–3 mos of age. A wide variety of breeds, including large-breed dogs, have been reported. The onset of neurologic deficits is acute and the progression is typically rapid. Clinical signs of forebrain disease (e.g. behavior change, blindness, circling) predominate, but signs of brain-stem dysfunction (e.g. head tilt, ataxic gait) are also often appreciated. Progressive enlargement of the skull may also be appreciated in these puppies.
   c. A definitive diagnosis of HPE is based upon gross and histopathologic examination of the brain at necropsy. A presumptive diagnosis is based upon typical signalment, history, and clinical signs, as well as evidence of hydrocephalus. CSF analysis may reveal a mixed-cell pleocytosis, increased protein, and xanthochromia.
   d. The sparse literature pertaining to this disease syndrome is primarily based upon pathology findings. This appears to be a rapidly progressive, usually fatal disease. However, in some dogs, the disease may stabilize. The appropriate therapy for this condition is unknown. A combination of antibiotic/corticosteroid therapy, with or without surgical shunting for hydrocephalus, should be considered in puppies with this disease syndrome. The author has reported successful medical and surgical (i.e. ventriculoperitoneal shunting) management of a suspected HPE case with external hydrocephalus (Fig. 7.57).



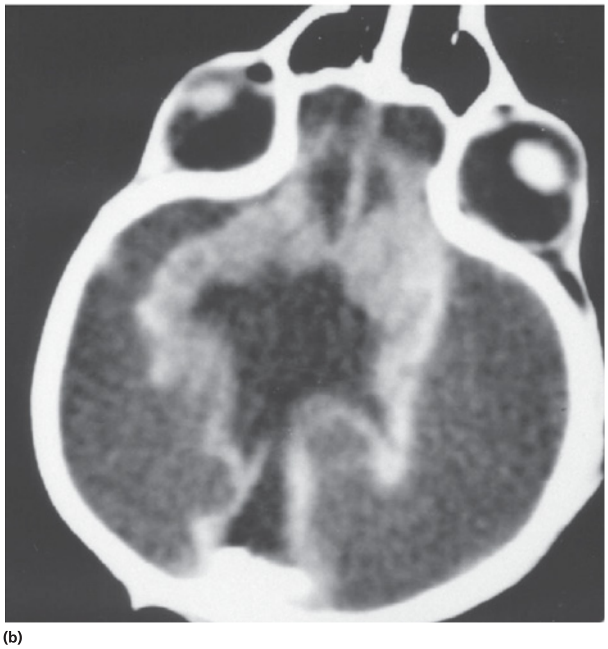


Figure 7.57 Transaxial (A) and dorsal (B) contrast-enhanced CT brain images of a dog with external hydrocephalus and suspected periventricular encephalitis. Note the extra-axial fluid accumulation around the brain. (Dewey, 2002. Reprinted with permission from JAAHA, November/December 2002. Copyright © 2002 American Animal Hospital Association [aaha.org]. All Rights Reserved.)[134]

G. Ischemic/vascular encephalopathy[12, 25, 47, 91, 104, 120, 132, 168, 214–216, 219, 235, 242, 303, 304, 330, 331, 416, 455, 461, 462, 478, 505, 511, 532, 534, 541, 543, 648, 717, 718, 721, 774, 797]

1. It has become apparent in recent years that focal ischemic events to the brain (i.e. infarcts, strokes) are common occurrences in dogs. The increased availability of MRI in veterinary medicine is the most likely reason for this realization. There are multiple potential causes for brain infarcts, including systemic hypertension (primary/essential hypertension or secondary to underlying disease such as chronic renal failure, hyperadrenocorticism, or pheochromocytoma), cardiac disease, hypercoagulability, increased blood viscosity (e.g. polycythemia vera, multiple myeloma), intravascular neoplasia (e.g. lymphoma, hemangiosarcoma), infectious disease, and atherosclerosis (e.g. associated with hypothyroidism, diabetes mellitus, or hyperlipidemia). In people with strokes, an underlying cause is not identified in about 40% of cases; these infarcts are termed “cryptogenic.” Recent evidence suggests that the percentage of cryptogenic strokes in dogs is similar to that in people. In contrast to humans, atherosclerosis appears to be rarely associated with canine brain infarcts; when it does occur in dogs, it is most likely to be associated with hypothyroidism. Brain infarcts are often categorized in terms of size (e.g. lacunar, territorial) and whether they are associated with appreciable hemorrhage (i.e. hemorrhagic, nonhemorrhagic). Brain infarcts in dogs are typically nonhemorrhagic and are most common in the cerebellum, cerebrum, and thalamic/midbrain regions. Multifocal brain infarcts have been reported, but are comparatively uncommon. Cerebellar and cerebral infarcts tend to be territorial, involving the territories of large arteries such as the rostral cerebellar artery and middle cerebral artery, respectively. These territorial infarcts tend to primarily involve the gray matter, with variable levels of white-matter involvement. Thalamic/midbrain infarcts tend to be smaller lacunar lesions, involving the smaller perforating arteries of this brain region. In one report, over half of the dogs with brain infarcts had an underlying metabolic disorder that could potentially lead to thromboembolic disease, the most common being chronic renal disease and hyperadrenocorticism. Systemic hypertension was documented in nearly 30% of those dogs whose blood pressure was documented. In another study of cerebellar infarcts in dogs, systemic hypertension was identified in over 40% of those patients in which blood pressure was measured. In one study and in the author’s experience, there is usually an underlying disease present that could potentially explain the presence of hypertension in these dogs, with chronic renal disease and hyperadrenocorticism being the most common disorders. Global brain ischemia is much less commonly encountered in dogs and cats, compared with focal brain infarcts. Global brain ischemia refers to hypoxia/anoxia experienced by the entire brain, usually associated with either cardiopulmonary arrest or anesthetic-related complications.
2. Although the age range for dogs with brain infarcts is wide, the majority are middle-aged to older dogs, with median and mean ages of 8–9 yrs. There is some evidence that brachycephalic breeds of dogs and cats may be predisposed to global brain ischemia, especially when ketamine is used in the anesthetic protocol. Cerebellar infarcts appear to be most common in small-breed dogs, most notably the CKCS. It has been postulated that this predisposition may be related to this breed’s propensity to develop heart disease, inherited platelet abnormalities, or to local aberrations in regional arterial (e.g. basilar artery) blood flow due to Chiari-like malformation (CLM), which is common in the breed. In people with atlantoaxial instability, basilar artery compression has been associated with cerebellar infarction. In the author’s experience, the combination of CLM and cerebellar infarct is common in the CKCS, whereas combinations involving cardiac disease and platelet abnormalities are not. Large-breed dogs appear to be predisposed to developing lacunar thalamic/midbrain infarcts. Greyhounds may be predisposed to brain infarcts; one proposed reason is the tendency for greyhounds to have higher resting mean arterial blood pressures than other breeds.

   In general, clinical signs of neurologic dysfunction are peracute to acute in onset with ischemic/vascular events to the brain. In some cases of focal infarcts, there may be mild transient paroxysmal premonitory signs prior to the infarct that may represent transient ischemic attacks (TIAs). For example, some dogs with territorial cerebellar infarcts have had historical complaints of transient vestibular dysfunction prior to presentation for the infarct. Also, in some cases, the progression of signs may occur for the initial 24 hrs, presumably due to associated brain swelling. Clinical signs are reflective of the area of the brain experiencing the ischemic damage. Paradoxical vestibular syndrome appears to be a common phenomenon with cerebellar infarcts. Although most MR images of territorial cerebellar infarcts in dogs suggest pure cerebellar involvement of the infarct, the majority of these patients have signs of medullary dysfunction (e.g. nonambulatory status) as well. This apparent discrepancy is believed to be explained by secondary medullary compression from the edema around the infarct at the time of the ischemic event. By the time the patient is imaged, this swelling is typically not apparent on the MRI. Another unusual clinical presentation common in dogs with thalamic/midbrain infarcts is the presence of central vestibular dysfunction. Dogs with infarcts in this area of the brain have had clinical signs such as ipsilateral head tilt (often in addition to a head turn, which would

Table 7.8 Characteristic MRI appearance of nonhemorrhagic brain infarcts over time.

Stage	Time to imaging	T2-weighted MRI findings	T1-weighted MRI findings	FLAIR findings	Contrast enhancement
Peracute	3–6 hrs	Hyperintense	Hypointense	Hyperintense	No
Acute	6–24 hrs	Hyperintense	Hypointense	Hyperintense	No
Early subacute	24 hrs–1 wk	Hyperintense	Hypointense	Hyperintense	Variable
Late subacute	1–6 wks	Hyperintense	Hypointense	Hyperintense	Yes
Chronic	> 6 wks	Hyperintense	Hypointense	Hyperintense	Variable

be expected with a forebrain lesion), strabismus, and nystagmus. Potential explanations for this unexpected phenomenon include: damage to the thalamic relay centers associated with the cerebellum and vestibular nuclei, damage to the medial longitudinal fasciculus (MLF) pathway in the midbrain and/or input of vestibular information to the thalamus (brachium of caudal colliculus), and the presence of concurrent small medullary and/or cerebellar infarcts that are not evident on MR imaging. The author believes that the vestibular signs are due to the thalamic/midbrain lesions, not due to medullary or cerebellar lesions inapparent on MR images. Because these aforementioned vestibular pathways associated with the thalamus and midbrain are more concerned with the conscious recognition of balance rather than efferent vestibular nuclei input to brain-stem nuclei and LMNs of appendicular muscles (i.e. coordinated execution of gross motor movements), it may be that the peracute interruption of these typically less important pathways is the key to their clinical manifestation in stroke victims specifically. In other words, there is likely to be more time for the brain to compensate for damage to these less utilitarian vestibular pathways in most other disease states (e.g. neoplasia) than with infarcts. In one study of 16 dogs with suspected thalamic infarcts, the specific location of the infarct in the thalamus was correlated to the nature of the associated neurologic dysfunction; paramedian and extensive dorsal thalamic infarcts tended to produce vestibular dysfunction, whereas ventrolateral infarcts were characterized by forebrain dysfunction (e.g. circling, contralateral proprioceptive placing deficits). Seizure activity has been reported in dogs with cerebral infarcts, but does not appear to be very common. In one report, only one of 11 dogs with cerebral infarcts exhibited seizure activity as a presenting complaint; two other dogs in this group developed recurrent seizure activity at a later date.

3. Although many cases of brain infarcts in dogs will not have an apparent underlying cause, the potential presence of such a cause should be investigated both for treatment and for prognostic reasons. Depending on the particular case, diagnostic tests (in addition to basic bloodwork and urinalysis) may include thoracic radiographs, abdominal ultrasound, serial blood pressure measurement, blood coagulation profile (including measurement of D-dimers and antithrombin III levels), endocrine testing (e.g. ACTH stimulation, low-dose dexamethasone suppression test, thyroid hormone profile), and echocardiography. The ideal imaging modality for suspected brain infarcts as well as suspected global brain ischemia is MRI. CT may be more sensitive in detecting acute hemorrhage in early hemorrhagic stroke, but offers no other advantages over MR imaging. MRI allows for greater detail in imaging (including detailed multiplanar images) and less artifacts (like beam-hardening artifact with caudal fossa images) compared with CT. In one study, however, the sensitivity for detecting vascular lesions on MR images in dogs was 38.9%, compared with 87.4% for neoplastic and 86% for inflammatory lesions. There are some specific MRI sequences (diffusion weighting, perfusion imaging, and magnetic resonance angiography) commonly employed in humans that can be used to improve the accuracy of stroke diagnosis, especially in the peracute stage of infarction (especially within the first few hours). These sequences, as well as susceptibility-weighted (e.g. gradient echo) sequences are discussed in Chapter 6. Table 7.8 summarizes the characteristic MRI appearance of nonhemorrhagic brain infarcts in dogs over time from infarction, using standard MRI sequences. Overall, nonhemorrhagic brain infarcts tend to be hyperintense on T2-W and FLAIR images, hypointense on T1-W images, and minimally to noncontrast-enhancing (Fig. 7.58). Contrast enhancement, usually at the periphery of the infarcted region, is typically appreciated 1–8 wks following the ischemic event, presumably associated with disruption of the BBB. The appearance of hemorrhagic infarcts on CT and MR images also varies with the time from the ischemic event, and is dependent upon the oxygenation state of hemoglobin. The “aging” stages of hemoglobin molecules progress sequentially as follows: oxyhemoglobin (peracute stage), deoxyhemoglobin (acute stage), methemoglobin (subacute stage), and finally hemosiderin and ferritin (chronic stage). Within the first several hours of a hemorrhagic infarct, the lesion is relatively isointense on T1- and T2-W MR

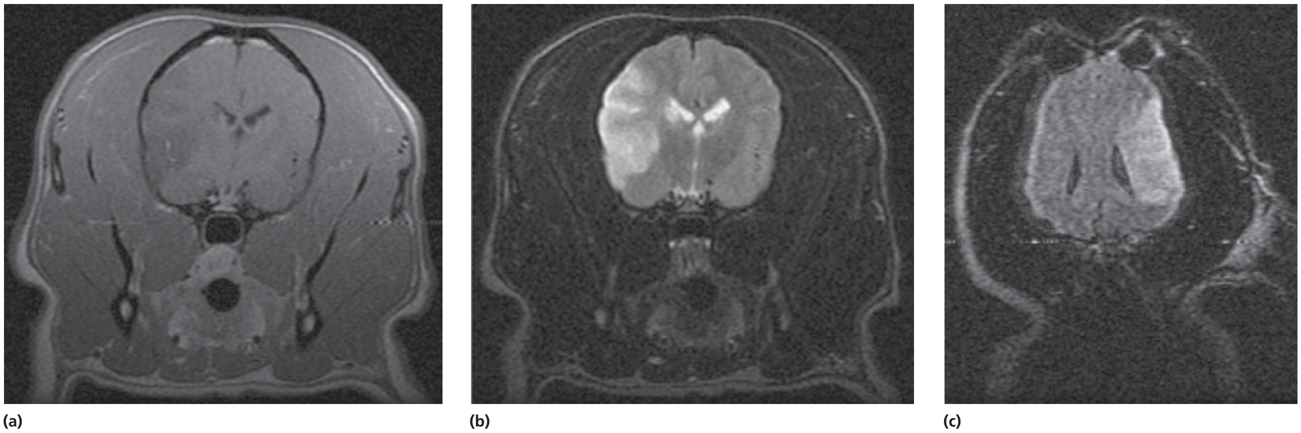


Figure 7.58 Transaxial T1-weighted with contrast (A), T2-weighted (B), and dorsal FLAIR (C) brain MR images from a dog with a nonhemorrhagic cerebral infarct.

images, but may show some hyperintensity on T2-W images, due to edema surrounding the infarct. Deoxyhemoglobin subsequently forms over the next 24 hrs, which is associated with low signal intensity on T1- and T2-W images. Intracellular methemoglobin predominates next, which is hyperintense on T1-W but hypointense on T2-W images. Subsequent accumulation of extracellular methemoglobin leads to a hyperintense signal on both T1- and T2-W images. Finally, hemosiderin and ferritin accumulate, which are low signal intensity on both T1- and T2-W images. Both MRI and CT findings associated with different stages of hemorrhagic infarcts are summarized in Table 7.9. Hemorrhagic infarcts are also more likely to exhibit contrast enhancement, compared with nonhemorrhagic infarcts (Fig. 7.59). With global brain ischemia, there is usually hyperintensity on T2-W and FLAIR images in the watershed zones of major arteries, indicating diffuse edema. These regions represent hypoxia-sensitive regions of the brain with the lowest cerebral perfusion pressure and include the cerebral cortex, basal nuclei, thalamus, hippocampus, and cerebellum. These areas also may contrast enhance following administration of intravenous gadolinium (T1-W with contrast; Fig. 7.60). CSF results in most cases of ischemic/vascular encephalopathy are either normal or characterized by nonspecific abnormalities consistent with a vascular event (e.g. mild neutrophilic or mononuclear pleocytosis, elevated protein concentration, xanthochromia).

4. The treatment of dogs with ischemic events to the brain is largely supportive. In the acute stage, mannitol should be administered to combat any associated brain swelling and edema. Other specific treatments should be directed against any underlying, potential causative disease, if such is identified. For example, treatment with enalapril, amlodipine, or a combination of these drugs may be indicated if systemic hypertension is documented.

The prognosis for dogs with focal brain infarcts is variable, but most have a guarded to fair prognosis for recovery of partial or full function. In one study of 33 dogs with brain infarcts, 10 dogs were euthanized; half of these were euthanized due to the severity of their underlying disease process, rather than failure of their neurologic status to improve. Another study of cerebellar infarcts also found a negative association between survival and presence of underlying systemic disease. The presence of an underlying or concurrent medical condition has also been associated with an increased chance of repeat brain infarction within a 10-mo period. In one study, dogs with right-sided strokes had a significantly higher mortality

Table 7.9 MRI and CT findings associated with different stages of hemorrhagic brain infarcts.

Stage	Time to imaging	T2-weighted MRI findings	T1-weighted MRI findings	CT findings
Peracute	3–6 hrs	Slightly hyperintense	Isointense	Hyperdense
Acute	6–24 hrs	Hypointense	Isointense	Hyperdense
Early subacute	24 hrs–1 wk	Hypointense	Hyperintense	Hyperdense
Late subacute	1–6 wks	Hyperintense	Hyperintense	Variable
Chronic	> 6 wks	Hypointense	Hypointense	Isodense

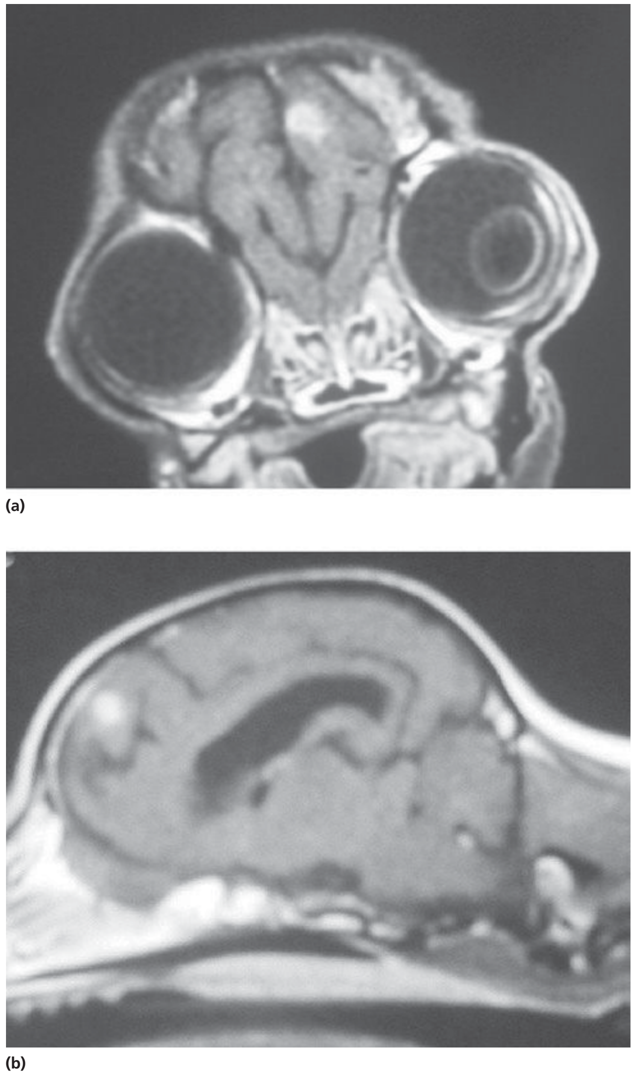


Figure 7.59 Transaxial (A) and sagittal (B) MR brain images (T1-weighted with contrast) of a dog with a focal hemorrhagic cerebral infarct.

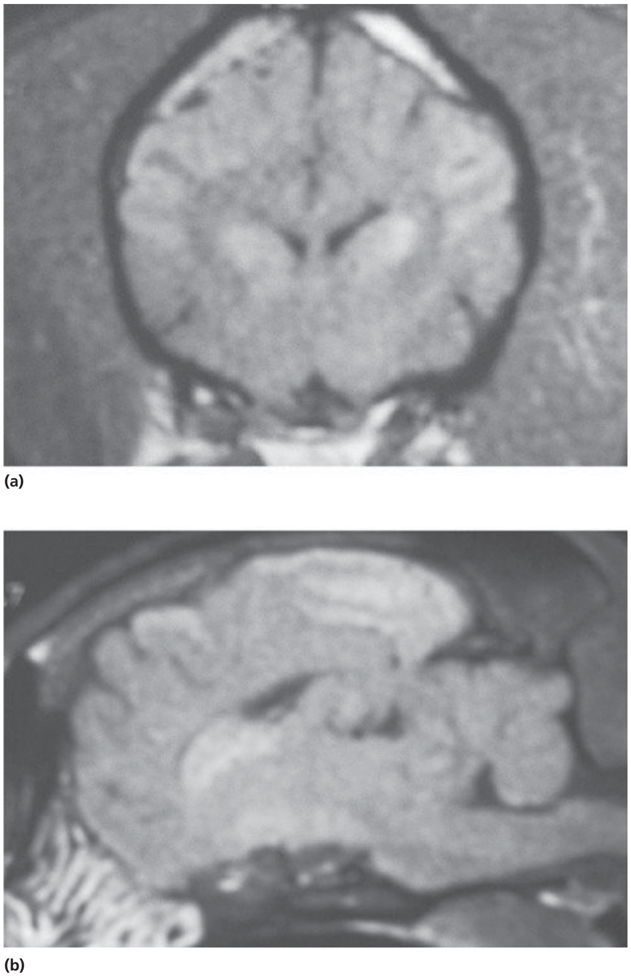


Figure 7.60 Transaxial (A) and sagittal (B) MR brain images (T1-weighted with contrast) of a dog that experienced anesthetic-related brain ischemia/hypoxia. Note the diffuse contrast uptake in the cerebral cortical and caudate nucleus/rostral thalamic regions.

rate than those with left-sided strokes. There are too few reported cases of global brain ischemia to estimate prognosis at this time.

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Video Resources

Video resources are available on the companion website: www.wiley.com/go/dewey/neurology

See videos 1, 7, 8, 14, 15 and 16.

CHAPTER 8

Head-Trauma Management

Curtis W. Dewey & Daniel J. Fletcher

Introduction[1, 17, 20, 22, 39, 56, 64, 67]

Severe head trauma is associated with a high degree of morbidity and mortality in humans and animals. Death typically results from progressive increases in intracranial pressure (ICP). Brain injury in dogs and cats is most often due to automobile trauma; other causes include missile injuries (e.g. gunshot wounds), animal bites, and falls. Traumatic brain injury has been documented to occur in 25% of severe blunt trauma cases in dogs and cats and is negatively associated with survival. Considerable controversy exists concerning therapy for severely brain-injured patients and this field is one of intense research in human neurology/neurosurgery. This chapter contains recent information regarding therapy for head-trauma victims. Retrospective and prospective clinical data pertaining to the treatment of canine and feline head trauma are lacking; therefore most of the clinical recommendations in this chapter are based upon information from human head-trauma studies and experimental head-trauma investigations. Opinions differ concerning what constitutes appropriate therapy for the severely brain-injured pet. However, few would refute that treatment needs to be expedient and aggressive for the majority of these patients. The first veterinarian the brain-injured pet encounters after the traumatic incident will likely dictate the eventual outcome for that patient. Dogs and cats can function well with considerable loss of cerebral tissue, if given time to recover from a severe brain injury. The ultimate goal in head-trauma management is to return the patient to the role in society occupied prior to the injury. It is of utmost importance to alleviate brain swelling and prevent damage to vital brain-stem structures.

Pathophysiology of head trauma[5, 6, 8, 17, 20, 22, 26, 27, 32, 34, 39, 49, 56, 64, 66, 67]

Brain injury can be conceptually divided into primary and secondary injury. Primary brain injury occurs immediately following impact and initiates a number of biochemical processes, which result in secondary brain injury. Both primary and secondary brain injury contribute to increased ICP. A basic understanding of the mechanisms of brain-tissue damage following injury and ICP dynamics is essential to logical therapy of the severely head-traumatized patient.

A. Primary brain injury

This type of injury refers to the physical disruption of intracranial structures that occurs immediately at the time of the traumatic event. Such injury includes direct damage to brain parenchyma, such as contusions, lacerations, and diffuse axonal injury. Damage to blood vessels may result in intracranial hemorrhage (Fig. 8.1) and vasogenic edema. Skull fractures can contribute to continued trauma to the brain parenchyma and blood vessels, especially if they are unstable (Fig. 8.2). The extent of primary brain injury is a function of the force of impact. Acceleratory and deceleratory forces of both the impacting object(s) and the intracranial contents will affect overall tissue damage. Direct parenchymal damage associated with primary brain injury is generally beyond the control of the clinician. However, stabilization of skull fractures and evacuation of intracranial hemorrhage may decrease the morbidity associated with these primary injuries.

B. Secondary brain injury

In addition to continued hemorrhage and edema, the damage caused by the primary brain injury activates a number of interrelated biochemical pathways that act in concert to perpetuate further brain-tissue damage and subsequent increases in ICP (Box 8.1).

Adenosine triphosphate (ATP) depletion disrupts the maintenance of cellular ionic homeostasis. Sudden, uncontrolled intracellular influx of sodium (Na^+) and calcium (Ca^{++}) occurs. Cellular swelling (cytotoxic edema) and depolarization result. The uncontrolled depolarization leads to the release of large amounts of glutamate, an excitatory neurotransmitter, into the extracellular environment. Glutamate causes further increases in intracellular Ca^{++} levels. Elevated Ca^{++} levels activate a number of tissue-damaging

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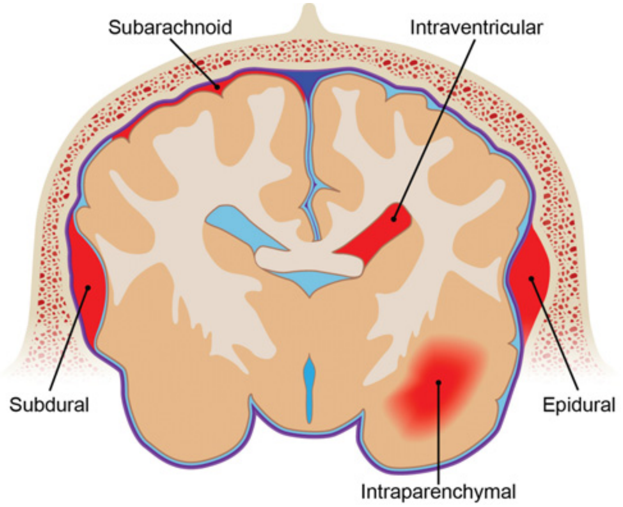


Figure 8.1 Clinically important forms of intracranial hemorrhage. Subarachnoid hemorrhage would occur as diffuse hemorrhage between the pia and arachnoid layers.

pathways, including the arachidonic acid cascade (phospholipase A_2 activation) and the xanthine oxidase (free-radical producing) pathway. Iron (Fe^{++}) is a vital cofactor in the xanthine oxidase pathway, and free-radical species generated via the Fenton reaction (e.g. hydroxyl and superoxide radicals) are preferentially damaging to cell membranes containing high levels of polyunsaturated fats and cholesterol. Brain tissue is rich in both Fe^{++} and membranes with high levels of PUFAs and cholesterol. Intraparenchymal hemorrhage also increases the amount of Fe^{++} available for the perpetuation of oxidative damage. Free-radical species are thus particularly damaging to neuronal membranes and probably play a major role in secondary brain injury. Their production is also induced by ischemia, arachidonic acid metabolites, catecholamine oxidation, and activated neutrophils. Other secondary autolytic processes induced after severe head trauma include the complement, kinin, and coagulation/fibrinolytic cascades. Elevated levels of nitric oxide (NO) and various

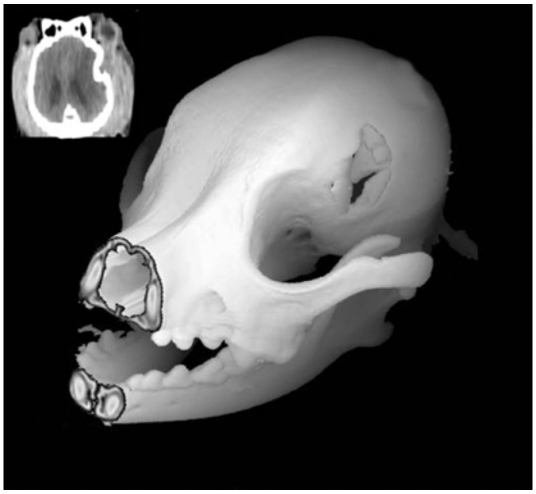


Figure 8.2 Three-dimensional CT reconstruction of a skull fracture in a dog that experienced severe head trauma. (Reproduced with permission from Dr. Charles Vite.)

Box 8.1 Mechanisms of secondary brain injury in head trauma patients.

Glutamate accumulation
- Occurs secondary to
  - ATP depletion
  - Neuronal cell injury
  - Positive feedback
  - Decreased conversion
  - Potentiated by low interstitial magnesium
- Results in
  - Loss of ionic gradients
  - Excitotoxicity
  - Free-radical oxygen species generation

Influx of sodium into neuronal cells
- Occurs secondary to
  - Glutamate accumulation
- Results in
  - Cytotoxic edema

Influx of calcium into neuronal cells
- Occurs secondary to
  - Glutamate accumulation
  - Primary injury
- Results in
  - Cytotoxic edema
  - Neuronal cell destruction through activation of proteases, lipases, and endonucleases
  - Reactive oxygen species production through calpain activation
  - Inflammatory mediator release
  - Mitochondrial dysfunction and ATP depletion

Free-radical production
- Occurs secondary to
  - Glutamate accumulation
  - Inflammatory mediator release
  - Increased cytosolic calcium concentrations
  - Ischemia-reperfusion injury
- Results in
  - Neuronal cell destruction

Inflammatory mediator release
- Occurs secondary to
  - Primary injury
  - Neuronal cell destruction with secondary injury
- Results in
  - Activation of nitric oxide with alterations in blood flow and vascular permeability
  - Inflammatory cell influx
  - Coagulation cascade activation and thrombosis

Loss of autoregulation
- Occurs secondary to
  - Primary injury
- Results in
  - Ischemia

All mechanisms contribute to neuronal cell death cytokines (e.g. tumor necrosis factor, interleukins) also contribute to parenchymal injury in the damaged brain. Most of the mediators of tissue damage produced by these various reactions perpetuate their own continued production as well as the production of other mediators. The maintenance of an ischemic environment perpetuates the above-mentioned processes and also leads to the accumulation of lactic acid (via anaerobic glycolysis). Lactic acid accumulation leads to further damage to brain tissue. Hypotension and hypoxemia, extracranial conditions that are common in the traumatized patient, can worsen brain ischemia and thereby enhance the events responsible for secondary brain injury. The result of these secondary processes is increased ICP. Unlike primary brain injury, the clinician has some control over secondary brain injury.

A. Intracranial pressure (ICP) dynamics

Intracranial pressure is the pressure exerted by tissues and fluids within the cranial vault. Normal ICP values for dogs and cats range between 5 and 12 mmHg. Cerebral perfusion pressure (CPP) is a primary determinant of cerebral blood flow (CBF) and hence brain oxygenation and nutritional support. CPP is defined by the following equation:

$$\text{CPP} = \text{MABP} - \text{ICP}$$

$$\text{MABP} = \text{mean arterial blood pressure}$$

The normal contents of the cranial cavity include brain parenchyma, blood, and cerebrospinal fluid (CSF). In the normal animal, these components exist in equilibrium with each other and ICP remains within normal limits. Between the MABP extremes of 50–150 mmHg, ICP remains constant. This phenomenon is called *pressure autoregulation*. Pressure autoregulation serves to link systemic blood pressure changes to brain vascular tone. If MABP rises, vasoconstriction occurs in the brain; if MABP falls, vasodilation occurs in the brain. In the normal animal, the former scenario prevents ICP from rising by decreasing CBF, and in the latter, prevents ICP from falling by increasing CBF. *Chemical autoregulation* refers to the direct responsiveness of brain vasculature to the partial pressure of carbon dioxide in arterial blood ($PaCO_2$); elevated $PaCO_2$ levels cause cerebral vasodilation, whereas decreased $PaCO_2$ levels cause cerebral vasoconstriction. Both forms of autoregulation often remain intact in people with severe head injury, but pressure autoregulation may be compromised in approximately 30% of patients. In some of these individuals, the lower MABP extreme may become “reset” to a higher value, resulting in significantly decreased blood flow to the brain with even mild systemic hypotension. With severe head trauma, both intracranial hemorrhage and edema can add to the volume of the intracranial compartment. Due to the inexpansible nature of the skull, one or more components of the cranial cavity must accommodate for the increased volume, or increased ICP will result. This accommodation or volume buffering is accomplished by fluid shifts in the brain vasculature and CSF pathways and is referred to as *intracranial compliance*. Compliance is expressed as the change in volume per unit change in pressure. Intracranial compliance has limitations, and decreases as ICP increases. If intracranial volume increases beyond the abilities of compensatory mechanisms, progressively larger increases in ICP result per unit of volume increase (Fig. 8.3), CPP is compromised, and ischemic death of brain tissue occurs. In cases of severe head trauma, intracranial compliance often is quickly exhausted. If MABP decreases (hypotension), especially in combination with hypoxemia, the brain vasculature will vasodilate in an effort to preserve blood flow. The increase in blood volume increases ICP, but CPP remains inadequate. In addition, the secondary autolytic processes occurring in the injured brain are enhanced by hypotension and hypoxemia, and further brain injury and edema occur with a resultant rise in ICP.

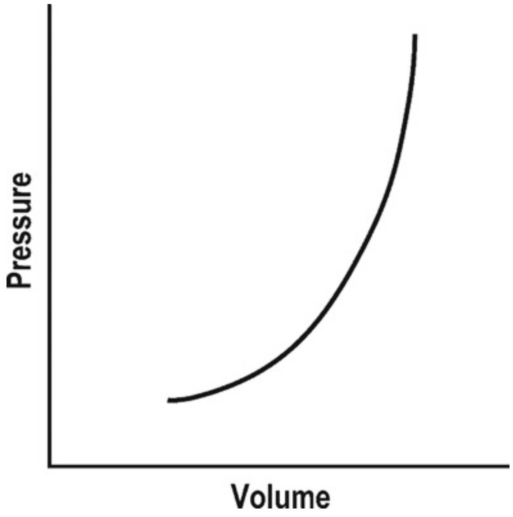


Figure 8.3 Typical pressure/volume curve for the intracranial compartment. (Dewey, 2000. Reproduced with permission from Elsevier.)[17]

Initial assessment and emergency treatment[2, 9, 11, 17, 19, 20, 22, 24, 32, 36, 46, 50, 53, 57, 59, 62–64, 74, 78, 79] (Video 17)

Initial physical assessment of the severely brain-injured patient focuses on imminently life-threatening abnormalities. Many patients suffering severe head trauma present to the clinician in a state of hypovolemic shock. Do not be in a rush to focus initially on the patient’s neurologic status; it may well improve once the shock state is corrected. Remember that traumatized, hypovolemic patients with no appreciable brain injury often exhibit depressed mentation, due primarily to the hypotensive state. The clinician must first focus on the ABCs of trauma management

Table 8.1 Intravenous fluid therapy and recommended doses for head trauma patients.

Fluid type	Recommended dose
Isotonic crystalloid (0.9% NaCl preferred)	20–30 ml/kg dogs 10–20 ml/kg cats Administered over 15–20 min Reassess after
Synthetic colloid (e.g. 6% hydroxyethyl starch)	5–10 ml/kg Administered over 15–20 min Reassess after
7.5% sodium chloride	4 ml/kg Administered over 15–20 min Reassess after Always follow with crystalloid therapy
3% sodium chloride	5.4 ml/kg Administered over 15–20 min Reassess after Always follow with crystalloid therapy
1:2 ratio of 23.4% sodium chloride and 6% hydroxyethyl starch or other synthetic colloid	4 ml/kg Administered over 15–20 min Reassess after Always follow with crystalloid therapy
Packed red blood cells	~1 ml/kg Administer over less than 4 hrs/unit Target normalization of perfusion parameters and PCV = 25–30%
Whole blood	~2 ml/kg Administer over less than 4 hrs/unit Target normalization of perfusion parameters and PCV = 25–30%
Fresh frozen plasma	10–15 ml/kg Administer over less than 4 hrs/unit Target normalization of coagulation times

(airway, breathing, cardiovascular status). In doing so, the brain will benefit as well as the rest of the patient. Quick assessment tests (QATs)—including packed cell volume (PCV), total solids (TS), Azostix (AZO), and blood glucose (BG)—are part of the initial patient assessment. Since hypovolemia and hypoxemia are strongly correlated with elevated ICP and increased mortality in human head-trauma victims, they need to be addressed immediately.

A. Fluid therapy (Table 8.1)

B. There is often concern that aggressive intravenous fluid therapy to counteract hypotension in the brain-injured patient may aggravate brain edema. There is both evidence to support and evidence to refute this concern. Because of this concern, there have been recommendations to volume-limit victims of severe head trauma. Such recommendations are not only unfounded, but *strictly contraindicated*. There is no debate over the disastrous consequences to the injured brain if hypotension is allowed to persist. Hypotension has been repeatedly shown to be a reliable predictor of sustained elevations of ICP and increased mortality in human head-trauma victims. Blood pressure must be restored to normal levels as soon as possible. A patient with a systolic blood pressure of less than 120 mmHg is considered hypotensive. Some volume replacement fluids (hetastarch, hypertonic saline) afford some protection to the edematous brain, even if used with large volumes of crystalloids (LRS, 0.9% NaCl). Hetastarch and hypertonic saline can improve MABP and thus CPP without exacerbating brain edema. If the patient is anemic, whole-blood or packed red blood cell (pRBC) transfusion may assist in maintaining normovolemia as well as adequate tissue oxygenation by improving blood oxygen content, the major determinant of which is hemoglobin concentration. Fluid support may include one or more of the following choices:

1. Synthetic colloids: 10–20 ml/kg to effect (up to 40 ml/kg/hr) for shock. This can be given as a rapid bolus in dogs; give it in 5 ml/kg increments over 5–10 min in cats. Hetastarch is the author's fluid of choice in restoring normal blood pressure in the euhydrated head-trauma victim. Dextran-70 is an acceptable alternative, but given as a sole fluid support it has not exhibited the beneficial effects demonstrated with hetastarch and hypertonic saline. Dehydrated trauma victims should receive isotonic crystalloid resuscitation.
2. Hypertonic saline (7%): 4–5 ml/kg over 3–5 min for shock. Hypertonic saline is also available as 23.4% solution, which cannot be administered undiluted, but may be mixed 1:3 with hetastarch or dextran-70 (e.g. 20 ml of 23.4% hypertonic saline + 40 ml hetastarch or dextran-70 in a 60 ml syringe) to produce a solution of synthetic colloid suspended in a 7% hypertonic saline solution. Sodium does not freely cross the blood–brain barrier (BBB); therefore, hypertonic saline can reduce cerebral edema via an osmotic pull of fluid out of the brain parenchyma and into the intravascular space. It also has positive inotropic effects, immunomodulatory effects, and reduces endothelial swelling. Although hypertonic saline has been shown to improve MABP and CPP and protect against increased ICP, sodium has recently been implicated as the major osmotic agent contributing to brain edema. Hypertonic saline may have a global protective effect on the brain, but theoretically may lead to increased compromise to focal areas of damaged parenchyma due to compromise of the BBB in these regions.
3. Isotonic crystalloids (LRS, 0.9% saline): 20–30 ml/kg bolus over 15–20 min for shock. May be repeated as necessary after reassessment. Since overhydration with subsequent worsening of brain edema and increased ICP is a concern with crystalloid administration, the "shock dose" (90 ml/kg in the dog, 60 ml/kg in the cat) of crystalloids should be given incrementally to effect as described above. If the entire volume is not necessary to restore euvolemia and normal MABP, fluid administration should be tapered when these physiologic goals are met. Since 0.9% saline has less free water than LRS, this crystalloid may be preferable for use in the brain-injured pet.

4. Blood products: Administration of 1 ml/kg of pRBCs or 2 ml/kg of whole blood will increase the PCV by 1%. The severity of anemia will dictate the total dose to be administered, but 10–15 ml/kg of pRBCs is a reasonable starting dose. Blood products are typically administered over 4 hrs, but may be given faster (to effect) if the patient is unstable. Boluses of blood products are acceptable in the severely anemic trauma patient. Goals of therapy with blood products are a PCV between 25 and 30%. Patients with demonstrated coagulopathy should also be treated with fresh frozen plasma (FFP) at a dose of 10–15 ml/kg 2–3 times per day until coagulopathy has resolved.

C. Oxygenation and hyperventilation

Hyperoxygenation is recommended for most acutely brain-injured animals. Oxygenation status of a head-trauma victim can be initially assessed based upon breathing rate and pattern, mucous membrane and tongue color, and thoracic auscultation. Pneumothorax and pulmonary contusions are common sequelae of trauma, and need to be addressed if present. It should be noted that, in the face of increased respiratory rate and effort, lung sounds may not consistently be decreased on auscultation in patients with pneumothorax. A rapid, shallow breathing pattern, pale oral mucous membranes, and evidence of respiratory distress should raise the clinician's index of suspicion for the presence of pneumothorax. Thoracentesis should be done in any trauma patient in whom there is a suspicion of pneumothorax, and should be considered a diagnostic test as well as a therapeutic intervention. If negative pressure cannot be obtained via thoracentesis, a chest tube should be placed immediately. If arterial blood gas analysis is available, the partial pressure of oxygen in arterial blood (PaO_2) should be maintained at or above 90 mmHg for dogs, and 100 mmHg for cats. Pulse oximeters are extremely useful and relatively accurate estimators of oxygenation status. However, the reliability of pulse oximeters varies with model used, with the PaO_2 level (pulse oximeters may overestimate oxygenation status at lower PaO_2 levels), and with the patient's hemodynamic status. In general, oxyhemoglobin saturation values (SpO_2) from pulse oximeters should be interpreted as shown in Table 8.2.

Patients who are conscious and not obviously deteriorating neurologically should be administered supplemental oxygen via facemask, nasal cannula, nasal oxygen catheter, or transtracheal oxygen catheter. Facemasks tend to stress dogs and cats, and should only be used temporarily, until another form of oxygen (O_2) delivery can be instituted (e.g. nasal O_2). The use of an O_2 cage is generally an ineffective method of administering supplemental O_2 to the severely brain-injured patient, as most of these patients require frequent or constant monitoring. Oxygen cages do not allow for concomitant close patient observation (requires opening the cage door) and maintenance of a high-oxygen environment. With nasal (Fig. 8.4) and transtracheal O_2 catheters, an inspired oxygen concentration of 40% is provided with flow rates of 100 ml/kg/min and 50 ml/kg/min, respectively. Oxygen concentrations as high as 95% can be delivered with proportionally higher flow rates. Nasal O_2 catheters must not be placed farther than the level of the medial canthus (to avoid entering the cranial vault through a fracture site), and inadvertent jugular vein compression should be avoided while placing a transtracheal O_2 catheter. High flow rates with nasal O_2 catheters may induce sneezing, which has the potential to raise ICP. Patients who are losing or have lost consciousness should be intubated and ventilated. Also, if adequate oxygenation cannot be maintained with high fractional inspired oxygen concentrations (FiO_2) greater than 60%, mechanical ventilation should be instituted. In the patient with oscillating levels of consciousness or airway obstruction secondary to trauma, a tracheostomy tube may be indicated for assisted ventilation. Arterial blood gas measurement is the best way to monitor $PaCO_2$ levels. End-tidal CO_2 measurement is a useful monitoring tool, but tends to underestimate the true $PaCO_2$ levels. Venous CO_2 levels ($PvCO_2$) are also helpful, and are usually less than 5 mmHg greater than $PaCO_2$. However, in patients with perfusion deficits, peripheral $PvCO_2$ levels can be significantly higher than arterial values, and should be interpreted cautiously. Ventilatory rates of 10–20 breaths per minute should keep $PaCO_2$ levels between 25 and 35 mmHg in the absence of significant pulmonary parenchymal disease. While this has been the recommended range of $PaCO_2$ levels to prevent excessive brain vasodilation, recent

Table 8.2 Interpretation of pulse oximeter SaO_2 values

SaO_2	PaO_2	Interpretation
95%	80 mmHg	Normal
89%	60 mmHg	Serious hypoxemia
75%	40 mmHg	Lethal hypoxemia

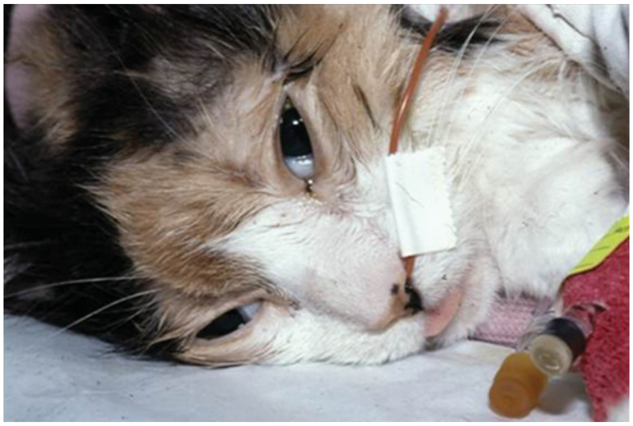


Figure 8.4 Nasal oxygen administration in a head-traumatized cat. (Dewey and Budsberg, 1993.)[19]

evidence suggests that $PaCO_2$ less than 30 mmHg may lead to excessive vasoconstriction with the subsequent impairment of CPP. Hyperventilation may be deleterious to patients whose ICP elevation is not due to hypercarbia-induced dilation of brain vasculature. Indiscriminate use of hyperventilation to decrease ICP should be avoided, as excessive vasoconstriction of brain vasculature can decrease CPP.

Secondary assessment and diagnostic procedures[1, 9, 11, 17, 20, 22, 32, 45, 64, 80]

Once normovolemia and appropriate oxygenation/ventilation are attained, the patient should be more carefully assessed for other injuries to the nervous system (e.g. vertebral fractures/luxations), as well as to other body systems (lungs, abdominal organs, musculoskeletal system). A complete neurologic examination should be performed at this time. If possible, it is best to perform a neurologic assessment of the patient prior to the administration of any sedative drugs (e.g. narcotics). Specific medical therapy for brain injury should begin coincident with the secondary assessment. Additional bloodwork as well as radiographs may be warranted. Imaging of the patient's head is often indicated, especially in those animals that fail to respond to aggressive medical therapy, or deteriorate after responding to such therapy. Skull radiographs are unlikely to reveal clinically useful information in cases of severe head trauma, but on occasion may reveal evidence of depressed fractures of the calvaria (Fig. 8.5). Computed tomography (CT) is the preferred modality for imaging the head in cases of severe brain injury. CT is preferred over magnetic resonance (MR) imaging in head-trauma cases for several reasons. CT images are obtained much more quickly than MR images (an important advantage in the critical patient scenario), patients may be more closely monitored with standard monitoring systems during CT than during MR because of the large magnetic field required for MR, and acute hemorrhage and bone are better visualized with CT than with MR imaging (Fig. 8.6).

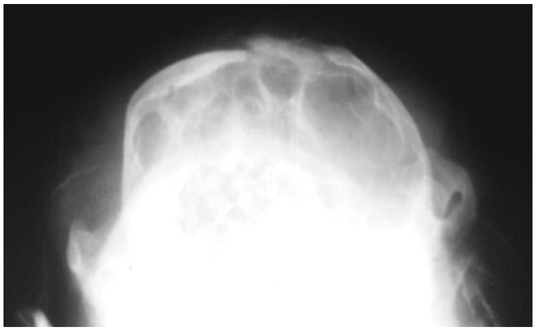


Figure 8.5 Depressed skull fracture in a dog with deteriorating neurologic status following severe head trauma. (Dewey and Budsberg, 1993.)[19]

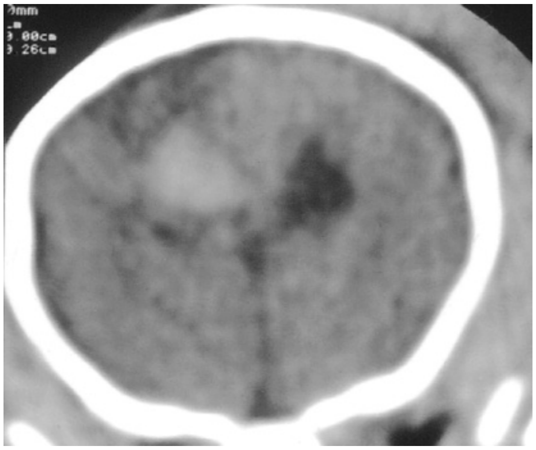


Figure 8.6 Noncontrast, CT brain image of a brain-injured dog. Note the evidence of intraparenchymal hemorrhage. (Dewey, 2000. Reproduced with permission from Elsevier.)[17]

Specific medical therapy for the head-trauma victim[3–5, 9, 11, 13, 16, 17, 19, 22, 23, 27, 29, 30, 32, 33, 39, 43, 44, 48, 51, 52, 57–59, 64, 65, 68, 70–73, 75, 77, 80–82]

A number of medical therapies have been recommended for the head-trauma victim, most of which are controversial and not definitively proven to affect outcome. In addition to these treatments, proper physical therapy and nutritional support are vital to a positive outcome. In the recumbent patient, the head should be kept slightly elevated (15°–30°) to assist in lowering ICP by facilitating venous drainage from the brain. This should be accomplished using a slant board that prevents lateral flexion of the neck, which can impede jugular venous flow.

A. Mannitol (20–25%)

Mannitol is an osmotic diuretic that has demonstrated efficacy in reducing brain edema and ICP in cases of severe brain injury. There are multiple proposed mechanisms of actions by which mannitol decreases ICP, including reflex vasoconstriction of brain vasculature via decreasing blood viscosity, reduction of CSF production, scavenging free-radical species, and osmotically drawing extravascular edema fluid into the intravascular space. The mechanism thought to be primarily responsible for mannitol's most immediate and profound effects on ICP is reflex vasoconstriction. This response of the brain vasculature to the decreased blood viscosity caused by an intravenous mannitol bolus is linked to the brain's pressure autoregulation mechanism; it allows for improved CPP at a lower brain-blood volume (decreased ICP). The effect of reflex vasoconstriction on ICP occurs within a few minutes, whereas the osmotic action has an effect within 15–30 min. Mannitol's effect on decreasing brain edema lasts between 2 and 5 hrs.

Mannitol is administered intravenously over 10–20 min at a dosage of 0.5–1.5 g/kg. Recent evidence in the human literature supports the concept that higher doses of mannitol (1.4 g/kg) are associated with better outcomes than lower doses (0.7 g/kg) in patients with severe brain injury; this concept, however, has been subsequently challenged by other investigators. Serum osmolality and electrolytes should be monitored with repeated mannitol use; osmolality should be maintained at or below 320 mOsm/l (to reduce the risk of acute kidney injury due to renal vasoconstriction), and electrolytes should be kept within normal limits. It is important to note that measured (by a technique such as freezing point depression), not calculated, osmolality should be monitored, as the increased osmolality is due to an unmeasured osmole (mannitol). Although monitoring measured osmolality and the osmolal gap (the difference between measured and calculated osmolality), and avoiding large changes in either, is recommended, a recent retrospective study of 95 human patients with head trauma showed that neither was correlated with the development of acute kidney injury in patients with head trauma. A useful guideline to prevent possible unwanted side effects of mannitol use is to limit the administration of mannitol to three boluses in a 24-hr period. However, due to the conflicting evidence in the literature regarding the potential for patients to develop kidney injury secondary to mannitol infusion, the authors recommend that mannitol be aggressively administered to patients with progressive neurologic signs that are responding to it. Since mannitol tends to crystallize at room temperature, it should be warmed to approximately 37°C (99°F) and administered through an in-line filter. A frequently raised theoretical concern about mannitol administration is the possibility of exacerbating ongoing brain hemorrhage due to mannitol's osmotic action. This concern is unfounded clinically and should be ignored. Another concern about mannitol use in the head-trauma victim involves the concept of "reverse osmotic shift"; with prolonged contact time (multiple doses or continuous infusions), the extravascular concentration of mannitol in the brain can accumulate and exceed the intravascular concentration. The result of this phenomenon is increased brain edema. With the appropriate use of mannitol, "reverse osmotic shift" is extremely unlikely to occur. In general, once the head-trauma victim is hemodynamically stable, mannitol should be considered a first-line therapy for decreasing ICP and improving CPP. It is important to maintain hydration in patients receiving mannitol, especially if multiple doses are administered. Key aspects of mannitol and hypertonic saline (discussed below) are presented in Table 8.3. Although previously proposed as having a synergistic effect on reducing cerebral edema when administered with mannitol, recent experimental evidence suggests that furosemide does not reduce cerebral edema alone or in combination with mannitol. Given that the administration of furosemide causes a reduction in intravascular volume, the authors do not recommend administration of this drug in patients with head trauma.

B. Hypertonic saline (7%)

Hypertonic saline is a hyperosmotic solution that may be used as an alternative or adjunct to mannitol in patients with head injury. Because sodium does not freely cross the intact BBB, hypertonic saline has similar osmotic effects to mannitol. Other beneficial effects include improved hemodynamic status via volume expansion and positive inotropic effects, as well as beneficial vasoregulatory and immunomodulatory effects. Rebound hypotension is uncommon with hypertonic

Table 8.3 Comparison of mannitol with hypertonic saline

	Mannitol	**Hypertonic saline**
Mechanism of action	Increases osmotic gradient across BBB Plasma expansion with decreased blood viscosity improves brain oxygen delivery and autoregulation results in cerebral vasoconstriction decreasing cerebral blood volume and ICP Free-radical scavenger	Increases osmotic gradient across BBB Volume expansion Increases cardiac output and blood pressure
Recommended dose	0.5–1.0 g/kg slow over 15–20 min Effects begin within minutes, peak within 15–120 min, duration 1–5 hrs No benefit of CRIs over boluses	7.5% NaCl: 4 ml/kg 3% NaCl: 5.4 ml/kg 1:2 ratio 23.4% NaCl: 6% Hetastarch: 4 ml/kg; Administered over 15–20 min Reassess after Always follow with crystalloid therapy
Side effects	Volume-depletion Electrolyte abnormalities (hyponatremia (pseudo-), hypernatremia, hypokalemia) Acid-base derangements (i.e. metabolic acidosis) Congestive heart failure Acute kidney injury (osmolality > 320 mOsm/l)	Electrolyte abnormalities (hypernatremia, hyperchloremia) Acid-base derangements (i.e. metabolic acidosis) Congestive heart failure Acute kidney injury (less common than with mannitol)
Relative contraindications	Hypovolemia	Significant sodium derangements Dehydration

CRI = continuous rate infusion.

saline administration because, unlike mannitol, sodium is actively reabsorbed in the kidneys, especially in hypovolemic patients. This makes it preferable to mannitol for treating patients with increased ICP and systemic hypotension due to hypovolemia. Combining hypertonic saline with a synthetic colloid can prolong this volume expansion effect. It is contraindicated in patients with hyponatremia, as it can cause rapid rises in serum sodium concentrations, leading to central myelinolysis and subsequent neurologic dysfunction. In euvolemic patients with evidence of intracranial hypertension, both mannitol and hypertonic saline can have beneficial effects. If an individual patient is not responding to one drug, the other may yield a beneficial response.

C. Glucocorticoids

Despite their traditional role in the treatment of central nervous system (CNS) trauma, there is little evidence to support the use of glucocorticoids in victims of severe head trauma. "Standard" dosing protocols of prednisone and dexamethasone are particularly unlikely to benefit brain-injured patients. Limited experimental evidence of efficacy exists for the "high-dose methylprednisolone" protocol in severe head trauma. This protocol involves the intravenous administration of a 30-mg/kg bolus of methylprednisolone sodium succinate (Solu-Medrol) at time 0, and 15 mg/kg boluses at 2 hrs and 6 hrs. The "high-dose" protocol was suspected to provide therapeutic benefit via free-radical scavenging action, rather than by the activation of steroid receptors. Recent evidence from a large, prospective, randomized, placebo-controlled clinical trial showed significantly increased mortality in people with traumatic brain injury treated with this high-dose protocol. Given this evidence of a detrimental effect in head- injured people and the potential side effects of these drugs in dogs and cats, including gastrointestinal hemorrhage, immunosuppression, and hyperglycemia, the authors do not recommend the use of corticosteroids in patients with head trauma.

D. Anticonvulsant therapy

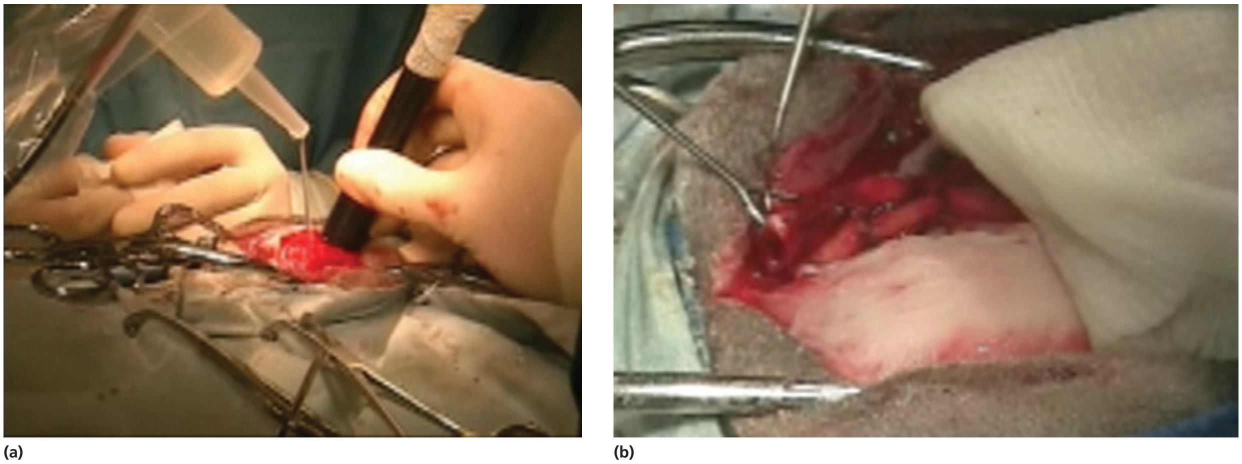
Seizures are common after head trauma in people, with reported incidence rates of up to 54%, and patients who have at least one seizure after traumatic brain injury have an 86% risk of having additional seizures within the next 2 yrs. There is recent evidence in dogs that head trauma does lead to an increased likelihood of seizures when compared with the general canine population, but the incidence rate is lower (6–7%) than that reported for people. Posttraumatic seizures are divided into three groups: immediate, occurring within 24 hrs of the trauma; early, occurring 24 hrs to 7 days post trauma; and late, occurring longer than 7 days after trauma. Several controlled clinical trials have been undertaken in human medicine to investigate the efficacy of prophylactic anticonvulsant therapy after head trauma, and a meta-analysis showed an overall reduction in the risk of immediate and early seizures with prophylactic anticonvulsant therapy (relative risk (RR) = 0.3, 95% confidence intervals (CI) = 0.21–0.52), but no effect on risk of late seizures (RR = 1.28, 95% CI = 0.9–1.8). Given these data, short-term prophylactic therapy for 7 days after trauma may be indicated in patients with head trauma, and anticonvulsant therapy should always be instituted for all patients with head trauma who develop immediate or early seizures.

E. Miscellaneous therapies

A number of free-radical scavenging agents have been investigated for potential use in victims of severe head injury. Some examples include lazaroids, dimethyl sulfoxide (DMSO), allopurinol, deferoxamine mesylate, and liposome-encapsulated forms of superoxide dismutase and catalase. Despite experimental evidence of efficacy for these drugs, clinical evidence to support the use of these agents in the head-trauma victim is currently lacking. Similarly, there exists some experimental, yet not clinical, evidence of efficacy for antagonists of opiate and glutamate receptors, as well as several calcium channel blockers. Induction of a barbiturate coma with pentobarbital has been advocated as a "last ditch" effort to decrease metabolic demands of the injured brain, thereby mitigating effects of ischemia and decreasing ICP. In addition to limited evidence of clinical efficacy, induction of a barbiturate coma in a brain-injured patient may be detrimental to survival. Barbiturates may lead to hypotension and/or hypoventilation, both of which will cause increased ICP. Recent experimental and clinical evidence in human head-injured patients supports the induction of moderate hypothermia (32°–34°C, 89.6°–93.2°F) as a means to decrease ICP and improve outcome. Although traditionally thought to decrease ICP via decreasing brain metabolic demands, induced hypothermia is now thought to provide beneficial results, mainly by inhibiting the release of inflammatory cytokines and glutamate. Hyperglycemia (over 200 mg/dl) has been associated with an increased mortality in severely head-injured people. In one veterinary study, the degree of hyperglycemia was found to be correlated with the severity of neurologic dysfunction in brain-injured dogs and cats; however, an association between the level of hyperglycemia and survival was not found. It is postulated that the provision of extra glucose to the ischemic brain helps to fuel anaerobic glycolysis, with resultant increases in brain lactic acid. Intensive insulin therapy to maintain euglycemia in patients with head trauma has recently been proposed; however, a small prospective clinical trial failed to show an outcome benefit from intensive insulin therapy. Larger clinical trials will be required to determine the utility of insulin therapy in hyperglycemic patients with head trauma.

Indications for surgery[5, 7, 9, 12, 14, 15, 17, 19, 21, 22, 28, 31, 32, 35, 39, 42, 59, 64]

In general, indications for surgical intervention are clearly defined in human head-trauma management. The guidelines



(a) (b)

Figure 8.7 (A) location of an intraparenchymal hematoma in a dog using intraoperative ultrasound. (B) removing the intraparenchymal hematoma.

for when to pursue surgery in brain-injured people center on the presence and extent of intracranial hemorrhage. Measurements of focal hemorrhage and accompanying midline shifts of the falx cerebri from CT images are combined with ICP measurements in making surgical decisions in people with severe head trauma. Surgical intervention has traditionally played a relatively minor role in canine and feline head-trauma management, due to the belief that clinically significant intracranial hemorrhage is rare in these species. There is some evidence that brain-injured dogs and cats may experience surgically manageable intracranial hemorrhage, similar to people (Fig. 8.7). With the increased availability of CT facilities for dogs and cats, surgery may begin to play a larger role in canine and feline head-trauma management. Other potential indications for surgery in the brain-injured dog or cat include open skull fractures, depressed skull fractures (with associated neurologic impairment), and the retrieval of potentially contaminated bone fragments or foreign material lodged in brain parenchyma (Fig. 8.8).

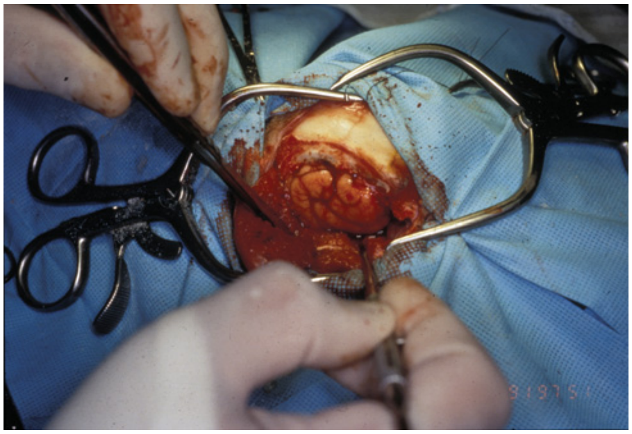


Figure 8.8 Decompressive craniotomy in a dog. The patient had a large bone fragment lodged in the cerebral parenchyma and a midline shift evident on CT imaging. (Reprinted with permission.)[19]

While the surgical removal of focal intracranial hemorrhage is an accepted and proven aspect of human head-trauma management, the use of decompressive craniotomy in human patients with diffuse traumatic brain injury is controversial. A recently completed randomized prospective study in humans with diffuse traumatic brain injury found no advantage to decompressive craniotomy compared with standard treatment methods; in fact, the craniotomy patients had worse Modified Glasgow Coma Scale (MGCS) scores than standard therapy patients, and there was no difference in the mortality rates between the two groups. The value of craniotomy solely as a decompressive surgery is unknown in canine and feline head trauma. It has been demonstrated, however, that in normal dogs and cats combined craniotomy/durotomy results in dramatic decreases in ICP. Surgical intervention should be strongly considered in head-traumatized dogs and cats that are deteriorating neurologically despite aggressive medical therapy.

Intracranial pressure (ICP) monitoring[3, 5, 7, 9, 11, 17, 18, 25, 35, 39–41, 47, 49, 60, 61, 64]

Medical and surgical decisions based upon ICP measurements, rather than on gross neurologic findings, have decreased morbidity and mortality in human head-trauma victims. In general, recommendations for human head-trauma victims are to maintain ICP below 20 mmHg and CPP at a minimum of 70 mmHg. Prognostic information can also be obtained from ICP measurements. ICP monitoring is a standard procedure for human head-trauma management, but has only recently been investigated in dogs and cats. A fiberoptic ICP monitoring device has been shown to be both technically easy to place and reliable in dogs and cats. With this monitor, ICP can be measured directly from brain parenchyma. The extremely high cost of the fiberoptic system will likely limit its use in veterinary medicine. An inexpensive, easily implantable, epidural ICP monitoring system

Table 8.4 Modified Glasgow Coma Scale

Motor activity	
Normal gait a reflexes	6
Hemi/tetraparesis or decerebrate activity	5
Recumbent, intermittent ext. rigidity	4
Recumbent, constant ext. rigidity	3
Recumbent, constant ext. rigidity and opisthotonus	2
Recumbent, hypotonic muscles, ↓ or absent reflexes	1
Brain-stem reflexes	
Normal PLR and oculocephalic reflexes	6
Slow PLR, normal to ↓ oculocephalic reflexes	5
Miosis OU, normal to ↓ oculocephalic reflexes	4
Pinpoint pupils, ↓ to absent oculocephalic	3
Unilateral, unresponsive mydriasis, ↓ to absent oculocephalic reflexes	2
Bilateral, unresponsive mydriasis, ↓ to absent oculocephalic reflexes	1
Level of consciousness	
Occasional alertness, responsive to environment	6
Depression/delirium, responsive but inappropriate	5
Obtunded, responsive to visual stimuli	4
Obtunded, responsive to auditory stimuli	3
Stuporous, responsive to noxious stimuli	2
Comatose	1

PLR = pupillary light reflex.
Source: Adapted from Platt *et al.*, 2001.[55]

Table 8.5 Modified Glasgow Coma Scale Score Category and Suggested Prognosis.

Score category	Actual MGCS score	Suggested prognosis
I	3–8	Grave
II	9–14	Guarded
III	15–18	Good

Source: Adapted from Platt *et al.*, 2001.[55]

has been evaluated in normal cats; this system was found to be comparable in accuracy to the fiberoptic ICP system.

Prognosis and complications[10, 17, 19, 22, 54, 55, 64, 69, 76]

The overall prognosis for victims of severe head trauma is considered guarded to poor. However, the recuperative ability of brain-injured dogs and cats is tremendous, and aggressive therapy may be successful in many apparently hopeless cases. Predicting the outcome of an individual patient is difficult, but several factors may assist the clinician in estimating prognosis. These factors include level of consciousness, presence or absence of brain-stem reflexes, age and general physical status, and presence and extent of other concurrent injuries. A dog or cat that is comatose with absent brain-stem reflexes from the time of impact is generally less likely to recover than a patient who is obtunded with intact brain-stem function. The MGCS scoring system, adapted from a human coma scale, has been shown in one retrospective study to predict survival to 48 hrs in dogs with head injury. Table 8.4 describes the components of the MGCS. The score in each domain is summed, yielding the overall MGCS, which ranges from 3 (severe neurologic deficits) to 18 (neurologically normal). Table 8.5 provides three categories of coma scale severity and the suggested prognosis for each. It is the authors' opinion that the severity of neurologic deficits at admission is poorly correlated with outcome in most dogs and cats with head injury, especially in neonatal or juvenile patients. Even patients with severe neurologic signs at admission can show dramatic improvement in the first 24–48 hrs. Trends in neurologic status over the first 48 hrs are likely to be more predictive of outcome in these patients than isolated evaluation of neurologic status at a single point in time. The MGCS provides a quantitative method for monitoring trends in neurologic status over time. Potential complications associated with brain-injured patients include coagulopathies (e.g. disseminated intravascular coagulation; DIC), pneumonia, fluid/electrolyte abnormalities (e.g. central diabetes insipidus), and sepsis. Seizure activity may develop around the time of trauma (suggesting intraparenchymal hemorrhage) or months to years after trauma (development of a glial "scar" seizure focus). Most of these complications are treatable and/or preventable. Client education is of paramount importance, as persistent or permanent neurologic deficits in patients with head trauma are common.

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Video Resources

with website

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See video 17.

CHAPTER 9

Seizures and Narcolepsy

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Seizures

Introduction[31, 107, 127]

Seizures are the most common neurologic problem in small-animal medicine. Overall, the incidence of idiopathic epilepsy (the most common cause of seizures in dogs) is between 0.5 and 5% of the pet dog population; some breeds, however, have much higher incidences of epilepsy within the breed. Clients are often emotionally distraught because of the violent, unpredictable nature of seizures. An accurate diagnosis is the first step in management. The underlying cause of the seizures is identified and treated if possible. In the case of idiopathic epilepsy, there is no cure, and management usually entails the daily administration of medication. Optimal management of this syndrome depends on the veterinarian and client working together as a team, with the client actively participating in decisions. With proper treatment, the patient and client can usually maintain a good quality of life. Managing seizure disorders presents a major challenge to the veterinarian, especially when a dog does not respond to "standard" (i.e. phenobarbital, bromide) therapy. A *refractory epileptic* is a dog who has poor seizure control, despite documented evidence of plasma drug concentrations of two or more typically effective antiseizure drugs that are within what is considered the therapeutic range. Such refractory cases account for between 25 and 30% of all epileptics. The *therapeutic range* is a range of plasma drug concentrations for a specific drug within which most patients are expected to achieve adequate seizure control. The therapeutic range is often a somewhat arbitrarily derived scale and should be used only as a guideline. A *responder* is a patient that has experienced at least a 50% reduction in seizure frequency following the addition of a specific antiseizure intervention (e.g. addition of a new drug). Owners may arrive at the veterinarian's office following their pet's first seizure, fully expecting their veterinarian to make their pet seizure-free. It is very important for the clinician to inform the pet owner that a small percentage of epileptics become seizure free with drug therapy (estimate of about 15% in dogs vs. 70–90% in people); success is typically considered a reduction in the frequency and duration of seizures. Nonetheless, *the goal of anticonvulsant therapy should be to eliminate seizure activity in the patient, or come as close to this goal as possible, without subjecting the patient to unacceptable side effects of drug therapy.* A common misconception concerning seizure management is that the achievement of no more than one seizure per month should be the goal of therapy. Such a goal would be of little benefit to the dog presenting with a history of monthly seizure activity. Alternatively, a dog that seizures daily prior to drug intervention and experiences two seizures per month afterwards would be incorrectly considered a treatment failure, using such arbitrary criteria. Concerns over potential side effects of drug therapy are based primarily on the use of phenobarbital and bromide. With the advent of the alternative anticonvulsant drugs to be discussed in this chapter, improved seizure control is often possible without concurrent adverse side effects. The veterinarian does need to consider, however, that all drugs have the potential for adverse effects on the patient, some of which can be serious.

Pathophysiology[25, 36, 38, 68, 98]

An epileptic seizure is the clinical manifestation of excessive and/or hypersynchronous electrical activity in the cerebral cortex. Neurons are inherently excitable. Defects that alter the excitability of a group of neurons can lead to marked and prolonged depolarization, called a *paroxysmal depolarizing shift*. This can involve neurons in a specific region of the brain (leading to a focal seizure) or involve the entire cerebrum (leading to a generalized seizure). Excessive depolarization can also spread from a focal hyperexcitable area (seizure focus) and excite other

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areas of the brain. Although the precise mechanisms involved are incompletely understood, theories include:

A. Inadequate neuronal inhibition—major inhibitory neurotransmitters include gamma-aminobutyric acid (GABA) and glycine.

B. Excessive neuronal excitation—major excitatory neurotransmitters include aspartate and glutamate.

C. A combination of A and B.

Idiopathic epilepsy is currently considered to represent a group of heterogeneous heritable disorders. In humans and (to a more limited degree) dogs, genetic epilepsy disorders have been identified. Some of these involve abnormal ion channels in the brain and some are suspected to be due to abnormal axonal organization. Regardless of the molecular basis of a specific patient's epilepsy disorder, there is a tendency in humans and dogs for untreated (or inadequately treated) epilepsy to worsen over time (i.e. increased frequency and/or duration of seizures). Proposed mechanisms for worsening seizure activity over time include *kindling* and *mirroring*. *Kindling* refers to recruitment over time of previously nonhyperexcitable neurons into a group of hyperexcitable neurons (the seizure focus) via constant stimulation of these neurons by the seizure focus within a cerebral hemisphere. *Mirroring* is similar to kindling, but involves recruitment of neurons into the seizure focus from the opposite cerebral hemisphere via the corpus callosum. Although any breed of dog can be afflicted with idiopathic epilepsy, there are a number of breeds that are predisposed to this disorder (Box 9.1).

Box 9.1 Dog breeds predisposed to epilepsy

Beagle
Belgian Shepherd
Belgian Shepherd (Tervuren)
Bernese Mountain dog
Border Collie
Boxer
Cocker Spaniel
Collie
Dachshund
Dalmatian
English Springer Spaniel
Finnish Spitz
German Shepherd dog
Golden Retriever
Irish Setter
Irish Wolfhound
Keeshond
Labrador Retriever
Lagotto Romagnolo
Miniature Schnauzer
Nova Scotia Duck Tolling Retriever
Saint Bernard
Siberian Husky
Standard Poodle
Vizsla

Types of seizures[9, 13, 19, 25, 45, 48, 56, 68, 80, 91, 97, 100, 125, 139]

A. Primary generalized seizures

Primary generalized seizures are those in which the initial clinical signs reflect involvement of both cerebral hemispheres. Impairment of consciousness is common and may be the initial sign. Motor manifestations are bilateral. Generalized tonic-clonic seizures, formerly called *grand mal seizures*, are the most common type of seizures in dogs and cats.

1. Generalized tonic–clonic seizures (Video 18)

   The first part of the seizure is the tonic phase, during which there is sustained contraction of all muscles. The animal suddenly loses consciousness and falls to its side in opisthotonus with the limbs extended. Breathing is often irregular or absent, and cyanosis is common. The patient often salivates, urinates, or defecates. The tonic phase lasts for a minute or so and then gives way to the clonic phase, during which there is paddling or rhythmic jerking of the limbs and chewing movements. The clonic phase lasts a variable period of time but usually no more than several minutes. Some animals suffer milder generalized tonic–clonic seizures in which consciousness is maintained.

2. Tonic seizures

   During a tonic seizure, the abnormal motor activity consists only of generalized muscle rigidity without a clonic phase.

3. Clonic seizures

   These seizures consist of paddling and jerking with no tonic component.

4. Atonic seizures

   These rare seizures are manifested as sudden, often brief, losses of muscle tone. There may be a brief drop of the head or the patient may suddenly collapse to the ground.

5. Myoclonic seizures (Video 14)

   These are characterized by brief, shocklike contractions that may be generalized or confined to individual muscle groups. There are other causes of myoclonic jerks; not all myoclonic jerks are seizures.

6. Absence seizures

   Generalized absence seizures in people are defined as abrupt, brief losses of consciousness associated with a specific pattern on electroencephalography (EEG). These were formerly called *petit-mal seizures*, although this term is often used erroneously by veterinarians to refer to any sort of mild seizure. True absence seizures are uncommonly recognized in veterinary medicine and characterized by brief episodes of unresponsiveness, sometimes accompanied by facial twitching and mild limb jerking and 4 Hz spike-and-wave complexes on EEG.

B. Focal (partial) seizures

Focal seizures are those in which the initial clinical signs indicate abnormal activity in one region of a cerebral hemisphere. Simple focal seizures do not impair consciousness, which is recognized as the ability to respond normally to stimuli, such as sound or touch. When consciousness is impaired, the seizure is classified as a complex focal seizure. Any portion of the body may be involved during a focal seizure, depending on the region of the brain affected. Motor signs, autonomic signs, and behavior signs are most common.

1. Focal seizures with motor signs
   Motor signs include rhythmic contractions of facial or masticatory muscles, abnormal movements of one limb, and turning the head to one side.
2. Focal seizures with autonomic signs
   Autonomic signs include hypersalivation, vomiting, gagging, diarrhea, and apparent abdominal pain.
3. Focal seizures with abnormal behavior
   Focal seizures in human patients can cause sensory symptoms such as abnormal skin or vision sensations. Such subjective sensations are difficult to verify in animals, but seizures manifested as licking or chewing at a region of the body and "fly-biting" are probably caused by similar sensations. Complex focal seizures may be manifested as impaired consciousness and bizarre behavior, such as unprovoked aggression or extreme, irrational fear (psychic or psychomotor seizures). In some cases, it is difficult to discriminate between a focal seizure and other types of episodes, such as syncope, narcolepsy, and behavioral disorders.
4. Focal seizure evolving to a generalized tonic–clonic seizure
   A focal seizure may progress to a generalized motor seizure. The secondary spread can occur so rapidly that the initial focal component is missed. In fact, in the past, focal seizures were rarely recognized in animals, but with more detailed history and review of videotaped seizures, it is clear that many dogs with idiopathic epilepsy suffer focal seizures with secondary generalization.

Occasionally, animals will display episodic involuntary movements of one or more body parts without an alteration of consciousness. It is unclear in these disorders whether the underlying cause is actually simple focal seizure activity or some other abnormality. Episodic head tremor occurs in Doberman Pinschers, English and French Bulldogs, Boxers and occasionally other breeds. Affected dogs suffer episodes of horizontal or vertical head tremor with no alteration in consciousness. Other types of episodic repetitive movements occur. These movement disorders may represent simple focal seizures, but some are more similar to human dyskinesias. Dyskinesias are involuntary movements due to abnormalities of the basal nuclei. Still another potential cause for these disorders is an abnormality of neuronal ion channels (ion channelopathies). These movement disorders are discussed in more detail in Chapter 10. Episodic movement disorders have been described in the following breeds: Scottish Terrier, Bichon Frise, Cavalier King Charles Spaniel, Norwich Terrier, Wheaten Terrier, Boxer dog, Chinook dog, and Border Terrier (Spike's disease). Discerning between an involuntary movement disorder and focal seizure activity is sometimes based on EEG results and/or response to antiseizure drugs. Unfortunately, since many of the new antiseizure drugs act on neuronal ion channels (i.e. there is overlap between diseases and underlying molecular mechanisms responsible for those diseases), a positive response to one of these drugs does not necessarily provide a diagnosis of focal seizure disorder.

Stages of a seizure[9, 13, 56, 127]

A. Prodrome
   A *prodrome* is a long-term indication of a forthcoming seizure. The patient may exhibit abnormal behavior, such as restlessness, clinging to the owner, and uncontrolled vocalizing during the hours to days before a seizure. Prodromes are not always recognized.

B. Aura
   An *aura* is the initial sensation of a seizure before there are observable signs. Auras usually last seconds to minutes and are caused by the initial abnormal electrical activity in the brain. In other words, the aura is the start of a seizure. Affected animals may hide, seek their owners, or seem agitated just before a seizure. The difference between a prodrome and an aura is that prodromes are long lasting and not associated with abnormal EEG activity, while auras are short lasting and caused by abnormal electrical activity.

C. Ictus
   The *ictus* is the seizure itself.

D. Postictal stage
   Postictal signs are transient abnormalities in brain function that are caused by the ictus and appear when the ictus has ended. These may include disorientation, restlessness, ataxia, blindness, and deafness. Postictal abnormalities usually resolve after several minutes, but they may last for days, especially after prolonged seizures.

Epilepsy[9, 13, 97, 127]

A. Epilepsy is a condition characterized by recurrent seizures over a long period of time. From a practical standpoint, a useful definition is two or more seizures occurring over a period of at least 1 mo. Epilepsy is not a specific disease; it is a clinical sign.

B. Provoked seizures, also called *reactive seizures*, are seizures that occur at the time of a systemic disorder or brain insult. If the seizures stop when the underlying condition resolves, the patient does not have epilepsy, because the condition is not chronic. Seizures caused by acute toxicity are an example.

C. Idiopathic epilepsy, also called *primary epilepsy*, refers to recurrent seizures in which there is no identifiable brain abnormality other than seizures. It is likely that most, if not all, idiopathic epilepsies have a genetic basis. Most idiopathic epilepsies in human patients are now classified as genetic epilepsy and as the genetic basis of idiopathic epilepsies in dogs and cats becomes clarified it is anticipated that these will likewise be reclassified as genetic.

D. Structural/metabolic epilepsy, previously called *symptomatic epilepsy* or *secondary epilepsy*, refers to recurrent seizures that are caused by an identifiable lesion or other specific etiology.
   1. Structural
      Brain lesions that may cause seizures include degenerative diseases (e.g. storage diseases), hydrocephalus, neoplasia, infectious/inflammatory disease (e.g. meningoencephalomyelitis), trauma, and ischemic/vascular disorders.
   2. Metabolic
      Metabolic disorders that may cause seizures include hepatic encephalopathy, hypoglycemia, electrolyte imbalances (e.g. hypocalcemia), and toxins (e.g. lead, ethylene glycol).

   In general, young animals are prone to infectious diseases, developmental disorders, and storage diseases. Young animals also are more likely to ingest toxins, such as lead. Older animals are at increased risk of neoplasia and vascular disorders. Metabolic causes are usually identified by laboratory analysis and historical evidence of toxin exposure. Diagnosis of structural brain lesions usually entails brain imaging and analysis of cerebrospinal fluid.

Idiopathic epilepsy[3, 11, 23, 36, 37, 39, 40, 44, 49, 50, 58–62, 66, 74, 78, 83, 86, 87, 89, 101, 112, 115, 122]

Idiopathic epilepsy is the most common cause of epilepsy in dogs. Cats with seizures often have an underlying identifiable cause, although idiopathic epilepsy does occur in cats. As mentioned previously, the majority of dogs with idiopathic epilepsy are likely to have specific heritable disorders as the cause of their seizures. There are several consistent features of idiopathic epilepsy in dogs.

A. The age of onset in dogs is usually 1–5 yrs of age, but it is not infrequent for seizures to begin at a young age (less than 1 yr; juvenile epilepsy) or at an older age (late-onset epilepsy). Dogs that have their initial seizure prior to 1 yr of age are frequently encountered. In one report, it was found that 75% of dogs that had their first seizure prior to 1 yr of age were diagnosed with IE (juvenile epilepsy). While it is certainly valid practice to screen young seizuring dogs for the presence of a portosystemic shunt (PSS), it should be kept in mind that this congenital anomaly is actually an uncommon cause of juvenile seizures in dogs. In one report of dogs in which age of seizure onset was > 5 yrs, 35% were diagnosed with primary (idiopathic) epilepsy. In another study of dogs with onset of seizure activity ≥ 7 yrs of age, no identifiable cause for seizures could be found in 21% of cases.
B. Idiopathic epilepsy is inherited in many breeds, including the Beagle, Belgian Shepherd, Belgian Tervuren, Bernese Mountain dog, British Alsatian, Border Collie, Dachshund, English Springer Spaniel, Finnish Spitz, Golden Retriever, Irish Wolfhound, Greater Swiss Mountain dog, Keeshond, Labrador Retriever, Lagotto Romagnolo, Petit Briquet Griffon Vendéen, Shetland Sheepdog, Standard Poodle, and Vizsla. But idiopathic epilepsy can occur in any breed of dog or cat.
C. Generalized tonic–clonic seizures and focal seizures with secondary generalization are the most common types of seizures, but other types of generalized or focal seizures can occur.
D. Seizures usually occur spontaneously and are more common at night or when the patient is resting or sleeping.
E. In a few patients, seizures are regularly elicited by a specific stimulus, called *epilepsy with reflex seizures*. The most commonly recognized stimuli in dogs are loud noises (typically lawn mower or snowblower engines) and visits to the veterinary hospital or groomer.
F. Initially, seizures are usually infrequent (every 4 wks or so), but without therapy or with inadequate therapy seizures tend to increase in frequency.

Diagnostic evaluation[12, 70, 84, 117]

A. Differential diagnosis
   The diagnostic evaluation is designed to determine whether the patient is having seizures, and, if so, the cause of the seizures. Seizures are recognized by their spontaneous onset, stereotypic signs, self-limiting time course, and exclusion of common imitators. Idiopathic epilepsy is a clinical diagnosis based on the typical age of onset, lack of interictal abnormalities, and exclusion of other causes. Symptomatic epilepsy should be suspected when seizures start before 1 yr or after 5 yrs of age, the patient suffers focal seizures, there is a sudden onset of multiple seizures, or there are interictal abnormalities detected on history, examination, or laboratory tests. Several disorders can be mistaken for seizures:
   1. Syncope is characterized by a partial or complete loss of consciousness, lack of violent motor activity, short duration, and lack of postictal signs. It is often associated with exercise and caused by cardiac or respiratory disease.
   2. Narcolepsy is usually manifested as episodes of flaccid paralysis or loss of consciousness precipitated by excitement such as feeding, greeting, or play.
   3. Myasthenia gravis can cause stiffness, tremor, or weakness with normal consciousness. Clinical signs of myasthenia gravis may be induced by exercise. Some myopathies can cause similar clinical signs.

4. Peripheral vestibular dysfunction is characterized by ataxia, head tilt, and abnormal nystagmus with no impairment of consciousness.
5. Episodes of encephalopathy can cause disorientation, ataxia, blindness, and abnormal behavior. Hepatic encephalopathy is an example.
6. Normal or abnormal movements during sleep consist of twitching, paddling, or vocalizing while the patient is asleep. Waking the animal can interrupt these, and there are no postictal signs.
7. Behavior disorders, such as stereotypy, can cause specific patterns of bizarre behavior. These episodes can usually be interrupted, and there are no postictal signs. It should be kept in mind that behavioral disorders can occur in some dogs with idiopathic epilepsy as a component of the disorder or as a comorbid disease.
8. Pain, especially neck pain, can cause episodes of muscle rigidity or stiffness and crying. Consciousness is not impaired.

B. History

1. A detailed and accurate history is the cornerstone of diagnosis. A description of the seizures should be elicited from the client, including seizure frequency and duration, as well as whether there are any focal signs at the start of the seizure, such as turning the head to one side or any jerking of one limb. In some cases it helps if the client videotapes the episodes.
2. Ask the client if the events occur at a certain time of day or in association with situations such as feeding or exercise.
3. Also inquire about any known or suspected familial history of seizures, significant injuries or illnesses, vaccination status, diet, and potential exposure to toxins. Clients should be asked whether any interictal abnormalities—such as changes in behavior, gait, appetite, weight, or sleep habits—have been observed.

C. Examination

A thorough physical examination is important to detect signs of systemic illness that might suggest an underlying cause for the seizures. The clinician should perform a complete neurologic examination to detect any persistent neurologic deficits. Cerebral lesions often cause focal, relatively subtle deficits, such as delayed proprioceptive positioning on one side or blindness in one visual field. Be careful when interpreting the neurologic examination shortly after a seizure, because of the possibility of temporary postictal deficits. Repeating the examination at a later time may be necessary to determine whether any deficits persist.

D. Laboratory evaluation

1. A CBC and serum chemistry profile is indicated to screen for metabolic causes of seizures.
2. Serum bile acids are tested in young animals to identify PSS.
3. Blood-lead determination should be performed in patients with possible exposure to lead, patients from areas with a high incidence of lead poisoning, and in animals less than 1 yr of age.
4. Thyroid function is evaluated in adult dogs because hypothyroidism may complicate seizures, and phenobarbital can affect thyroid testing.

E. Ancillary diagnostic testing

Cerebrospinal fluid analysis and computed tomography (CT) or magnetic resonance (MR) imaging are indicated in dogs with interictal neurologic deficits, seizures refractory to drug therapy, or an onset of seizures at less than 1 yr or greater than 5 yrs of age. These tests are also indicated in any cat with seizures, because idiopathic epilepsy is less common in this species. Although patients with idiopathic epilepsy characteristically have normal MR imaging results, transient MRI brain lesions secondary to seizure activity are occasionally encountered. These lesions tend to be hyperintense on T2-weighted images, do not cause distortion of surrounding brain parenchyma, and tend to occur in several brain regions (e.g. pyriform, temporal, and frontal lobes and the hippocampus). EEG may be helpful in confirming epileptic activity when the veterinarian is unsure whether the events are seizures or nonepileptic episodes.

General aspects of treatment[10, 15, 26, 31, 41, 55, 127]

The goal of therapy is to reduce the frequency and severity of the seizures to a level that does not substantially compromise the quality of life for the pet and family while avoiding serious side effects. Though infrequently addressed in the veterinary literature, there are data that support the assertion that idiopathic epilepsy does have a negative impact on lifespan for dogs with the condition, as has been demonstrated for human epilepsy. In one large prospective study, the most common reason for euthanasia in dogs with epilepsy was inadequate seizure control. Serious adverse effects of phenobarbital and phenobarbital/bromide treatment were reported as an important contributing factor in the decision to euthanize in that study. There is some evidence that males may be more predisposed to idiopathic epilepsy than females. In one study, neutered males with idiopathic epilepsy had shorter survival times than intact males; in this same study, neutered males were more likely to experience cluster seizures, and a history of cluster seizures overall (regardless of gender) had a negative impact on survival time.

Therapy is started once the risks of further seizures outweigh the risks of treatment. The risks of seizures include the seizures themselves as well as the emotional effects on the family. The risks of therapy include drug side effects and the effort and expense of daily medication and monitoring.

Patients with a single seizure, provoked seizures, or isolated seizures separated by long periods of time generally do not require treatment. Treatment is indicated for patients with any episode of unprovoked status epilepticus (SE), multiple seizures in a short period of time, or an underlying, progressive disorder responsible for the seizures. Patients treated early in the course of epilepsy may have better long-term control of their seizures compared to those that have multiple seizures before treatment is started. Establishing an arbitrary number of "acceptable" seizures per month (e.g. one seizure per month) to apply to epileptics is not recommended by the authors for several reasons. One reason, already mentioned, is that untreated seizure activity may lead to increased seizure frequency over time. In addition, a dog or cat that has seizures once a month will not benefit from this approach. In the authors' experience, clients often do not consider monthly seizure activity an acceptable endpoint of therapy. In one study evaluating owners' perspectives concerning epileptic dogs treated with phenobarbital and/or bromide, a seizure frequency of less than one seizure every 3 mos was perceived as adequate control. A more realistic measure of success of an antiseizure drug is a reduction of seizure frequency by at least 50%, with minimal drug side effects. The client needs to understand the goals of therapy, potential side effects, and cost and effort associated with treatment and monitoring. They should appreciate the importance of the regular administration of medication and need to know what to do if a dose is missed (in general, the missed dose is given as soon as the mistake is recognized, then the next dose is given on schedule). Having the client keep a log of the time, date, and characteristics of each seizure and any side effects helps in the assessment of therapeutic efficacy.

Because of the variability in pharmacokinetics among patients, initial dose recommendations are a general guide only. Because of sensitivity to side effects and lack of prior metabolic induction, most new patients are started at the lower end of the dose range. Autoinduction of metabolism will often require an increase in dose in the weeks to months after starting therapy. On the other hand, patients with frequent or severe seizures are often best managed by starting at the higher end of the dose range or using a loading dose. Once the seizures are controlled, the dose may need to be adjusted downward to minimize side effects. Any drug used should be given an adequate chance to work and should not be discarded prematurely. Antiseizure drugs often must be administered for several weeks or longer before obtaining maximum effects. Furthermore, it may take several months or more to adequately evaluate seizure control in a patient that has seizures separated by long periods of time. A common cause of poor seizure control is failure to maximize the dose before discarding a particular drug. This may lead to the need to backtrack at a later date for a second, more aggressive trial. This can be difficult, however, because once a client is convinced a particular drug is ineffective they are often reluctant to agree to a second trial. The therapeutic monitoring of serum drug concentrations can be helpful in determining the optimal dose. Indications for therapeutic monitoring include:

A. When steady-state blood levels are reached after starting treatment, changing dose, or immediately after a loading dose.

B. When seizures are not controlled despite an apparently adequate dose. This helps determine the need for dose adjustment before the drug is changed or a second drug is added.

C. When signs of dose-related toxicity occur, to determine whether a dose decrease is necessary.

D. Every 6–12 mos to verify that changes in pharmacokinetics or compliance have not caused blood concentrations to drift out of the intended range.

Table 9.1 Antiseizure drugs in dogs and cats.

	Dosage	
Drug	**Dog**	**Cat**
Phenobarbital (PB)	3–5 mg/kg, bid	2.5 mg/kg, bid
Potassium bromide (KBr)	35 mg/kg divided, bid	Not recommended
Gabapentin	10 mg/kg, tid	5–10 mg/kg, tid
Felbamate	15 mg/kg, tid	Unknown
Zonisamide	5 mg/kg, bid if not on PB; 8–10 mg/kg bid if receiving PB	10 mg/kg, qd
Levetiracetam	20 mg/kg, tid	20 mg/kg, tid
Pregabalin*	2–4 mg/kg, bid	1–2 mg/kg, bid
Topiramate*	5–10 mg/kg, bid to tid	Unknown
Imepitoin	10–30 mg/kg bid	Unknown

*It is recommended to start both pregabalin and topiramate at a low initial dose (e.g. 2 mg/kg bid) for the first week or two.

First-line antiseizure drugs (Table 9.1)

A. Phenobarbital[15, 21, 27, 31, 127]

1. One of two traditional first-choice drugs for dogs, phenobarbital is the initial drug of choice for cats. Proposed mechanisms of actions include increasing neuronal responsiveness to GABA, antiglutamate effects, and decreasing calcium flow into neurons.
2. Phenobarbital is metabolized primarily by the liver with an elimination half-life is 40–90 hrs in the dog and approximately 40–50 hrs in the cat after oral administration. Ten to 15 days are required to reach steady-state kinetics. Phenobarbital is a potent inducer of hepatic microsomal enzyme activity (e.g. cytochrome P450) and can thus lead to accelerated administration of itself as well as other hepatically metabolized drugs.
3. The initial dose is 3–5 mg/kg orally q 12 hrs in dogs. The range is similar in cats, but a lower initial dose of 2.5 mg/kg orally q 12 hrs is typically administered. After that, the dose is tailored to the individual patient based on seizure control, side effects, and therapeutic monitoring.
4. Serum levels should be checked 2 wks after initiating therapy or changing the dose. The target range is 20–35 μg/ml (85–150 μmol/l). Traditionally, it has been recommended to obtain a "trough" sample immediately before a dose is due. There is no clinically significant impact of the

timing of blood collection (i.e. trough vs. peak level) on the serum phenobarbital level measured in the majority of dogs; however, it is difficult to identify the minority of dogs in which sample time *is* important. Serum separator tubes should be avoided because the silicone will bind phenobarbital.

5. Sedation, ataxia, polyuria/polydipsia, and polyphagia are common dose-dependent side effects. Sedation and ataxia often improve after several weeks of therapy. Blood dyscrasia is a rare, possibly idiosyncratic adverse effect in dogs that necessitates withdrawal of the drug. Superficial necrolytic dermatitis is a less common side effect in dogs. Uncommon phenobarbital-associated side effects reported in cats include facial pruritus, generalized pruritus with distal limb edema, thrombocytopenia, and leukopenia. There is one report of a cat with severe cutaneous eruptions and lymphadenopathy associated with phenobarbital use; the suspected hypersensitivity reaction resolved shortly after discontinuing phenobarbital therapy.
6. Elevation of liver enzymes, especially alkaline phosphatase, is common in dogs. This does not necessarily indicate clinically significant liver disease or the need to stop therapy. A common mistake is to withdraw phenobarbital based only on laboratory findings of elevated liver enzyme activity. The risk of liver toxicity appears to be greater with blood concentrations higher than 35 μg/ml or when multiple, potentially hepatotoxic drugs are used.
7. Phenobarbital decreases thyroxine and free thyroxine and increases thyroid-stimulating hormone in dogs, usually without inducing clinical signs of hypothyroidism. Phenobarbital has no measurable effect on adrenal function tests in dogs.

B. Bromide[14–17,31,43,96,104,131,132]

1. Bromide is commonly used as the initial therapy for the dog, although phenobarbital is more effective with fewer side effects. Bromide is also added to phenobarbital when the seizures are not adequately controlled despite serum phenobarbital levels of 20–35 μg/ml. The bromide ion is believed to hyperpolarize neuronal membranes after traversing neuronal chloride channels. Bromide is renally excreted and is a good choice for dogs with liver disease.
2. Bromide appears to be considerably less effective in cats than in dogs. Additionally, between 35 and 42% of cats taking bromide develop pneumonitis characterized by coughing, dyspnea, and a bronchial pattern on chest radiographs. These signs typically resolve within 1–2 mos of stopping bromide. Because of questionable efficacy and the potential for severe side effects, bromide is not recommended by the authors for use in cats.
3. Bromide is administered as potassium bromide or sodium bromide in solution or capsules. Use of the solution is typically less expensive and makes it easier to adjust the dose. There is no difference in efficacy for the potassium or sodium salt, although potassium bromide is preferred when sodium intake must be restricted (e.g. congestive heart failure). Sodium bromide is preferred when potassium intake must be restricted (e.g. hypoadrenocorticism). Bromide can be compounded by many pharmacists.
4. The elimination half-life is 24 days in dogs, 11 days in cats. It takes approximately 80–120 days to reach steady-state kinetics in dogs, 6 wks in cats.
5. The initial maintenance dose for potassium bromide is 20–35 mg/kg, orally once daily, or divided twice daily. If sodium bromide is used, the dose should be decreased by 15% (i.e. 17–30 mg/kg) to account for the higher bromide content of the sodium salt. The dose is subsequently adjusted based on clinical effects and therapeutic monitoring.
6. A loading dose is used if faster control of seizures is necessary. However, side effects are more common with loading doses.
   a. 24-hr loading dose
      1. A total dose of 400–600 mg/kg of potassium bromide is administered orally over 24 hrs.
      2. This is divided into doses of 100 mg/kg (the lower end of the range) q 6 hrs, for a total of four doses.
      3. If the patient appears obtunded prior to a dose, skip it and resume when the patient is alert again.
      4. After loading, begin the regular dose the next day.
      5. This schedule is used in patients that need adequate seizure protection immediately.
      6. The patient should be hospitalized for this loading procedure.
   b. Five-day loading dose
      1. Administer 450 mg/kg of potassium bromide over 5 days.
      2. The daily loading dose (90 mg/kg) is added to the maintenance daily dose (35 mg/kg) for a total oral daily dose for each of the 5 days of 125 mg/kg/day. This dose should be divided bid to avoid gastrointestinal irritation.
      3. On day 6, the maintenance dose is started.
7. A serum bromide level is checked within 1 wk after loading or 3 mos after starting a maintenance dose. The timing of sample collection is unimportant because of the long half-life. The target range is 1–3 mg/ml for patients taking bromide alone and 1–2 mg/ml for those taking bromide and phenobarbital.
8. Bromide competes with chloride for renal elimination. High chloride intake increases bromide elimination, which increases the dose requirement. Thus, the chloride content of the diet should not be drastically altered during treatment.

9. Renal insufficiency decreases bromide elimination, so in dogs with persistent isosthenuria or azotemia, the initial dose of bromide should be halved and serum bromide concentrations monitored closely.
10. When adding bromide in dogs taking phenobarbital, the phenobarbital dose can be gradually tapered if the seizures are well controlled once the serum concentration of bromide is at least 1.5 mg/ml.
11. Side effects of bromide in dogs are usually dose-dependent and include pelvic limb stiffness and ataxia, sedation, vomiting, polydipsia/polyuria, polyphagia, hyperactivity, megaesophagus, and pruritic skin rash. Uncommon behavioral abnormalities (e.g. aggressiveness) have been attributed to bromide administration. Pancreatitis has been associated with bromide use, either alone or in combination with phenobarbital. Chloride levels are often artificially elevated on serum chemistry panel results because some assays cannot distinguish between chloride and bromide ions. Anecdotally, the authors have encountered several canine seizure cases in which the dogs developed a persistent cough that seemed to be associated with bromide therapy. Coughing activity resolved shortly after bromide discontinuation in these dogs. If a bronchial asthma-like condition is a potential side effect of bromide therapy in dogs, it is likely a comparatively rare development in contrast with cats. Development of a persistent cough in a dog receiving bromide therapy should alert the clinician to the possibility of a bromide-related side effect, especially if other diagnostic tests do not lead to a cause for the cough.

C. Diazepam[15, 24, 57, 127]
  1. Benzodiazepines are believed to exert anticonvulsant activity by enhancing GABA effects in the brain. Benzodiazepines are metabolized primarily by the liver. The short half-life of diazepam in dogs (2–4 hrs) and the development of tolerance limit the use of this drug for maintenance therapy. Diazepam is used in dogs and cats intravenously or rectally for the emergency treatment of seizures.
  2. In cats, diazepam can be used as a maintenance drug (0.5–2.0 mg/kg/day, PO, q 8 or 12 hrs). Fatal hepatic necrosis has been associated with oral diazepam in cats. Liver enzymes are checked at 1 wk and 1 mo after starting therapy.

Second-line drugs

Several other drugs are used when seizures are not adequately controlled with phenobarbital and bromide or the patient cannot tolerate first-line drugs because of adverse effects. Because of limited clinical experience, there is no clear consensus on the order in which second-line drugs should be tried, but in the authors' experience, zonisamide and levetiracetam (LEV) in dogs and in cats may offer the best combination of efficacy and tolerability in patients refractory to first-line therapy. These drugs are also considered first-line therapy when clients wish to minimize adverse effects. In particular, zonisamide appears to work very well in dogs as a first-line drug in the authors' experience, with minimal side effects. Since zonisamide has become a generic drug, cost concerns have diminished considerably.

A. Clorazepate[15, 20, 31, 110, 127]
  1. Clorazepate is a benzodiazepine that is sometimes effective when added to phenobarbital and/or bromide in dogs. Clinical experience in cats is limited.
  2. Clorazepate has an elimination half-life of between 3 and 6 hrs in dogs after oral administration. The initial dose is 0.5–1.0 mg/kg orally every 8 hrs. Sustained-delivery tablets are available but offer no advantage over regular-release tablets in dogs.
  3. Serum levels of the active metabolite (nordiazepam) tend to decrease with time, so subsequent dose increases are usually necessary. The long-term use of clorazepate may lead to the development of tolerance to antiseizure effects. Hepatotoxicity is also a potential side effect of clorazepate use.
  4. Clorazepate often increases phenobarbital concentrations, which can lead to side effects, so phenobarbital levels should be closely monitored.
  5. In the authors' experience, the main indication for oral clorazepate use is as a short-term at-home treatment for dogs having cluster seizures.

B. Primidone[31, 114]
  1. The efficacy of primidone is similar to that of phenobarbital in dogs. However, clinical experience suggests that primidone carries a greater risk of liver disease compared to phenobarbital. Therefore there is no reason to use this drug in dogs.
  2. Primidone may be toxic to cats.

C. Felbamate[1, 2, 29, 31, 105, 134, 141]
  1. Felbamate improves seizure control in some dogs refractory to phenobarbital and bromide. Anecdotally, it also appears to be effective as an antiseizure drug when used alone. There are several proposed mechanisms of action for felbamate, including interfering with voltage-gated sodium channels, antagonizing *N*-methyl-d-aspartate (NMDA) preferring glutamate receptors, and interfering with the binding of glycine. Approximately 30% of the oral dose of felbamate undergoes hepatic metabolism, the remainder being excreted in the urine. The elimination half-life in dogs is typically between 5 and 6 hrs (range: 4–8 hrs). Felbamate may also offer some protection to neurons from hypoxic or ischemic damage. Felbamate is well absorbed after oral administration in adult dogs, but bioavailability in puppies may be only 30% that of adults. The half-life of elimination has also been shown to be much shorter in puppies than in adult dogs

(approximately 2.5 hrs). There is no clinical information available concerning the use of felbamate in cats.

2. The initial dose is 15 mg/kg every 8 or 12 hrs. This can be increased in 15 mg/kg increments every 2 wks until seizures are controlled, side effects occur, and/or the drug becomes cost-prohibitive. Doses as high as 70 mg/kg every 8 hrs are required and tolerated well in some dogs. The toxic dose of felbamate in dogs is 300 mg/kg/day. The reported therapeutic range for felbamate in people is very broad, ranging from 20 to 100 μg/ml. Because of this factor, the high cost of felbamate assays, and the low toxicity potential of felbamate, drug monitoring is usually not pursued.
3. Side effects are uncommon, and this drug is typically not sedating. Nervousness, hyperexcitability, and decreased appetite can occur at high doses. Felbamate may increase the risk of liver dysfunction, especially in dogs taking other potentially hepatotoxic drugs. Other side effects attributed to felbamate use in dogs include reversible blood dyscrasia (e.g. thrombocytopenia, leukopenia), keratoconjunctivitis sicca (KCS), and generalized tremors in small-breed dogs (considered rare).
4. Caution should be exercised when felbamate is used with other drugs metabolized by the liver, especially through the cytochrome P450 system. For example, felbamate may increase plasma levels of phenobarbital.
5. Because of the potential for hepatotoxicity, it is recommended that serum biochemistry analysis be performed every 6 mos for dogs receiving felbamate, especially if it is given concurrently with phenobarbital. It may also be advisable to evaluate CBCs every few months in the unlikely event that blood dyscrasia develops.
6. Due to the problems of hepatotoxicity and blood dyscrasias (typically aplastic anemia in people) occasionally associated with felbamate use in people, a new derivative of the drug (fluorofelbamate) has been developed and is undergoing clinical trials for human use. A reactive aldehyde intermediate that is formed during felbamate metabolism has been linked to the drug's hepatic and hematologic side effects. This toxic intermediate is not produced during the metabolism of fluorofelbamate. In experimental animal epilepsy models, fluorofelbamate has been shown to have equal or superior anticonvulsant potency in comparison with felbamate.

D. Gabapentin (and pregabalin)[15, 31, 33, 47, 93, 102, 108, 118, 127]

1. Gabapentin, a structural analog of GABA, is sometimes beneficial in dogs with seizures that are refractory to other drugs. Previously suspected mechanisms of action for gabapentin include inhibition of voltage-gated neuronal sodium channels and enhancement of the release or actions of GABA in the brain. Recent evidence supports the main mechanism of action to be through the inhibition of voltage-gated neuronal calcium channels via specific binding of the drug to the α2δ-subunit of these channels. The inhibition of calcium flow reduces release of excitatory neurotransmitters, including glutamate, noradrenaline, and substance P. Although gabapentin is excreted completely by the kidneys in people, about 30–40% of the dose undergoes hepatic metabolism in dogs. However, there does not appear to be any appreciable induction of hepatic microsomal enzymes in this species. The elimination half-life for gabapentin is 3–4 hrs in dogs and 2.5–3.5 hrs in cats.
2. The recommended dose range for gabapentin in dogs is 25 to 60 mg/kg body weight, divided into doses administered every 6–8 hrs. The authors recommend an initial dose regimen of 10 mg/kg body weight q 8 hrs. The suspected therapeutic range for dogs is 4–16 mg/l, but drug monitoring is seldom pursued for gabapentin.
3. Side effects appear to be uncommon and are typically limited to mild sedation, pelvic limb ataxia, and increased appetite with attendant weight gain.
4. Gabapentin appears to be a moderately effective anti-seizure drug for dogs. In one study evaluating gabapentin as an add-on drug for dogs with refractory seizures, there was no significant decrease in overall seizure frequency over a 4-mo evaluation period. Despite this, three of 17 dogs were seizure-free during this period, and four others had experienced a 50% or more decrease in seizure frequency. In a similar study of 11 dogs, five dogs experienced a 50% or more reduction of seizures after starting gabapentin, and there was an overall significant decrease in seizure frequency.
5. There exists only anecdotal information regarding gabapentin use in cats. An oral dose of 5–10 mg/kg body weight administered every 8–12 hrs has been suggested, but to the authors' knowledge there are no data regarding the safety or efficacy of chronic gabapentin administration to cats.
6. Pregabalin, a new gabapentin analog (effectively the next generation of gabapentin), has recently been approved for human use and is commercially available. Pregabalin has an increased affinity for the α2δ-subunit of voltage-gated calcium channels, compared with gabapentin, and is purportedly more effective in people than its predecessor. The elimination half-life of pregabalin in dogs is approximately 7 hrs. In a small, prospective clinical trial involving epileptic dogs, pregabalin (as an add-on therapy) was associated with an overall reduction in seizures of 57%. The responder rate in this study was 78% and those dogs had a mean seizure reduction of 64%. The main adverse effect of pregabalin appears to be sedation. The target dose for epilepsy is about 3–4 mg/kg, q 8–12 hrs. However, the starting dose should be 2 mg/kg, q 12 hrs for at least the first week, in order to avoid severe sedation. The dose can be increased, if necessary, by 1 mg/kg (q 12 hrs) per week until the target dose of 3–4 mg/kg is reached.

The elimination half-life of pregabalin in cats is approximately 11 hrs. The authors have had anecdotal success treating epileptic cats with pregabalin. The dose range we have used for cats, based on pharmacokinetic data, is 1–2 mg/kg, q 12 hrs. As with dogs, it is best to start at the low end of the range (i.e. 1 mg/kg, q 12 hrs) in order to avoid excessive sedation.

E. Zonisamide[18, 28, 35, 53, 71, 79, 113, 136, 138]

1. The sulfonamide derivative zonisamide has several potential mechanisms of action, including blockage of T-type calcium and voltage-gated sodium channels and binding to the chloride channel associated with GABA.
2. Zonisamide is metabolized primarily by hepatic microsomal enzymes and the half-life of elimination in dogs is approximately 15 hrs. In people, it has been shown that the elimination half-life of zonisamide is dramatically shorter in patients already receiving drugs that stimulate hepatic microsomal enzymes (e.g. phenobarbital) as compared with patients who are not receiving such drugs. A similar phenomenon appears to occur in dogs also. The half-life elimination in cats is 33 hrs.
3. When used as an add-on therapy for dogs already receiving phenobarbital, the recommended dose regimen is 10 mg/kg PO, q 12 hrs. This dosing schedule has been shown to maintain canine serum zonisamide concentrations within the therapeutic range reported for people (10–40 μg/ml) when used as add-on therapy. For dogs not receiving phenobarbital, it is recommended to start zonisamide at a dosage of 5 mg/kg PO, q 12 hrs. The authors generally check trough serum zonisamide concentrations after approximately 1 wk of zonisamide treatment.
4. Zonisamide has a high margin of safety and is well tolerated in dogs. Mild side effects—such as transient sedation, ataxia, and vomiting—may occur and are more common when the drug is used as an add-on therapy (about half of the patients will experience some level of side effect). Hepatotoxicity associated with zonisamide use has been reported in dogs but is considered to be uncommon. In addition, the development of renal tubular acidosis in one dog was associated with zonisamide use.
5. Zonisamide appears to be a very effective add-on antiseizure drug in dogs. In one study, zonisamide was found to decrease seizure frequency by at least 50% in seven of 12 dogs with refractory idiopathic epilepsy. In this responder group, the mean reduction in seizure frequency was 81.3%. In six of the seven responder dogs, phenobarbital was able to be reduced by an average of 92.2%. In another similar study, nine of 11 dogs receiving zonisamide were responders, with a median seizure reduction of 92.9%.
6. Zonisamide has been shown to be effective as a sole antiseizure drug in people. Anecdotally, zonisamide appears to be effective as a sole antiseizure drug in dogs as well. In addition, side effects are typically minimal to absent with zonisamide when used as the sole antiseizure drug in dogs.
7. There are clinical data regarding the safety or efficacy of zonisamide in cats, although the authors have treated several cats with zonisamide as initial therapy and as add-on therapy with apparent success. A suggested dose is 10 mg/kg once daily. In one chronic-dosing pharmacokinetic study in cats, three of six cats dosed orally at 20 mg/kg daily for 9 wks exhibited somnolence, ataxia, vomiting, and diarrhea. The authors have found that some cats treated with zonisamide will develop anorexia which will only resolve with discontinuation of zonisamide administration.

F. Levetiracetam (LEV)[6, 8, 22, 30, 32, 42, 51, 52, 73, 75, 76, 81, 88, 92, 124, 135]

1. Levetiracetam is a pyrrolidine-based antiseizure drug. Previously suspected modes of actions include inhibiting voltage-gated calcium channels and ameliorating allosteric inhibition of GABA and glycine channels. The main mechanism of action of LEV appears to be linked to its specific binding to synaptic vesicle protein 2A (SV2A) in the brain. The mechanism of action related to this binding appears to be related to neuronal calcium flow, but the exact mechanism is unknown. LEV has demonstrated neuroprotective properties and may ameliorate seizure-induced brain damage. The drug has also been reported to have an "antikindling" effect, which may diminish the likelihood of increasing seizure frequency over time.
2. LEV is nearly 100% bioavailable after oral dosing in dogs and cats with a half-life of elimination of approximately 4 hrs in dogs and 3 hrs in cats. Despite the short half-life, there is evidence that the anticonvulsant actions of LEV may persist for some time after serum drug levels have dissipated. Approximately 70–90% of the drug is eliminated unchanged in the urine, the remainder being hydrolyzed in the serum and other organs. There is no hepatic metabolism of LEV, and it is very safe in dogs. However, there is evidence that LEV metabolism is accelerated substantially over time in dogs concurrently receiving phenobarbital. Salivation, restlessness, vomiting, and ataxic gait are observed at doses exceeding 400 mg/kg/day. These side effects resolve within 24 hrs of drug discontinuation (data on file at UCB Pharma Inc.).
3. The dose of LEV that has been recommended for dogs and cats is 20 mg/kg, q 8 hrs. Major side effects at this dose are uncommon, with sedation and ataxia being reported most commonly. Dogs often experience no apparent side effects from LEV therapy. The effective serum LEV concentration in people is thought to be between 5 and 45 μg/ml, though the clinical relevance of this range is somewhat in question. At 20 mg/kg, every 8 hrs, LEV was initially reported to improve seizure control in dogs with epilepsy. Subsequent to that report, however, LEV was shown to be ineffective as an add-on antiseizure drug in a placebo-controlled clinical trial. There was also one

report suggesting that LEV has a distinct "honeymoon" effect in dogs, working fairly well initially then trailing off in efficacy over time. In the placebo-controlled LEV study, it was found that 38% of dogs had LEV plasma drug concentrations below what is considered the lower limit of the therapeutic range for the drug. The authors suspect that a higher initial dose of LEV should be used in epileptic dogs (e.g. 30 mg/kg, q 8 hrs), especially if they are concurrently receiving phenobarbital therapy. In another more recent retrospective study in epileptic dogs, LEV was determined to be an effective antiseizure drug, when used either as a maintenance drug or as pulse therapy (for cluster seizures). Side effects were much more likely (65 vs. 34%) in the pulse therapy group.

4. LEV is well tolerated and apparently effective in epileptic cats when used as an adjunct to phenobarbital at a dose of 20 mg/kg, q 8 hrs. In one report, the responder rate was 70%, with an average reduction in seizure activity of 92.4%. Two of 12 cats were transiently (1–2 wks) lethargic and exhibited inappetence after starting oral LEV; these side effects resolved without changing the dose of LEV. There does not appear to be a prominent "honeymoon" effect for LEV with cats, as has been observed with dogs.
5. An injectable form of LEV has been shown to be well absorbed when given IV, IM, or per rectum in dogs. This form of LEV has also been shown to be an effective emergency antiseizure drug in this species.

G. Topiramate [63]

1. Topiramate is a sulfamate-substituted monosaccharide that is thought to work on multiple cell-signaling mechanisms. These mechanisms include enhancing of GABAergic activity, inhibition of voltage sensitive calcium and sodium channels, inhibition of kainate-evoked currents, and inhibition of carbonic anhydrase isoenzymes.
2. The elimination half-life of topiramate in dogs is 2–4 hrs.
3. In one clinical study of 10 epileptic dogs, five of 10 dogs (50%) treated with topiramate as an add-on to phenobarbital and bromide were considered responders (≥ 50% seizure reduction) in the short term (6-mo follow-up) and three of these dogs remained responders over a longer term (additional 3–9 mos) follow-up.
4. The proposed dose range from the clinical study in dogs is 5–10 mg/kg q 8–12 hrs. It was recommended to start at a low dosage first (2.0 mg/kg q 12 hrs) and build up to a higher dose, in order to minimize sedation.
5. Reported side effects of topiramate in dogs included sedation and ataxia.

H. Imepitoin[106, 128]

1. Imepitoin is an imidazolinone derivative that is a low-affinity partial agonist at the benzodiazepine site of $GABA_A$ receptors.
2. The elimination half-life of imepitoin in dogs is 1.5–2 hrs. It has a very high bioavailability (92%) and exhibits dose linearity. Imepitoin does not appear to affect hepatic microsomal P450 enzymes and is excreted primarily in the feces. Imepitoin does not cause elevations of hepatic enzymes (ALT, SAP, GGT). Reported side effects of this drug include sedation, PU/PD, increased appetite and mild, transient hyperactivity. Side effects in dogs receiving imepitoin were significantly less likely than in dogs receiving phenobarbital in a clinical trial.
3. In one large prospective clinical trial, imepitoin was comparable in efficacy to phenobarbital for the treatment of canine idiopathic epilepsy.
4. The oral dose range for imepitoin based on one pilot study and the large prospective trial is 10 to 30 mg/kg, bid. The mean doses in these studies were 15 and 20 mg/kg bid, respectively.
5. Imepitoin is not yet available for clinical use in the United States; it is available for clinical use in Europe.

Drugs under investigation for dogs[69, 140]

Rufinamide and Lacosamide are two commercially available antiseizure drugs that have shown some level of efficacy in treating human epilepsy disorders. Both drugs are believed to act by prolonging the inactivation of sodium channels in the brain. Lacosamide has also been used for neuropathic pain control in people, and is available in both an oral and injectable form. A proposed oral Rufinamide dosage regime for dogs, based on a pharmacokinetic study, is 20 mg/kg, q 12 hrs. There is no proposed Lacosamide dose schedule for dogs as of yet, but the elimination half-life is about 3.5 hrs for this drug, based on limited pharmacokinetic data. There are no clinical data regarding the use of either of these drugs in canine epilepsy. Both of these drugs are considerably expensive.

Ineffective and contraindicated anticonvulsant drugs[15, 31, 111, 120, 126, 127]

There are several older drugs used in human patients that are ineffective in dogs, usually because of short elimination half-lives. These include phenytoin, carbamazepine, valproic acid, and ethosuximide. These drugs are also either known or suspected to be toxic to cats. More-recently introduced drugs that have been suggested for canine use include vigabatrin, lamotrigine, oxcarbazepine, and tiagabine. There are limited data regarding the use of these newer drugs in canine seizure management. However, their short elimination half-lives in combination with their expense make it unlikely that they will be useful drugs for the management of seizures in dogs. One study investigating vigabatrin as an add-on therapy in refractory epileptic dogs found it to be of questionable efficacy; also, two of the 14 dogs receiving the drug developed hemolytic anemia. Lamotrigine has an elimination half-life of only 2–3 hrs in dogs and undergoes significant hepatic metabolism to a potentially cardiotoxic compound. Oxcarbazepine appears to induce its own hepatic metabolism in dogs, having only a 1-hr elimination half-life after 8 days of repeated oral dosing. The half-life of tiagabine in dogs is about 2 hrs; in addition, this drug has been shown to result in marked sedation and visual impairment at fairly low doses. None of these newer antiseizure drugs is recommended for cats, as toxicity data for this species are nonexistent.

Other treatments[4, 5, 46, 64, 65, 77, 85, 90, 121, 142]

A. Surgery
Surgery is an accepted alternative for human patients with certain types of refractory epilepsy. Focal cortical resection is based on using EEG or other techniques to identify the region of the cortex where the seizures originate (the seizure focus) and surgically resecting the focus. Because the ability to identify the seizure focus in veterinary patients is currently limited, resective surgery has not been pursued in animals with idiopathic epilepsy. Surgical division of the corpus callosum is designed to prevent a seizure originating in one cerebral hemisphere from spreading via the corpus callosum to the other hemisphere. This technique has been used in a small number of dogs with refractory seizures, but long-term results in a large number of dogs have not been reported.

B. Vagus nerve stimulation
Electrical stimulation of the vagus nerve by an implantable pulse generator, similar to a pacemaker, is an effective adjunctive therapy for medically refractory focal and generalized seizures in human patients. The mechanism of the antiseizure effects is not completely understood, but stimulation of afferent fibers in the vagus nerve probably acts to modify electrical activity in the brain to lessen seizure susceptibility. This technique improves seizure control in some dogs with epilepsy poorly controlled with medication. Adverse effects are minimal, but currently the expense of the device limits the use of this technique in dogs. Applying digital ocular pressure (ocular compression) may have some clinical utility in the emergency setting; this maneuver is believed to provide an antiepileptic effect via vagal stimulation.

C. Acupuncture
Several reports describe acupuncture to treat dogs with epilepsy. Techniques vary, but they include implantation of gold beads or acupuncture needles at specific locations. Although controlled trials assessing safety and efficacy are lacking, the use of acupuncture by a veterinarian trained in this technique can be considered in dogs with medically refractory idiopathic epilepsy.

D. Ketogenic diets
The beneficial effects of fasting in people with epilepsy have been recognized for centuries. In 1921, Wilder proposed that the ketosis and acidosis resulting from minimal caloric intake produced an antiseizure effect. As a result, he introduced a high-fat, low-carbohydrate, and low-protein diet that induced a metabolic condition similar to fasting. The ketogenic diet is used primarily in children with medically refractory epilepsy. Several forms of the diet are recognized. For example, in the 3:1 ketogenic diet, 87% of calories are from fat, 6% from carbohydrates, and 7% from protein. The major drawback is compliance, as the diets are unpalatable and require precise calculation and close monitoring. It is important to realize that a ketogenic diet is not just a high-fat diet but includes severe restriction in carbohydrates and protein. Simply adding a source of fat to a standard diet does not constitute a ketogenic diet.

A trial of a high-fat, low-carbohydrate diet (57% fat, 5.8% nitrogen-free extract, 28% protein) in dogs with epilepsy failed to show improved seizure control compared to a control diet.

Refractory epilepsy[25, 31, 82, 96, 127, 133]

Epilepsy is refractory when the patient's quality of life is compromised by frequent or severe seizures despite appropriate drug therapy. Approximately 25 to 30% of dogs with epilepsy are believed to be refractory cases. In patients with apparent refractory epilepsy, it is essential to search for errors in diagnosis or management that may be responsible for treatment failure. Diagnostic errors include failure to recognize nonepileptic paroxysmal disorders and underlying causes for the seizures. A thorough history, careful examination, and appropriate use of ancillary diagnostic tests, such as imaging and cerebrospinal fluid analysis, help avoid diagnostic errors. The use of ineffective drugs, incorrect dosing, and poor compliance are common causes of treatment errors. Other factors that may impede efficacy should also be considered. For example, intact female epileptics may exhibit refractoriness to drug therapy because estrogen lowers the seizure threshold; an association between seizure activity and the estrous cycle has been documented in intact female epileptic dogs. Therapeutic monitoring is helpful in identifying low blood concentrations caused by insufficient dosage or poor compliance. Referral to a neurologist should be considered if seizures are not controlled after 3 mos of diligent therapy or if the diagnosis is uncertain. In a large (> 300 dogs) retrospective study of epileptic dogs, risk factors for refractoriness to drug therapy in epileptic dogs were identified; these risk factors included sex (male dogs are more likely to be refractory) and a history of cluster seizures.

Status epilepticus and cluster seizures[7, 34, 72, 94, 95, 99, 107, 116, 119, 123, 137]

A. Status epilepticus (SE)
Status epilepticus is (1) a continuous seizure lasting at least 5 min or (2) two or more discrete seizures without full

recovery of consciousness between seizures. This severe form of seizure activity is relatively frequent among dogs with idiopathic epilepsy, but it can occur with seizure disorders of any etiology. Approximately 60% of dogs with idiopathic epilepsy require admission for emergency treatment of status at some point. Large-breed dogs are at an increased risk. Status is a life-threatening emergency. Continuous seizure activity of 30 min or longer may cause systemic dysfunction—including hypoxia, altered blood pressure, and hyperthermia—and can lead to temporary or permanent brain lesions. The most common type of SE is generalized tonic–clonic status. With a prolonged seizure, the clinical manifestations can eventually become subtle, with only altered mentation and small twitching movements of the face or limbs. This situation is called electromechanical disassociation and should still be treated.

B. Cluster seizures

Cluster seizures (serial seizures, acute repetitive seizures) are two or more seizures occurring over a brief period but with the patient regaining consciousness between the seizures. For practical purposes, the occurrence of more than three seizures in a 24-hr period should be considered an emergency condition that may evolve into SE and should be treated. Cluster seizures activity is a common clinical presentation in dogs with idiopathic epilepsy; in one large retrospective study of epileptic dogs, cluster seizure activity was documented in 41% of patients. This study also found that German Shepherd and Boxer dogs were overrepresented in the cluster seizure group, and that intact males and females were more likely to suffer cluster seizures than neutered epileptic dogs.

C. In-hospital treatment

1. Stop the seizure
   a. Administer diazepam at 0.5–1.0 mg/kg, IV. Repeat for a total of three doses as necessary to stop the seizure. The duration of antiseizure effects is 30 min or less, so a longer-lasting antiseizure drug should also be administered (see below). Other injectable benzodiazepine drugs have been suggested for clinical use for the emergent management of canine and feline seizure activity, though data are currently limited to pharmacokinetic information. Midazolam has a rapid onset of action and short elimination half-life after IV or IM administration. This drug may be more effective and somewhat safer than equivalent doses of diazepam. A recommended dose for IV or IM midazolam for dogs and cats is 0.5 mg/kg body weight. Lorazepam has more potent activity than diazepam at the benzodiazepine receptor and lasts longer than diazepam after IV administration. Intravenous lorazepam use has become preferable to IV diazepam in human emergency seizure management. In dogs, an IV lorazepam dose of 0.2 mg/kg body weight is well tolerated and results in serum drug concentrations within the therapeutic range reported for people. Both midazolam and lorazepam are well absorbed after intranasal administration to dogs, but apparently not with rectal administration. Intranasal administration of drugs to a dog during seizure activity carries some risk of being inadvertently bitten by the patient.
   b. If three doses of diazepam do not stop the seizure, there are several options:
      1. Administer injectable LEV of 20–60 mg/kg over 5 min. This results in rapid achievement of plasma LEV concentrations within or above the therapeutic range for at least 8 hrs. Intramuscular injection has 100% bioavailability and is an option if intravenous access is not immediately available.
      2. Administer propofol at 1–2 mg/kg, IV. Be prepared to place an endotracheal tube and assist ventilation. Antiseizure effects can be maintained with a constant infusion of propofol at 0.1–0.6 mg/kg/min, titrated to effect.
      3. Administer ketamine at 5 mg/kg IV. A constant rate infusion of 5 mg/kg/hr of ketamine can be administered to maintain antiseizure effects.
      4. Administer pentobarbital intravenously at 2–15 mg/kg, IV, over several minutes, to effect. This drug enters the brain slowly, compared with diazepam, so allow several minutes to assess effects. Endotracheal intubation will be necessary.
      5. Administer phenobarbital at 2–6 mg/kg IV, to effect. This may take even longer to effect anticonvulsant action (15–20 min). However, some prefer this drug because it has more anticonvulsant activity than pentobarbital at doses that do not induce anesthesia.
      6. Induce general anesthesia with isoflurane.
2. Provide supportive care and initiate diagnostic evaluation
   a. Administer oxygen, usually by facemask in conscious animals or by endotracheal tube in unconscious patients. Assist ventilation as necessary.
   b. Place an intravenous catheter and obtain a blood sample to check glucose, calcium, packed cell volume, and total solids. Hydration and blood pressure are maintained as necessary with fluid therapy.
   c. Monitor temperature and treat hyperthermia if necessary. Wet towels and a fan are helpful in cooling patients. Active cooling is stopped once body temperature falls to 104°F to avoid hypothermia. Cool water enemas are effective but make it more difficult to monitor rectal temperature.
3. Prevent further seizures
   a. Start phenobarbital. Approximately 20 min are required for phenobarbital to enter the brain and exert antiseizure effects. If the seizures have stopped and the animal is conscious enough to swallow, initiate oral phenobarbital at 3–5 mg/kg, q 8–12 hrs.

If the patient cannot swallow or has a weak gag reflex, administer IM until the animal is awake enough to swallow.

b. Some status/cluster patients may not be conscious enough to swallow orally administered drugs. Also, some patients may already have an adequate phenobarbital level at the time of the status/cluster episode and need to be started on another drug. In these situations, intrarectal bromide can be administered as a loading dose over a 24-hr period. The loading schedule for liquid potassium bromide by rectum is 100 mg/kg, q 4 hrs, for six doses (total of 600 mg/kg body weight). The bromide is administered via a syringe and red rubber feeding tube. This dosing schedule will effectively achieve a serum bromide level in the lower end of the target range. Rectally administered bromide is nearly 100% bioavailable. Side effects of this protocol include mild sedation and transient diarrhea.

c. Seizure activity may resume. This is common because of the short duration of antiseizure effects with diazepam. After again stopping the seizure activity, there are several options:
    1. Diazepam infusion at 0.5–2.0 mg/kg/hr in 5% dextrose or 0.9% saline.
    2. Propofol infusion at 6 mg/kg/hr.
    3. Infusions are titrated to effect to control seizures. Blood pressure, body temperature, tissue oxygenation, and hydration are kept within normal limits. The patient is turned at least every 4 hrs. Palpate the urinary bladder and express if needed at least three times daily. The patient is kept warm, clean, and dry. Some patients require heavy sedation for 24–72 hrs, yet will still recover. Overall, about two-thirds of dogs hospitalized for SE recover and leave the hospital.

D. At-home treatment
  1. Despite appropriate maintenance therapy, some patients, especially large dogs, tend to suffer cluster seizures that require emergency treatment. The resulting financial and emotional drain on the client is a common cause of euthanasia. Rectal administration of diazepam by the client is effective in decreasing the need for emergency veterinary treatment in these patients.
  2. Rectal administration results in higher and earlier peak serum concentrations compared with either oral or IM routes. The client administers 1 mg/kg diazepam parenteral solution by rectum using a 1-inch teat cannula or rubber catheter attached to a syringe. A dose of 2 mg/kg is recommended for dogs on chronic phenobarbital therapy, which increases benzodiazepine clearance. Treatment is administered at the first sign of a seizure and can be repeated for a total of three times within a 24-hr period.
  3. If seizures continue, or the patient appears excessively depressed, the client is instructed to seek urgent veterinary care.
  4. Some pharmacists can compound diazepam suppositories, and a gel formulation of diazepam (Diastat) for rectal administration is available for human patients. However, one study indicated that diazepam suppositories were slowly absorbed with poor bioavailability in dogs (Probst CW, unpublished data).

Narcolepsy[54, 67, 103, 109, 129, 130]

Introduction

Narcolepsy is a syndrome characterized by abnormalities in the sleep/wake cycle, including excessive sleepiness and cataplexy (sudden loss of muscle tone in response to emotional stimuli).

Pathophysiology

There are two forms of narcolepsy in dogs. A familial form occurs in Doberman Pinschers and Labrador Retrievers as an autosomal recessive trait associated with a mutation involving the hypocretin receptor-2. A familial form also occurs in Dachshunds. A sporadic form occurs in dogs of any breed and is caused by a loss of hypocretin-1-producing neurons in the hypothalamus. Acquired brain lesions, such as encephalitis, are rare causes. Hypocretin 1 and 2 are a pair of excitatory neuropeptides produced in the hypothalamus that are critical in the regulation of the sleep/wake cycle.

Clinical signs

The onset of signs in familial narcolepsy can occur as early as 4 wks of age, but in mild cases signs may not become apparent until 6 mos of age. Sporadic narcolepsy typically occurs in adult dogs. Cataplexy is usually the most prominent sign. There are several characteristics of cataplexy.

A. Episodes are typically elicited by excitement, such as that caused by food, water, or play, but they can occur spontaneously.
B. There is abrupt onset and termination of attacks.
C. The duration varies from a few seconds to 30 min or more.
D. There is partial to complete paralysis that may involve all muscles or be restricted to certain limbs or the head and trunk.
E. Consciousness is preserved at the onset, and the eyes are open. But if the attack lasts more than a minute or two, the

patient asleep with rapid eye movements and twitching of the facial and limb muscles (REM sleep).

F. Touching the dog or making loud noises can often terminate an attack.

Excessive sleepiness is recognized in many affected dogs and has several manifestations.

A. Prolonged periods of otherwise normal sleep.
B. Difficulty arousing the patient during sleep.
C. Apparent drowsiness throughout the day and inability to remain awake for normal periods of time.
D. A sudden onset of REM sleep from an active state (sleep attack). The patient is unconscious with closed eyelids and often has mild twitching of the face and distal limbs.

Diagnosis

Diagnosis is based on the history, clinical signs, and exclusion of other paroxysmal disorders, such as epilepsy, syncope, and myasthenia gravis. Response to treatment also supports the diagnosis.

Treatment

A. Cataplexy is usually treated with antidepressants. The tricyclic antidepressants (imipramine, protriptyline, amitriptyline) act via blocking cellular norepinephrine reuptake in the central nervous system (CNS). Imipramine also blocks serotonin reuptake. Fluoxetine is a selective serotonin reuptake inhibitor. Dose recommendations for these drugs are:
   1. Imipramine (0.4–1.0 mg/kg PO, q 8 or 12 hrs)
   2. Protriptyline (5–10 mg/kg PO, q 24 hrs)
   3. Amitriptyline (1–2 mg/kg PO, q 12 hrs)
   4. Fluoxetine (1 mg/kg PO, q 24 hrs)
B. Excessive sleepiness is usually treated with stimulants. Methylphenidate and dextroamphetamine are sympathomimetics. Selegiline is a monoamine oxidase B (MAO-B) inhibitor that acts to increase CNS dopamine levels. Dose recommendations for these drugs are listed below.
   1. Methylphenidate (0.25 mg/kg PO, q 8 or 12 hrs) often improves sleepiness and cataplexy.
   2. Dextroamphetamine (5–10 mg PO, q 8 or 12 hrs) may help with sleepiness and cataplexy.
   3. Selegiline (1 mg/kg PO, q 24 hrs) is also effective for excessive sleepiness, but not for cataplexy.

Prognosis

Although there is no cure for narcolepsy, medication is often effective in minimizing signs. The dose is titrated to effect. Some dogs improve without treatment.

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Video Resources

Video resources are available on the companion website: www.wiley.com/go/dewey/neurology

See videos 14 and 18.

CHAPTER 10

Involuntary Movements and Paroxysmal Disorders

Simon Platt

Introduction

Involuntary movement abnormalities result in some of the most dramatic clinical presentations in veterinary medicine. Classically, involuntary movement disorders are present during periods of inactivity rather than during voluntary movement. Some involuntary movements are persistent, while others are episodic. Certain involuntary movements have characteristics that allow for the identification of specific causes, whereas others are only a reflection of dysfunction of the nervous or musculoskeletal systems. Clinically, it is important to first identify the type of involuntary movement present. Subsequently, a more directed approach can be used to establish the cause of the movement disorder.

Paroxysmal events are characterized by the sudden and reversible onset of neurologic dysfunction in an otherwise normal animal. Some movement disorders can be paroxysmal. The animals do not lose consciousness and rarely have a structural lesion identifiable within the central nervous system (CNS). The underlying cause of many of these events may be a functional abnormality related to neurotransmitter imbalances or receptor abnormalities and dysfunction. Several stereotypical events have been described in specific breeds and are discussed below. Confirmation of the specific syndrome is difficult or impossible in the clinical setting but depends heavily on the exclusion of structural CNS abnormalities such as neoplasia, inflammation, and cerebrovascular disease.

Types of involuntary movements

Terms such as tics, twitches, shivering, shuddering, and fasciculation are often used to describe episodic, irregular muscle movements or depolarization associated with muscle contractions (Table 10.1). Involuntary movements, however, are usually manifested through abnormal motion of the limbs, trunk, or head.

A. Myoclonus[6,7,22]

Myoclonus is a shocklike contraction of a muscle, or muscles, that tends to occur repeatedly in a rhythmic pattern and may persist during sleep. It is akin to the rhythmic depolarization and contraction that occurs in the heart with each beat. Myoclonus can be focal, multifocal, or generalized; it often presents in a thoracic limb; however, a pelvic limb or the facial muscles including the tongue may also be involved. Myoclonus may be physiological (such as that seen when falling asleep or during sleep), epileptic, or symptomatic associated with CNS disease. An idiopathic, essential, myoclonus has been recognized in people but has not been described in veterinary medicine. Myoclonus in dogs is usually the result of distemper infection, which establishes a pacemaker-like depolarization of local motor neurons; however, it has been associated with lead toxicity and other causes of CNS inflammation.

Myoclonus is often described to originate from spinal disease causing a localized persistent movement abnormality due to abnormal lower motor neuronal discharges. This usually affects one or two limbs and occasionally the jaw. The muscle contractions occur rhythmically and are most obvious in resting animals; they are present throughout activity and do not disappear during sleep. It can also arise from apparent cerebral disease as a type of seizure.

B. Tremor[6,7,16,22,24]

Tremor is one of the most common involuntary movement disorders in humans, and is also surprisingly common as a clinical abnormality in dogs. Tremor is an involuntary rhythmic, oscillating movement of fixed frequency resulting from alternate or synchronous contraction of reciprocally innervated antagonistic muscles. It can be focal, affecting just one limb or the head, for example, or generalized. Electromyographically, tremor is characterized by rhythmic bursts of motor neuron activity occurring in opposing muscle groups. The contraction of muscles with opposing function gives tremor a biphasic nature. This biphasic character differentiates tremor from other abnormalities of movement. While

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Table 10.1 Types of involuntary movement and paroxysmal disorders.

Clinical sign or syndrome	Definition
Cramp	Muscle cramps are involuntarily and forcibly contracted muscles that do not relax
Dyskinesia	Difficulty or distortion in performing voluntary movements
Dystonia	Sustained muscle contractions cause twisting and repetitive movements or abnormal postures
Fasciculation	Involuntary contractions or twitching of groups of muscle fibers
Myoclonus	Rhythmic movement of a portion of the body resulting from sudden involuntary contraction and relaxation of muscle groups
Myokymia	Continuous involuntary muscle twitching that give the appearance of wormlike rippling of muscle
Myotonia	Sustained muscular contraction following an initiating stimulus
Rigidity	Increased resistance to change in position or angle of joint(s)
Spasm	A brief, automatic jerking movement
Spasticity	A state of increased tone of a muscle
Tetanus	Sustained muscular contraction without a period of relaxation
Tetany	Intermittent tonic muscular contractions
Tremor	Any abnormal repetitive shaking movement of the body

seen during the awake state, true tremor should cease with sleep. As for myoclonus, tremors may be physiological; idiopathic (or essential), such as that seen in senile tremor of dogs; or pathological, due to a nervous system disease.

Tremor is ultimately a disorder of movement. Therefore, lesions in any of the regions of the CNS and peripheral nervous system (PNS) and musculoskeletal system primarily responsible for normal movement, may generate a tremor. This makes localization challenging when considering the clinical signs alone. In humans, important motor areas include the basal nuclei and other components of the extrapyramidal system, the cerebellum, diffuse neuronal cell bodies involved in segmental and supraspinal reflex mechanisms, components of the lower motor neuron, and the interconnecting pathways. Additionally, abnormalities of the mechanical apparatus of the limbs (e.g. bones, joints, tendons) may also result in tremor as a result of pain and weakness. However, species differences do exist, and it is important to note that lesions involving the basal nuclei and substantia nigra commonly result in tremor in human beings but not in dogs.

Tremors that occur or worsen when an animal is trying to perform purposeful movements (intention tremors) are most often associated with cerebellar disease. Fine tremor (decreased amplitude and increased frequency) is more often associated with diffuse neuronal disease or muscle weakness. The causative lesion may give rise to other signs of neurologic dysfunction that can help further define the localization, such as dysmetria associated with cerebellar disease.

C. Myokymia and neuromyotonia[3,6,22,27,28,31,33]

These refer to the involuntary rippling of muscles that persists even during sleep and under anesthesia. The disorders represent a continuum of signs that result from motor axon or terminal hyperexcitability. This hyperexcitability can be caused by a wide variety of disorders of the CNS and PNS but is particularly related to changes in ion channel function. Electromyography (EMG) in myokymia reveals short bursts of ectopically generated motor unit potentials, firing at rates of 5–62 Hz and appearing as doublets, triplets, or multiplets (these bursts fire rhythmically or semi-rhythmically, and sound like soldiers marching). Neuromyotonia is characterized by muscle stiffness and persistent contraction related to an underlying spontaneous repetitive firing of motor unit potentials. On EMG there are prolonged bursts of motor unit potentials, firing at rapid rates of 150–300 Hz, which begin and end abruptly, do not occur repetitively in a rhythmic fashion, and have characteristic waning amplitude. There are few descriptions in companion animals, but it appears to be an emerging problem in Jack Russell Terriers.

Fasciculations arise from ectopic electrical activity in the distal axon and are typically the manifestation of irritability of the neuronal cell body or its associated axons. Myokymia is a result of spontaneous discharges of large motor units and indicates neuronal disease, followed by a sprouting of the motor unit territory in response to denervation. The term neuromyokymia has been used to implicate the role of the neuronal axon in this disorder.

D. Dyskinesia[19,20,23,25,30]

Dyskinesia is defined as impairment of the power of voluntary movements resulting in fragmented or incomplete movements. Dogs reported with these abnormalities may exhibit abnormal postures, such as holding up a limb in an attempt to move or adopting a kyphotic posture of the spine without being able to initiate movement. The pathophysiologic mechanisms underlying these movements are poorly understood but may represent a central neurotransmitter or pathway abnormality, or possibly a local muscular abnormality. The impaired movement can appear as and have been termed muscle "cramps," which are defined as paroxysmal—prolonged and severe contraction of muscles that may be painful and can be either focal or generalized. Examples of diseases associated with cramps which may be dyskinesias include Scotty cramp, episodic falling of Cavalier King Charles Spaniels, "epileptoid cramping" of Border Terriers, and extreme generalized muscular stiffness in male Labrador Retrievers. Muscle cramps have also been described secondary to systemic diseases such as hypoadrenocorticism.

Dyskinesias are movement disorders that occur spontaneously during activity or at rest, causing involuntary contractions of groups of muscles in a conscious animal. The descriptions of these conditions indicate that the most common clinical sign is that of dystonia causing increased muscle tone in one or several limbs, possibly leading to collapse. The movements can be triggered by excitement or exercise. The localization of the purported functional neurotransmitter-based abnormalities responsible for these disorders may be CNS or PNS. In general, movement disorders may have origins in the cerebrocortical neurons, basal nuclei, or PNS.

Diagnostic approach

The clinical presentation of movement disorders is complex, often variable, and sometimes even bizarre. Establishing the correct diagnosis can, therefore, be difficult. Obtaining an accurate history of the patient is important to define the onset and progression of the condition in addition to elucidating any underlying systemic health problems that could be causing the disorder.

Physical examination is essential as some tremor disorders may be associated with systemic disease. Many tremor syndromes may also be associated with neurologic deficits; therefore a neurologic examination can help to localize the causative lesion or associated deficits and determine the next stages necessary in the diagnostic work-up.

The following tests should be considered in most patients with movement disorders:

- Hematology, serum chemistry analysis, and urinalysis can help rule out systemic disease, including hypoglycemia, hypocalcaemia, and electrolyte abnormalities.
- Testing for possible toxin exposure can be difficult without knowledge of which toxin to look for; serum cholinesterase activity can be dramatically lowered in cases of organophosphate toxicity; blood lead levels should be considered with a history of possible exposure. Home drug kits are available over the counter in many US pharmacies and online in Europe. They can rapidly determine the presence of prescription drugs (e.g. tricyclic antidepressants, barbiturates, benzodiazepines, methadone, oxycodone) as well as illicit drugs (e.g. marijuana, cocaine, opioids, methamphetamine, ecstasy, amphetamines, phencyclidine). These human drug test kits have not been validated in animals.
- Thoracic and abdominal radiographs and ultrasonography should be performed to rule out systemic neoplasia.
- CSF analysis is necessary to rule out CNS inflammatory diseases.
- Serum and CSF immunoassays can confirm the infectious nature of a CNS inflammatory disease.
- Electroencephalography could potentially determine whether the event is a seizure. At the time of the event the practicality of this diagnostic test often prevents its effective use. However, in between events, the detection of abnormal cerebrocortical activity may suggest that the event is more likely to be a seizure than a pure movement disorder.
- Advanced imaging techniques, such as computed tomography and magnetic resonance imaging (MRI), can help to rule out destructive inflammatory lesions in the CNS as well as focal mass lesions such as neoplasia.

Establishing the etiology using clinical characteristics

The clinical characteristics of the abnormality may not only suggest that it is a movement disorder rather than one of the many mimics but also aid in the underlying etiology. Various classification schemes have been proposed based on the presence of activity at the time of the disorder, whether they are continuous or episodic, involve the muscle or nerves, and whether there is too much or too little movement. Ultimately, these schemes can be overcomplicated in veterinary medicine when so few of these disorders are seen and definitively diagnosed. More simply, the abnormalities can be investigated by dividing them into localized or generalized syndromes.

A. Localized tremor syndromes

   1. Localized limb tremors/myoclonus

      Recent classification schemes have suggested calling tremors a form of myoclonus (often action related, indicating they are more pronounced with activity). In this text, tremors and myoclonus are kept as separate entities with “myoclonus” referring to rhythmic activity of large groups of muscles causing flexion and extension of limbs as opposed to diseases causing more “fine” movement abnormalities of small muscle groups (tremor).

      There are many different causes of limb tremors and it should be remembered that focal seizures can cause involuntary movements of a single limb. Some specific diseases are described below.

      a. Spinal disease[1]

         Tremor can occur in one limb or body area. Tremor restricted to only the pelvic limbs may be seen in dogs with lumbar and sacral disease. This tremor may result in part from muscle weakness secondary to spinal cord or peripheral nerve impingement, or possibly occurs as the reflection of pain. Pelvic limb tremor may result from compressive diseases such as lumbosacral vertebral canal stenosis, neoplasia, and discospondylitis.

      b. Senile tremor[22]

         Older dogs can have tremors of the pelvic limbs (senile tremor); however, the etiology and pathogenesis of this syndrome remains unknown.

      c. Vascular diseases

         Limb tremors may also be seen with poor perfusion to the limb resulting from cardiac, pulmonary, or vascular disease, or anemia. Localized cyanosis secondary to a right to left shunting patent ductus arteriosus can result in pelvic limb tremor, most commonly seen during or following exercise. Partial vascular thrombosis and occlusion of the femoral arteries may result in similar tremor.

d. Neuromuscular diseases[3,10,14,27–29,31,33]
Diseases associated with muscle weakness such as neuropathy and myopathy may be associated with muscle tremors (see Chapter 18). Tremors associated with these diseases, however, are often of short duration, episodic, and present during attempts at muscle activity.

Myokymia and neuromyotonia—Myokymia is one of the clinical signs of neuromyotonia. Neuromyotonia is clinically characterized by a combination of muscle twitching or myokymia, persistent muscle contraction, muscle stiffness or cramps, and impaired muscle relaxation. Axonal voltage gated potassium channel abnormalities may be responsible for the condition secondary to autoantibody damage, toxicity, or genetic mutations. A missense mutation in KCNJ10 has recently been documented in the whole-genome sequence of a single affected Jack Russell Terrier, revealing that homozygosity for this mutation was significantly associated with spinocerebellar ataxia with myokymia, seizures, or both in these dogs. KCNJ10 encodes the inwardly rectifying potassium channel Kir4.1.

This condition has been sporadically reported in dogs and cats but it most well documented in Jack Russell Terriers. In dogs, the age of onset of PNS signs ranged from 2 mos to nearly 3 yrs. Males and females can be affected with a male-to-female ratio of 3:2 in Jack Russell Terriers. Focal myokymia is generally caused by a structural lesion of the corresponding lower motor neuron. The clinical and clinicopathological findings, treatment, and outcome of myokymia and neuromyotonia in 37 Jack Russell Terriers were recently reported. The most characteristic clinical signs were episodes of rhythmic, undulating muscle contractions that induced vermicular movements of the overlying skin. Collapse and recumbency were also seen in these dogs, which exhibited rigidity. The episodes were mostly triggered by excitement, exercise, or hot weather and could last from 10 min to several hours. Frequently, dogs and cats do not only show hyperexcitability of the motor nerve but often also have signs of suspected sensory (e.g. facial rubbing) and presumed autonomic nerve hyperactivity (e.g. hyperthermia, hyperventilation, tachycardia, gastrointestinal signs), prior to or during a neuromyotonic attack respectively. However, it is also possible that hyperthermia is only the consequence of severe muscle rigidity and that cardiorespiratory and gastrointestinal signs result from extreme hyperthermia. Most affected Jack Russell Terriers suffer from a hereditary form of spinocerebellar ataxia (SCA), previously called hereditary ataxia, characterized by head tremor, hypermetria, truncal ataxia, and reduced menace responses. Some affected Jack Russell Terriers with hereditary SCA also experience generalized tonic–clonic seizures.

Electrophysiological investigation can reveal neuromyotonic discharges which characteristically are represented by semi-rhythmic bursts of doublet, triplet or multiplet discharges of a single motor unit.

Drugs that cause a membrane stabilizing effect on all cell membranes, including those of the peripheral nerves, have been effectively used; these include the sodium channel blockers procainamide and mexiletine, both of which have been used in dogs, as has slow release phenytoin with variable effect. Coldwater baths have been more uniformly successful, especially when combined with general anesthesia.

e. Orthostatic tremors[11,21]
This disorder has been recognized in young Great Danes and Scottish Deerhounds. This is a postural tremor seen only in the limbs when the dogs are weight bearing. The tremors are absent when walking, leaning, or lying down. The neurologic examination of affected dogs is normal. Characteristic surface EMG readings have been reported with motor unit action potentials of 13–16 Hz (Fig 10.1).

2. Localized head tremors[1]
Dogs occasionally have tremor involving only the head. This type of tremor most likely results from tremor of the neck muscles but its pathophysiology is poorly understood. Head tremors which are exacerbated by an intentional movement such as eating or drinking are termed *intention* or *ataxic* tremors. This abnormality

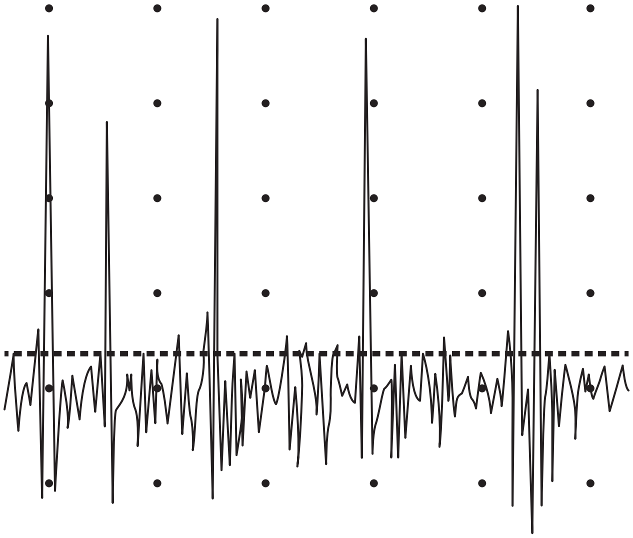

Figure 10.1 Surface EMG recording from a Great Dane with orthostatic tremors. Horizontal scale = 50 ms/division.

indicates cerebellar dysfunction. Paroxysmal or continuous nonataxic tremors of the head are often considered to result from cerebral or thalamic diseases. Focal facial movement abnormalities or intermittent head movements/jerks should also be considered potential seizure disorders and investigated appropriately.

a. Nonataxic head tremors[1,15,35]

1. Metabolic, systemic, and toxic diseases

Head tremors or bobs have been reported in a dog undergoing peritoneal dialysis for renal failure and in a dog with iatrogenic hypoparathyroidism. The author and others have seen dogs with a variety of systemic illness receiving multiple drugs therapies have similar tremors. Metaclopromide treatment and doxorubicin administration are notable examples. Additionally, dogs with syncope due to third-degree heart block can have intermittent head tremors.

2. Idiopathic head tremor/head bob

This head tremor syndrome appears to occur without definable cause in some breeds such as Doberman Pinschers (especially dogs less than 1 yr of age), Boxers, and Bulldogs. However, a variety of breeds can be affected. These dogs have no other clinical abnormalities and are usually young (median age of onset in Bulldogs is 2 yrs). Head tremors may be either in an up–down or in a side-to-side plane for a median duration of 3 min. The frequency of the tremors is reported to be between 4.88 and 6.17 Hz (median, 5.75 Hz) with variable amplitudes. There is a variable frequency of occurrence reported (1–20 episodes/day; median: 2/day). Certain exceptional conditions such as illness, surgery, some medications, heat, pseudopregnancy, or pregnancy have been reported to trigger episodes.

Sometimes the episode is referred to as a head bob and it is usually more prominent when the dog is less active or asleep. Dogs seem to be able to stop this movement if they desire, are conscious, can walk, and can respond to verbal commands. This is almost the opposite of an intention tremor, as the tremor can be stopped when the dog is focused on a goal-oriented task such as eating. The pathogenesis of this disease is not known. In human beings, a nodding of the head can occur with lesions of the thalamus and the author has seen this in a dog with a thalamic lesion. A "yes" head tremor also may accompany midline cerebellar lesions. Full diagnostic workup (blood work, CSF analysis, and imaging of the brain) is normal with the idiopathic condition. There is little information on the most appropriate treatment: although there may be a partial response to antiepileptic drugs, usually they are ineffective. Fortunately, these tremors rarely impact the animal's quality of life and, at least in English Bulldogs, spontaneous resolution can be common.

3. Infectious/inflammatory causes

Although unusual, animals with a head tremor or head bob as their only clinical sign can have an inflammatory or infectious disease (see Chapter 7 for a description of the different causes of encephalitis). In addition, myoclonus of the head or face can be seen with inflammatory diseases of the CNS. This may be more common with distemper virus infections and has been called "chewing gum fits" due to the rhythmic jaw movements seen clinically. However, it may be difficult to distinguish this form of localized myoclonus from continuous focal seizure activity. Focal facial movement abnormalities or intermittent head movements/jerks should always be considered as potential seizure disorders and investigated appropriately.

b. Ataxic head tremors[7]

Tremors that occur when an animal intends to move in a goal-oriented activity are most often the result of cerebellar disease. This tremor may involve the whole body but is usually most obvious in the head. The head usually moves in an up-and-down ("yes") direction at a frequency of 2–4 Hz. This type of tremor is exaggerated by goal-oriented movement, such as eating. This is most likely a dysmetria of head movement.

B. Generalized syndromes[1,2,8,32]

Generalized tremors and involuntary movements are surprisingly common in dogs. Neurolocalization can be difficult as they could result from focal vestibulocerebellar diseases or more diffuse CNS or PNS diseases. These events can result secondary to intoxications, drug therapies, congenital myelin abnormalities, storage diseases, encephalitis, hypertension, or vascular disease, or may arise without a definable cause. These underlying etiologies can be ruled out with a good history, a minimum database, a cerebrospinal fluid (CSF) tap, and advanced imaging. When all the tests are normal, consideration should be given to whether the syndrome is a tremor—in which case it may be idiopathic in nature (essential tremors)—or whether it is a paroxysmal onset of abnormal muscle tone and movement—in which case one of the several breed-related "dyskinesias" should be considered.

1. Essential tremors/geriatric (senile) canine tremors

Physiological and essential tremors are most common in people. Essential tremors are considered exaggerated forms of physiological tremors and when they occur in later life they are termed senile tremors. Some older dogs will exhibit a fine tremor of the pelvic limbs as they age and the condition can be slowly progressive. It is a postural related tremor and as such is only present when the dog is standing. There is no effect on strength or gait in these dogs and no pain is detected. No treatment is necessary unless symptomatic therapy is required to improve a perceived quality-of-life issue.

2. Paroxysmal dyskinesias[4, 17, 20, 23, 26]

Paroxysmal dyskinesias are episodes of abnormal, involuntary hyperkinetic movement or muscle tone. These events are distinguished from seizures by the presence of a normal consciousness, although an EEG would be necessary to definitively determine this. A movement disorder has been described in young Bichon Frise dogs with an extreme variability of frequency and random occurrence. A rapid muscular contraction causes hyperflexion and/or extension of an individual limb. The thoracolumbar spinal column can be affected by altered muscle tone during the event, causing a kyphotic posture. A similar condition has also been described in young Boxer pups provoked by excitement, causing abnormal facial, truncal, and limb movements with sustained hyperflexion.

No successful treatment regimens have been described. It remains to be seen whether a genetic disorder confirms these as truly breed-related disorders (as documented below). Several drugs have been reported to cause similar dyskinesias and include phenobarbitone and propofol in dogs. These disorders are usually reversible with drug tapering or withdrawal.

a. Scotty cramp

Clinical episodes of dystonia are most commonly seen in Scottish Terriers from 6 wks to 3 yrs of age and may be elicited by stress, excitement, or exercise. The thoracic limbs are initially affected, becoming abducted shortly after exercise begins; this is followed by arching of the lumbar spine and pelvic limb stiffness, which can progress to somersaults, falling, and tightly flexed pelvic limbs. Loss of consciousness is not a feature and the signs resolve within 10 min, but can recur multiple times over a 24-hr period. Similar conditions have been described in Dalmatians, a Cocker Spaniel, a Wirehaired Terrier, Wheaton Terriers, Norwich Terriers, and Border Terriers. In Border Terriers, the disease has been termed Spike's disease or canine epileptoid cramping syndrome (CECS). A breeder-run website contains further information on this condition (www.borderterrier-cecs.com). A recent report of 29 Border Terriers with this syndrome revealed that most dogs had their first episode before 3 yrs of age (range: 0.2–7 yrs). The majority of episodes lasted between 2 and 30 min (range: 0.5–150 min). The most frequent observations during the episodes were difficulty in walking (27 of 29), mild tremor (21 of 29), and dystonia (22 of 29). Episodes most frequently affected all four limbs (25 of 29) and the head and neck (21 of 29). Borborygmi were reported during episodes in 11 of 29 dogs. Episodes of vomiting and diarrhea occurred in 14 of 29, with 50% of these being immediately before or after episodes of CECS (7 of 14). Most owners (26 of 29) had changed their dog's diet, with approximately 50% (14 of 26) reporting a subsequent reduction in the frequency of episodes.

This recessively inherited nonprogressive disorder is thought to be associated with relative deficiencies of the inhibitory neurotransmitter 5-hydroxytryptamine (serotonin).

A presumptive diagnosis is based on clinical signs and breed. All laboratory tests are within normal limits. Signs can be induced with exercise 2 hrs after using methysergide (0.3 mg/kg orally), a serotonin antagonist.

Treatment consists of daily oral dosing of acepromazine maleate (0.1–0.75 mg/kg q 12 hrs) or diazepam (0.5 mg/kg q 8 hrs). Vitamin E (125 IU/kg/day) has also been advised for these dogs. Serotonin reuptake inhibitors such as fluoxetine may be useful in affected dogs. Nonsteroidal anti-inflammatories are contraindicated. Prognosis is fair, as the disease is nonprogressive; appropriate lifestyle changes can result in a good quality of life. In CECS, dietary treatment using hypoallergenic foods has been suggested but no evidence exists for this at this time.

b. Episodic hypertonicity in Cavalier King Charles Spaniels[9, 13]

This condition, also known as episodic falling syndrome in Cavalier King Charles Spaniels has been described in the United Kingdom, the United States, and Australia and is suspected to have an inherited component. The genetic locus for this condition has recently been mapped to canine chromosome 7 with approximately 13% of the breed suggested to be carriers of the disease.

The syndrome is often seen in animals between 3 and 7 mos of age but can affect animals up to 4 yrs of age. Variable periods of exercise induce a bounding pelvic limb gait in which the limbs may be abducted and appear stiff. This may progress to "bunny-hopping," arching of the spine, and collapse. As in Scotty cramp, the animals are normal between the events, there is no loss of consciousness, and the events may be triggered by exercise, stress, and excitement.

The pathogenesis is at present unknown but preliminary studies implicate an abnormality of CNS neurotransmission. Recent work has identified a genetic deletion affecting the brevican gene in affected dogs and has confirmed the disease as an autosomal recessive. Brevican belongs to a family of aggregating extracellular matrix proteoglycans where it has a role in governing synapse stability; it is highly expressed in the CNS.

Laboratory tests and electrodiagnostic examinations are normal. Therefore, diagnosis is by exclusion and correlation of an appropriate history with clinical signs.

Treatment with the benzodiazepine drug clonazepam (0.5 mg/kg q 8 hrs) can result in an almost complete remission of the signs, but tolerance to this drug does develop. The carbonic anhydrase inhibitor acetazolamide may have therapeutic benefit in these dogs.

c. Startle disease in Irish Wolfhounds[12]

Hyperekplexia, or startle disease, is characterized by noise- or touch-induced nonepileptic seizures that result in muscle stiffness and apnea in people.

Defective inhibitory glycinergic transmission due to genetic mutations affecting the glycine receptor is usually the cause. It has been suggested that familial reflex myoclonus in Labrador Retrievers could be a glycinergic transmission disorder and represent a startle disorder. A startle disease has recently been documented in Irish Wolfhounds in the United States with a microdeletion in the gene encoding a presynaptic glycine transporter. The condition was seen to develop in 5- 7-day-old pups, evoked by handling and abating when relaxed or sleeping. The puppies affected could not stand and had a rigid posture in all four limbs with generalized tremor. Progressive feeding difficulty was noted and euthanasia was performed by 3 mos of age. Carriers of this disease can now be identified.

d. Generalized muscle stiffness in male Labrador Retrievers[30]

Young male Labradors have been described with a paroxysmal generalized rigidity of CNS origin. Signs have been seen to start between 2 and 41 mos of age, with a mean age of onset being 17 mos, stabilizing in adulthood. The disease seems to first affect the pelvic limbs and then progresses to the thoracic limbs causing them to present for exercise intolerance. All affected dogs seem to exhibit generalized muscle stiffness, persisting at rest and resulting in restricted joint movements. The dogs have a flexed posture and a bradykinesia or extreme slowness of movements and reflexes.

Currently it is thought that this condition arises from basal nuclei and reticular formation abnormalities together with motor neuron disinhibition caused by a decrease in the number of spinal cord interneurons. Initial pedigree analysis suggests an X-linked hereditary disease.

Conscious-needle EMG showed continuous motor unit activity in the proximal limb and epaxial muscles while the dogs were standing or laterally recumbent. Serum creatine kinase levels are normal, as is the CBC, serum chemistry, and CSF. Therefore, diagnosis is by exclusion and correlation of an appropriate history with clinical signs.

A poor quality of life can lead to requests for euthanasia. Clinical signs can progress but have been seen to stabilize. Treatment with nonsteroidal anti-inflammatory drugs has been shown to provide partial and temporary improvement in some dogs. No specific and uniformly successful treatment is known.

e. Paroxysmal dyskinesia in Chinooks[19]

A paroxysmal dyskinesia has been described in related Chinooks characterized by an inability to stand or ambulate, head tremors, and involuntary flexion of one or multiple limbs, without autonomic signs or loss of consciousness. Episode duration varies from minutes to an hour. Based on pedigree analysis, the disorder was considered to be consistent with a partially penetrant autosomal recessive or polygenic trait. There has been some consideration given to whether this disorder is an atypical seizure episode—but the same can be said for any of the aforementioned dyskinesias.

f. Lafora's disease (myoclonic epilepsy) in Miniature Wirehaired Dachshunds[18, 34]

Familial myoclonic epilepsy with similarities to Lafora's disease in humans has been reported in several Miniature Wirehaired Dachshunds.

Presenting clinical signs include repetitive muscle contractions (twitching), seizures, and jerks in response to visual, auditory, or sensory stimuli. Age of onset has ranged from 6 to 13 yrs, with both males and females affected.

A genetic expanded repeat mutation of the EPM2B genes that code for the protein malin has been reported in Miniature Wirehaired Dachshunds and Basset Hounds with Lafora's disease.

Neurologic examinations and routine laboratory and CSF evaluations are within the normal range. MRI may reveal generalized ventricular dilation and cortical atrophy but these are not specific findings. EEG activity in dogs with Lafora's disease is characterized by bilateral synchronous polyspike wave paroxysms. The presence of intense periodic-acid–Schiff positive, diastase-resistant inclusions (polyglucosan bodies; Lafora bodies) in fresh frozen muscle biopsy specimens may aid in establishing the diagnosis in cases with a consistent clinical phenotype. Some laboratories and human hospitals will test for the EPM2B mutation.

Phenobarbitone therapy at standard anticonvulsant doses may result in some clinical improvement of the seizure activity but has not been completely successful in the author's experience. Equivocal efficacy has also been reported with the use of gabapentin and potassium bromide. A diet high in antioxidants has been shown to slow the progression of the clinical signs. The prognosis depends on the frequency and severity of the events and how these affect the dog's quality of life. Similar pathology has been described in older Beagles and Basset Hounds.

g. Dancing Doberman disease[5]
A condition affecting Dobermans and causing intermittent flexion of one or both pelvic limbs has been reported. Muscle atrophy, weakness, and postural reaction deficits may be seen in chronic cases. The gastrocnemius muscle appears to be the primary focus of the disease with EMG changes detectable, including positive sharps, fibrillation potentials, and complex repetitive discharges. The underlying cause is not known, but sciatic-tibial nerve biopsy may reveal axonal disease, which may be primary or secondary in origin.

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CHAPTER 11

Disorders of Hearing and Balance: The Vestibulocochlear Nerve (CN VIII) and Associated Structures

Sean G. Sanders

Functional neuroanatomy of the vestibular system[22, 27, 34, 45, 67, 86, 122]

The vestibular system is a component of the nervous system responsible for the maintenance of posture and balance relative to the head and body. This system functions in close coordination with the cerebellum, with portions of the cerebellum providing functions similar to the vestibular nuclei. The components of the vestibular system can be anatomically and functionally divided into those found peripherally (outside of the brain stem) and those found centrally (within the brain stem and cerebellum, Fig. 11.1). Separation of diseases affecting these two main areas is important both for differential diagnosis and prognosis in animals with vestibular system abnormalities.

The vestibulocochlear nerve is the only cranial nerve that does not exit the skull. The sensory neurons of both the vestibular and the auditory portion of cranial nerve (CN) VIII are bipolar neurons with cell bodies located in either the spiral ganglion (auditory) or the vestibular ganglion deep within the bony labyrinth of the petrous temporal bone. The dendritic zones of these neurons are in synaptic contact with specialized hair cells in various receptor organs of the inner ear. The “hair” bundles of these specialized cells are actually stereocilia that function in transforming mechanical deformation (from fluid movement within the membranous labyrinth) into neural signals.

Three components make up the bony labyrinth within the petrous temporal bone (Fig. 11.2A and B). These include the three semicircular canals, a vestibule, and the cochlea (which originates in the vestibule). The latter is important for auditory functions. The components communicate with each other and are filled with a fluid resembling cerebrospinal fluid, known as *perilymph*. These organs comprise membranous structures filled with another type of fluid, known as *endolymph*. Collectively, the organs are called the *membranous labyrinth*.

The semicircular ducts are located in the semicircular canal and are involved with vestibular function. The utricle and saccule are also involved with vestibular function and are located within the large vestibule. The vestibular labyrinths detect either static or kinetic positional signals.

The three semicircular canals are oriented at right angles to each other in order to detect angular movements of the head. The receptor of the semicircular ducts is the crista ampullaris (Fig. 11.2B). Like the macula, the crista ampullaris is covered by hair cells that project their cilia into a gelatinous structure known as the cupula. As the endolymph in the semicircular canals moves in relation to outside forces, the cupula moves and deforms the hair cells, which then stimulate the dendritic endings of sensory neurons of the vestibular portion of CN VIII. The crista ampullaris is a “kinetic” labyrinth because it senses the position of the head in any plane and rotational angle.

The static labyrinths are the utricle (utriculus) and saccule (sacculus). The receptor of the utricle and saccule is the *macula*. The macula is covered by hair cells, which are the actual receptor cells. Along the luminal surface of the hair cells are cilia that project into a gelatinous substance known as the otolithic membrane. The otolithic membrane contains otoliths known as *statoconia*. As the otolithic membrane moves relative to gravitational forces, the hair cells are deformed. This generates an action potential that is propagated through the vestibular portion of the vestibulocochlear nerve (CN VIII). The utricle and saccule are responsible for localizing the static position of the head in space and in linear acceleration or deceleration.

Axons from bipolar neurons within the petrous temporal bone (i.e. spiral and vestibular ganglion neurons) enter the cranial vault through the internal acoustic meatus at the cerebellomedullary angle (rostral medulla oblongata). The combination of vestibular and auditory axons at this level compose CN VIII. These axons enter the brain stem at the level of the trapezoid body and caudal cerebellar peduncle.

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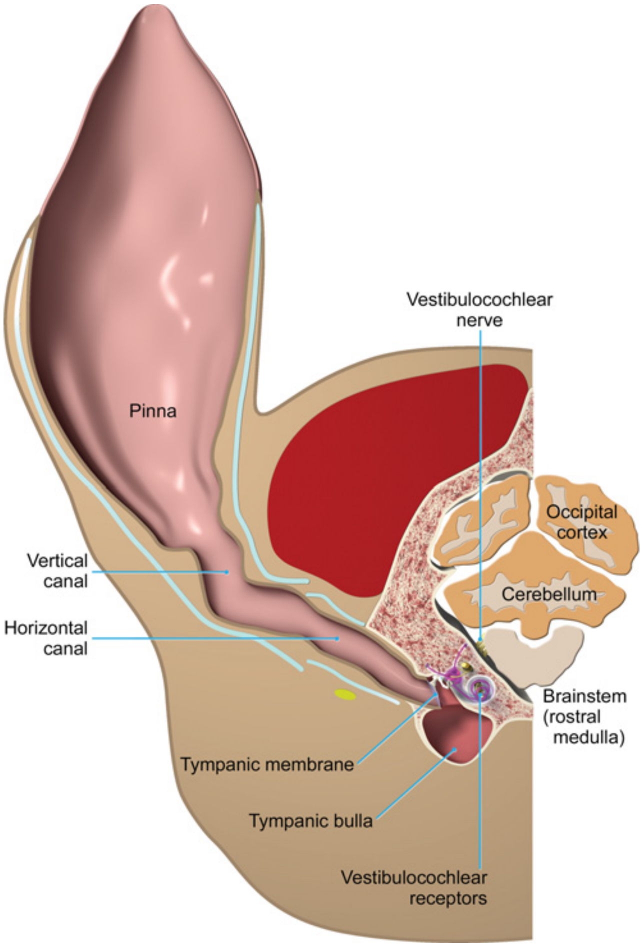

Figure 11.1 Schematic illustration of the anatomy of the ear and the location of the vestibulocochlear receptors in relation to the brain stem and cerebellum. (The Ohio State University. Reproduced with permission.)

Vestibular axons enter the brain stem and travel in several different pathways. The majority of the axons will synapse on the vestibular nuclei. A small number of axons will bypass the vestibular nuclei and ascend into the cerebellum via the caudal cerebellar peduncle. Some of these axons will synapse on the fastigial nucleus and some of the axons will ascend into the cerebellar cortex into the ipsilateral flocculonodular lobe.

There are four vestibular nuclei on either side of the brain stem located in the ventrolateral wall of the fourth ventricle (Fig. 11.3). Axons from these nuclei project to the spinal cord (vestibulospinal tracts) and rostrally within the brain stem (the medial longitudinal fasciculus, or MLF). Fibers that descend the spinal cord are found primarily in the vestibulospinal tracts (primarily lateral vestibulospinal tract) and mainly influence limb extensor tone. The lateral vestibulospinal tract projects from the lateral vestibular nucleus to all levels of the spinal cord in the ipsilateral ventral funiculus (see Fig. 11.4). These axons will then synapse on interneurons in the ventral gray matter of the spinal cord to mediate facilitation of extensor muscles and inhibition of flexor muscles on the ipsilateral side.

The MLF travels both rostrally to influence eye position and caudally into the spinal cord. The caudal or spinal limb of the MLF is sometimes referred to as the *medial vestibulospinal tract*. The group of axons that course rostrally will terminate within the nuclei of CN III, IV, and VI. This circuit influences the position of the eyes relative to the head in space and is responsible for the oculocephalic reflex. The oculocephalic reflex is the physiological nystagmus that is generated when the head is moved from side to side.

Within the spinal cord, the medial vestibulospinal tract is located in the ipsilateral ventral medial portion of the ventral funiculus. These fibers, in conjunction with the lateral vestibulospinal tract, are responsible for maintaining the position of the body and limbs relative to the head. Finally, vestibular information is projected to other areas in the brain stem and cerebrum. The vomiting center, located within the reticular formation of the medulla, will receive afferent input from the vestibular portion of the vestibulocochlear nerve. These afferents likely play a role in motion sickness. A final pathway of the vestibular portion of CN VIII will ascend to the cerebrum (involving synapse in thalamic relay nuclei) along with portions of the cochlear nerve to provide a conscious awareness of the body's position in space.

Functional neuroanatomy of the auditory system[15, 27, 34, 45, 90]

The sensory neurons of the auditory portion of CN VIII are bipolar neurons with their cell bodies located in the spiral ganglion within the bony labyrinth of the petrous temporal bone. The axons project to their respective receptor organs found in the bony labyrinth where their dendritic zones form synapses with mechanoreceptors (hair cells).

The auditory and vestibular receptors develop together embryologically and make up the inner ear. Sensory receptors for hearing are located in the cochlea in the organ of Corti. The cochlea is divided into three compartments. The two outside compartments contain perilymph. They are known as the *scala vestibuli* and the *scala tympani*. The middle compartment, known as the *scala media* or *cochlear duct*, contains endolymph secreted by the stria vascularis (the vascular endothelium lining one wall of the middle compartment of the cochlear duct). Between the cochlear duct and the scala vestibuli is the flexible vestibular membrane (Reissner's membrane). The cochlear duct contains the basilar membrane, along which the organ of Corti lies. The organ of Corti houses the receptors (hair cells) necessary for audition. The cochlear duct does not communicate with the outside compartments (scala vestibuli and scala tympani); however, the outside compartments communicate with one another through an opening at the apex of the cochlea known as the *helicotrema*. At the base of the scala vestibuli there is an opening to the middle ear. This opening is called the oval window or vestibular window (although it has nothing to do with vestibular function). The three *ossicles* (Latin

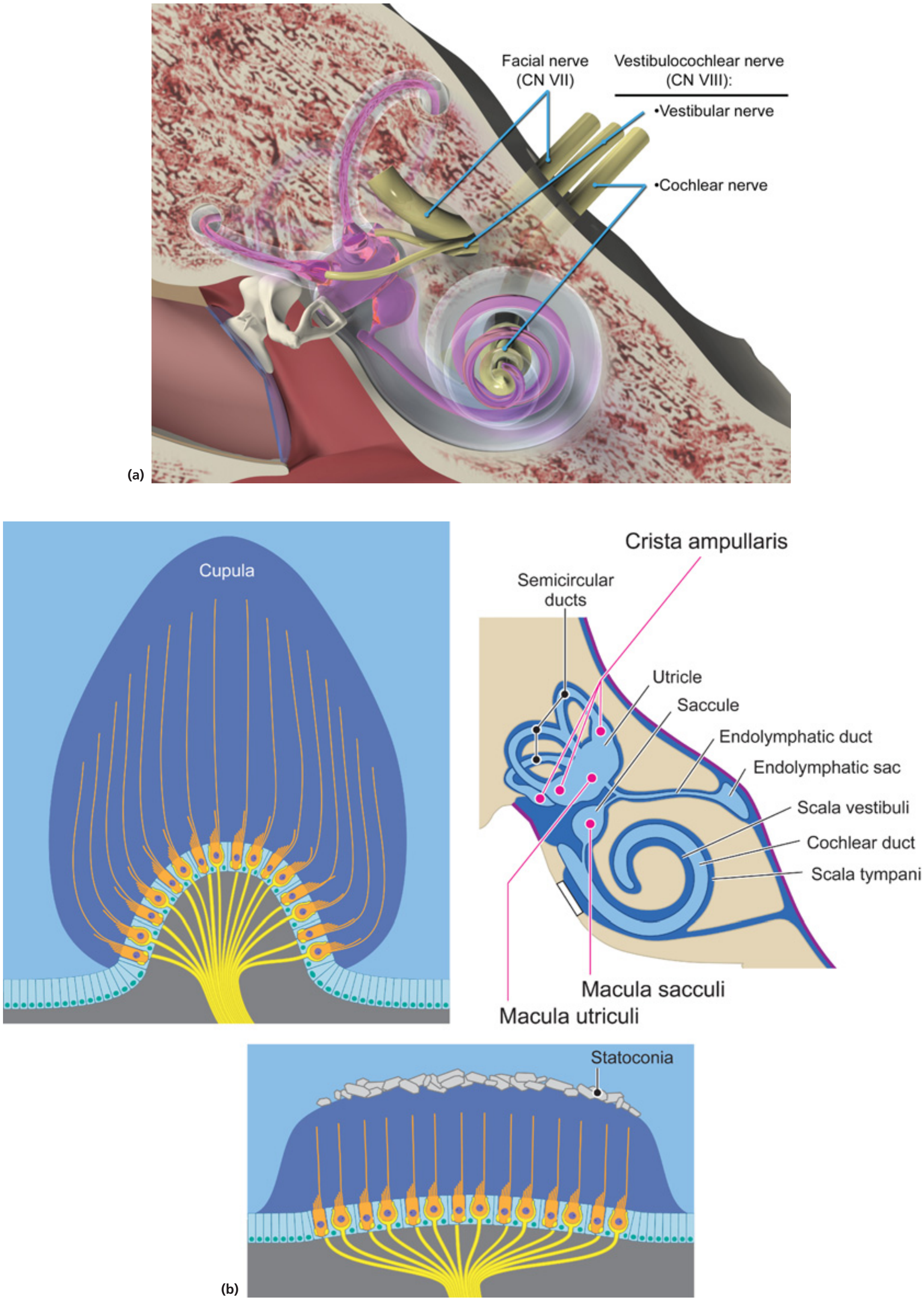
Facial nerve
(CN VII)
Vestibulocochlear nerve
(CN VIII):
•Vestibular nerve
•Cochlear nerve
(a)
Cupula
Crista ampullaris
Semicircular
ducts
Utricle
Saccule
Endolymphatic duct
Endolymphatic sac
Scala vestibuli
Cochlear duct
Scala tympani
Macula sacculi
Macula utriculi
Statoconia
(b)

Figure 11.2 (A) Schematic illustration of the vestibulocochlear receptors and nerve in the petrosal portion of the temporal bone and their relationship with the facial nerve. (B) Schematic illustration depicting the structures of the vestibular/auditory apparatus. The image at the center depicts the relationship between the vestibular and cochlear receptors. The top image shows the crista ampullaris, the receptor from the semicircular canals, and the bottom image depicts the macula with the statoconia, which is the receptor from the utricle and sacculae. (The Ohio State University. Reproduced with permission.)

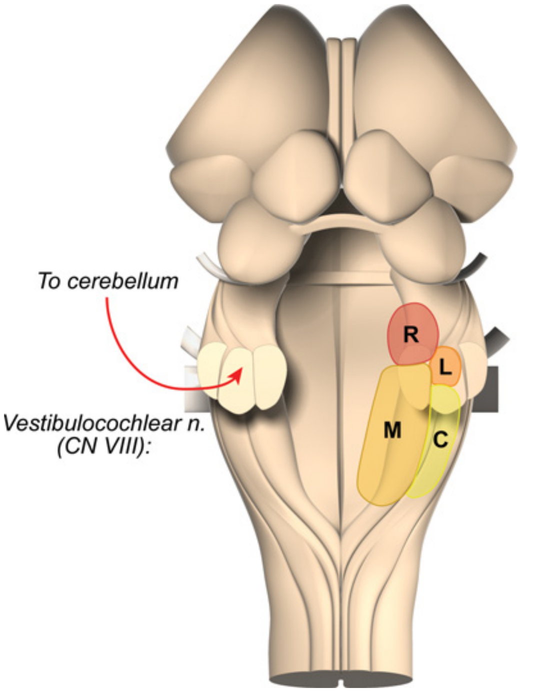
To cerebellum
Vestibulocochlear n. (CN VIII):
R
L
M
C

Figure 11.3 Dorsal aspect of the brain stem. The cerebellum has been removed. M, medial vestibular nucleus; C, caudal vestibular nucleus; L, lateral vestibular nucleus; R, rostral vestibular nucleus. (The Ohio State University. Reproduced with permission.)

for "little bones") are located in the middle ear. The first of these bones, the malleus, is attached to the tympanic membrane.

As the tympanic membrane vibrates from sound waves in the outer ear, the vibrations are transferred to the malleus. The malleus is attached to the second ossicle, the incus. The incus is attached to the third ossicle, the stapes, which is attached to the oval window. Because ultimately the goal will be to move the fluid in the cochlear duct, and because fluid resists movement much more than air does, the ossicles act as an amplifier of the sound waves traveling through air to overcome the increased pressure necessary to move the fluid. The muscles of the middle ear, the tensor tympani (innervated by CN V), and the stapedius (innervated by CN VII) will reflexively contract in response to loud noises to dampen the activity of the ossicles and prevent damage to the inner ear. It is also thought that these muscles are active during vocalization in order to dampen the sound emanating from the pharynx. As the stapes pushes on the membrane of the oval window, perilymph in the scala vestibuli moves toward the helicotrema and deforms the vestibular membrane. Deformation of the vestibular membrane leads to a deformation of the basilar membrane secondary to compression of the endolymph within the cochlear duct. The distance that the compressive fluid wave travels along the basilar membrane will depend on the frequency of the sound. The basilar membrane is stiff and narrow at the base of the cochlear duct and becomes floppy and wide as it extends to the apex. A high-frequency sound will dissipate quickly at the stiff narrow end of

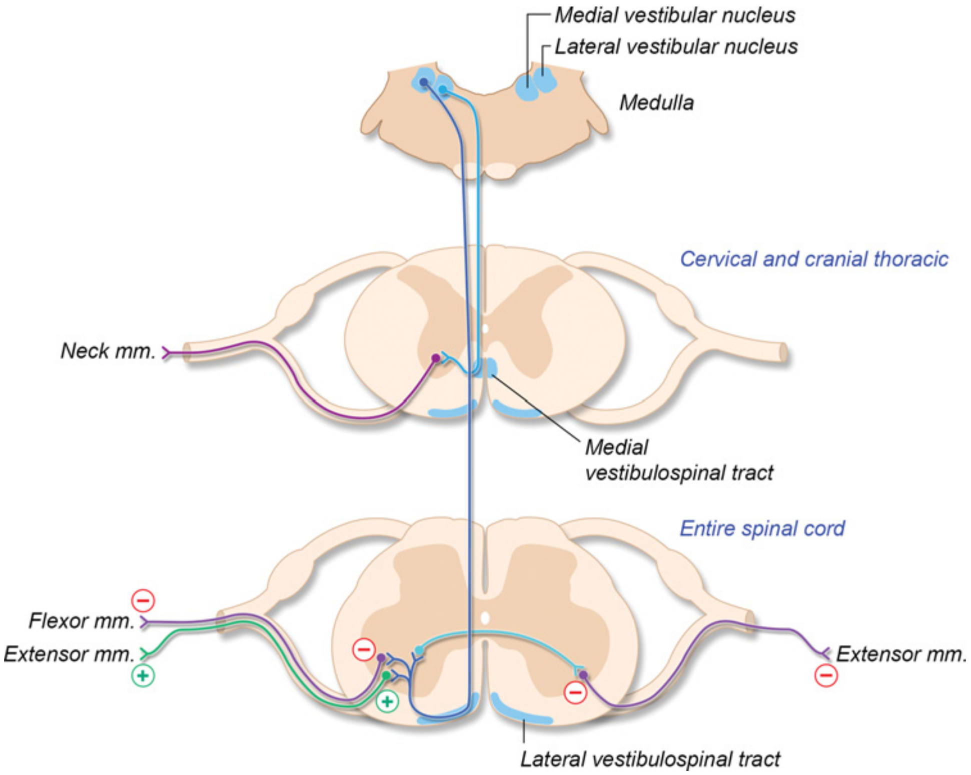
Medial vestibular nucleus
Lateral vestibular nucleus
Medulla
Cervical and cranial thoracic
Neck mm.
Medial vestibulospinal tract
Entire spinal cord
Flexor mm.
Extensor mm.
Extensor mm.
Lateral vestibulospinal tract

Figure 11.4 Schematic illustration depicting the course of the lateral vestibulospinal tract. (The Ohio State University. Reproduced with permission.)

the basilar membrane, while a low-frequency sound will travel far along toward the apex. Therefore, the longer the basilar membrane, the higher the frequency of sound perceived by the animal. Dogs have much longer basilar membranes than humans and are therefore able to "hear" higher-frequency sounds (such as a dog whistle). The area of the basilar membrane that is maximally deformed by the fluid wave will establish a place code for that frequency and produce maximal activation of the hair cells sitting atop the basilar membrane. The deformation of the hair cells will activate the dendrites of the auditory portion of the vestibulocochlear nerve.

Fibers from the cochlear portion of the vestibulocochlear nerve leave the spiral ganglion and enter the brain stem at the level of the junction of the medulla oblongata and pons, synapsing in the cochlear nucleus. From the cochlear nucleus, axons will either ascend the brain stem through the acoustic stria or cross midline in the trapezoid body (Fig. 11.5). In the medulla they may synapse in the dorsal or ventral trapezoid, and some will continue on in the lateral lemniscus pathway (pons) to its termination in the caudal colliculus (midbrain). Efferents from the caudal colliculus will cross midline and descend to brain stem lower motor neurons as tectobulbar projections to help mediate brain stem reflexes. Some fibers will join the tectospinal tract, which originates in the rostral and caudal colliculus and descends to the cervical spinal cord in the ventral funiculus. These fibers contain reflex information from both visual and auditory inputs in order to provide reflex movements of the head and neck in response to auditory and visual stimuli. The caudal colliculus is involved in reflex auditory functions. Auditory efferent axons will project from the caudal colliculus to the medial geniculate nucleus in the thalamus to mediate conscious auditory perception. The thalamocortical projections travel from the medial geniculate nucleus in the thalamus through the internal capsule and into the auditory cortex of the temporal lobe (cerebrum). The projections are predominantly contralateral; however, multiple areas of crossing of the pathways occur, so the representation of sound on each side of the cerebral cortex from the auditory system is rather diffuse.

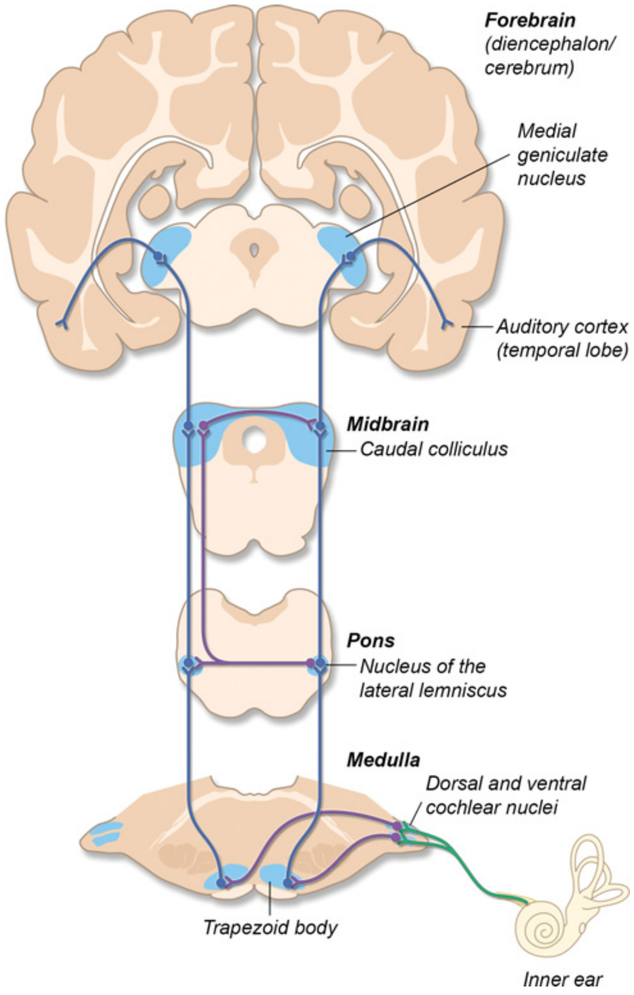

Figure 11.5 Schematic representation of the auditory pathway. (The Ohio State University. Reproduced with permission.)

Clinical evaluation of the vestibular system[4, 10, 15, 31, 34, 45, 57, 67, 74, 86, 90, 126]

The vestibular system functions normally to maintain the animal's position in space. This coordinated activity of sensory input and reflex output is performed at a subconscious level. The maintenance of balance, posture, and tone contribute to normal equilibrium. The vestibular system is also intimately connected with the extraocular muscles responsible for reflex ocular movements and tracking objects in space. Signs of vestibular disease are usually manifested as unilateral or asymmetric ataxia. With pure vestibular disease, the strength of muscle contraction is normal.

Careful observation of the patient in a relaxed environment is very helpful when evaluating an animal for vestibular dysfunction. Allowing the patient to walk around the examination room and become accustomed to its surroundings may provide the investigator with important clues. Excessive barking or meowing may be appreciated in deaf dogs and cats. Of primary importance is the differentiation of peripheral from central vestibular disease. Behavioral changes (fear, aggression) or mental status changes (depression, dementia) are signs that indicate a central lesion. A thorough history along with a complete physical and neurologic examination are some of the most important diagnostic tools a clinician can have; however, without an adequate understanding of the anatomy and physiology of the vestibular system, even the most expertly performed neurologic examination is useless if not interpreted correctly. Additionally, false interpretations of a neurologic examination without additional diagnostic tests may lead to the unnecessary euthanasia of animals. A clear understanding of the concept of disease progression over time is also helpful when establishing a list of differentials.

Clinical signs of vestibular dysfunction

The vestibular apparatus can be thought of as contributing equal, tonic input to each side of the head. When the vestibular nuclei are excited in the brain stem, there is ipsilateral facilitation of extensors and contralateral facilitation of flexors in the muscles of the limbs and trunk mediated via the vestibulospinal tracts. When the system is functioning correctly, the two opposing vestibular systems (left and right) balance each other out and the body's position in space is maintained at equilibrium. If a lesion prevents the activation of one side of the vestibular apparatus, the ipsilateral vestibular nuclei will not be excited as much as the functioning, contralateral side. The imbalance in the system will cause the relative facilitation of extensors on the normal side and the lack of facilitation of extensors on the side of the lesion. Therefore, the body will be "pushed" by the normal extensors in the direction of the abnormality. This is manifested clinically as a head tilt, circling, leaning, falling, or rolling to the side of the lesion (Fig. 11.6).

Because the vestibular system also contributes to the generation and maintenance of the oculovestibular reflexes, abnormalities of movements of the eyes can be very helpful clinically when trying to localize a lesion. When the head is rotated, the brain will try to keep the eyes focused on the visual field in order to keep the visual stimulus centered on the retina for optimal visual acuity. To perform this reflex activity, there is vestibular input to the brain stem nuclei of CN III, IV, and VI. As the head is rotated, the extraocular muscles opposite the direction of rotation will contract to "pull" the eyes back toward the center of the desired visual field. Once the muscles reach their limit, the eyes will quickly release and snap back in the direction of rotation and then again slowly move back toward the center of the visual field. This reflex activity is known as the oculocephalic reflex and represents a form of physiologic nystagmus. Nystagmus is a rhythmic, involuntary oscillation of the eyes. In the description above, the slow phase of the nystagmus was opposite the rotation. Nystagmus can have equal movements (no fast or slow phase), which is then referred to as *pendular nystagmus*, or it can have a fast phase and a slow phase, in which case it is referred to as *jerk nystagmus*. Pendular nystagmus is not a sign of vestibular disease. It is often observed in normal Siamese, Himalayan, and crosses of these breeds as a congenital defect in the visual pathways. When the vestibular apparatus is damaged on one side, there is an imbalance of neural activity in the vestibular nuclei because the vestibular apparatus on the normal side continues to supply the vestibular nuclei with a constant signal. This imbalance is "interpreted" by the brain stem as rotation or movement of the body. A nystagmus will be generated, even though the body and head are stationary, with the slow phase directed toward the side of the lesion. By convention, the nystagmus is described by reference to the fast phase. A nystagmus can be characterized by the position the animal is in when the movement is generated and by the actual movement of the eyeballs themselves. For a postural

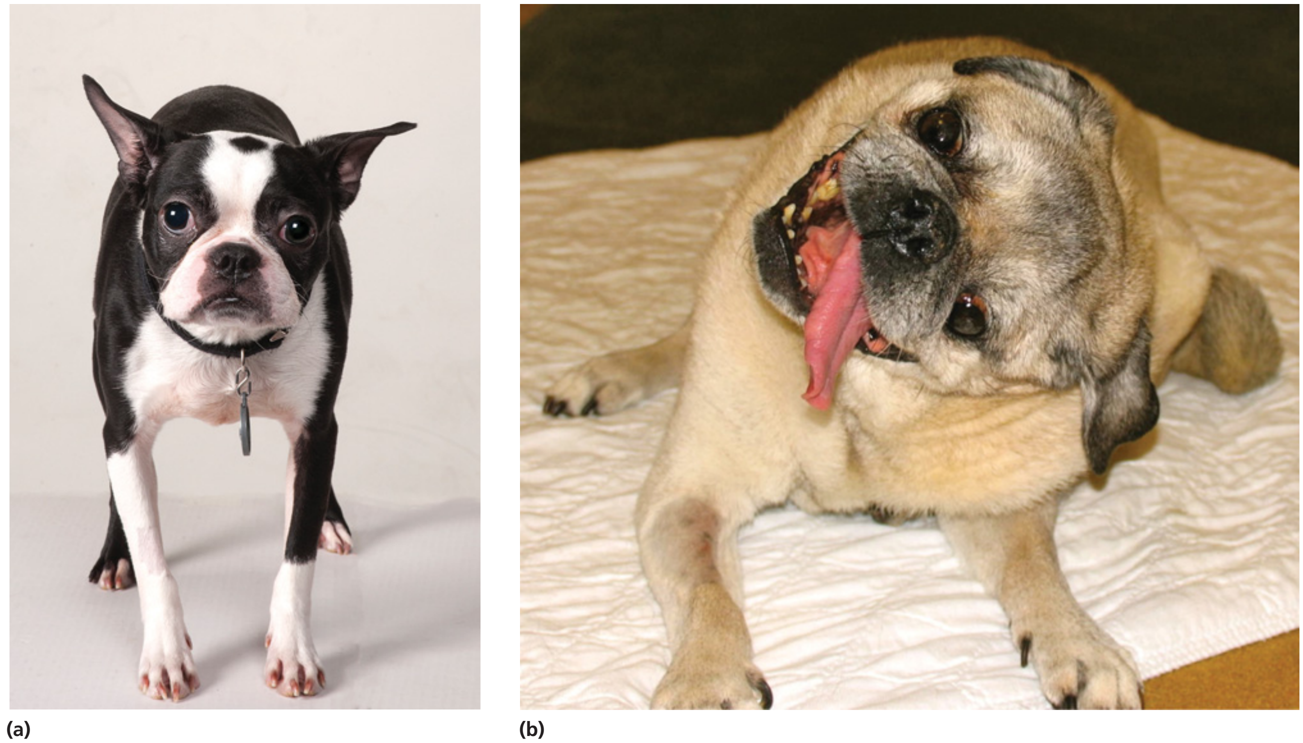
(a) (b)

Figure 11.6 Two dogs displaying head tilt of different severities. (A) Mild left-sided head tilt. To facilitate visualization, draw an imaginary horizontal line at the center of the eyes. (B) Severe left-sided head tilt. The severity of the head tilt has no relationship with lesion localization, i.e. central or peripheral vestibular disease.

description, the nystagmus may be spontaneous or positional. With a spontaneous nystagmus, the movement is present when the animal is in a normal postural position. With positional nystagmus, the involuntary eye movements are elicited when the animal is placed in an abnormal position, such as turned on its back or held upside down. The nystagmus may also be described based on the plane in which the eyeballs are moving. The movements can either be horizontal, vertical, or rotary. The nature of the movement (horizontal, vertical, or rotary) is dependent on which semicircular canal is affected. The vertical semicircular canals cancel each other out; therefore, horizontal or rotary nystagmus is seen with peripheral vestibular disease. Because injury to the peripheral vestibular apparatus rarely involves one semicircular canal, usually there are components of both rotary and horizontal nystagmus, and the character may change between examinations. Finally, nystagmus can be described as either conjugate, in which case both eyes are moving in the same direction, or dysconjugate, in which case each eye is moving in a different direction.

Strabismus is an abnormal position of the eye. Strabismus is often present in dogs and cats with vestibular disease. This is usually seen as a deviation of the eye ventrally and laterally on the ipsilateral side (Fig. 11.7). This strabismus may be positional (induced when the head is rotated dorsally) or spontaneous (always present). In some cases, the strabismus may be induced upon rotation of the head dorsally, and then the eye slowly returns to the normal position of looking straight up at the examiner. This may be seen with careful observation of both eyes while looking for subtle differences in the position of the globe. This type of strabismus is not due to paralysis of any of the cranial nerves that innervate the extraocular muscles of the eye but due to a disorder of vestibular input.

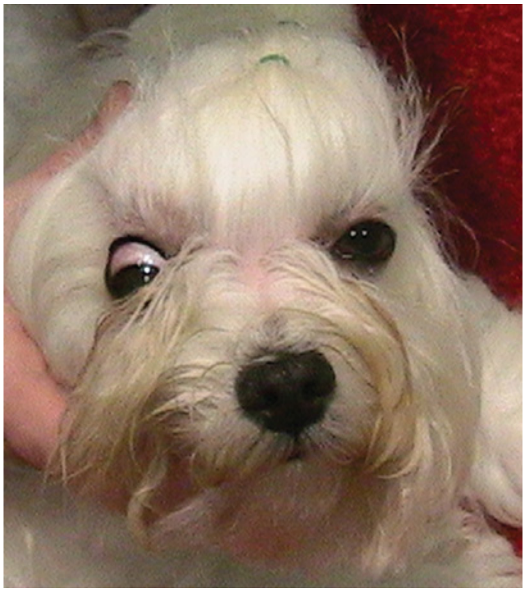

Figure 11.7 Dog with a positional ventrolateral strabismus. This patient was tentatively diagnosed with granulomatous meningoencephalomyelitis.

Motion sickness secondary to vestibular function is rarely reported in dogs and cats, but probably occurs, especially in cases of acute vestibular dysfunction. Vomiting and salivation secondary to vestibular disease have been treated with various medications. Some are thought to have weak anticholinergic activity and therefore decrease the firing rate of the neurons at the vestibular nuclei. The vomiting center is located within the reticular substance of the medulla, and there are direct connections from the vestibular nuclei to the vomiting center. It is thought that relief from motion sickness may result by suppressing the activity of the vestibular nuclei. Drugs that have commonly been used are the phenothiazine derivative chlorpromazine (at a dose of 0.2–0.4 mg/kg SQ q 8 hrs in dogs and cats), and the antihistamines diphenhydramine, dimenhydrinate, and meclizine. The phenothiazines are thought to exert their effect through action at D_2-dopaminergic, M_1-cholinergic and α_2-adrenergic receptors. They are not particularly effective in preventing vomiting associated with motion sickness in dogs and cats and it suggested that the effectiveness that is observed may be due to the sedative effects of the drugs. The antihistamines also exert some anticholinergic effect and are far more effective in preventing vomiting associated with motion sickness in people then compared to dogs and cats. A suggested dose for diphenhydramine is 2–4 mg/kg PO or IM q 8 hrs in the dog or cat. Dimenhydrinate can be given at 4–8 mg/kg PO, q 8 hrs in the dog or cat. There are several suggested dosing regimens for oral meclizine: the authors recommend 25 mg q 24 hrs for medium- to large-breed dogs and 12.5 mg q 24 hrs for smaller dogs and cats. None of the above-mentioned drugs is labeled for use in small animals. Maropitant is a veterinary-labeled drug specifically manufactured for the treatment of motion sickness in dogs and cats. It has been shown to be effective in the prevention of vomiting induced by motion sickness in dogs (by 79% of those treated when compared to placebo). Its mechanism of action is through antagonism of the NK_1 receptors which bind substance P in the emetic center and in particular at afferent inputs from the vestibular apparatus and cerebral cortex to the nucleus tractus solitarius. Antagonism of substance P receptors is a highly effective means of preventing vomiting induced by emetogenics such as cisplatin, copper sulfate, and apomorphine in dogs and cats. A dose of 8 mg/kg PO q 24 hrs given 1 hr before an anticipated event, which would induce motion sickness, is recommended. Treatment for more than two consecutive days is not recommended. As always, contraindications and adverse side effects of each drug should be reviewed before administration.

Clinical localization of peripheral versus central vestibular disease (Videos 8, 19 and 20)

There are numerous clinical signs that can help the practitioner in localizing a vestibular lesion. The primary goal is to decide whether the problem is within the peripheral vestibular system or the central (brain) vestibular system. An accurate history and physical and neurologic examination are essential to success. The first priority is to determine whether vestibular disease is a

Table 11.1 Differentiation of peripheral vs. central vestibular disease.

Neurologic sign	Peripheral	Central
Proprioceptive deficits	No	Usually
Altered mentation	No	Possible
Head tilt	Yes	Yes
Deficits other than CN VII or VIII	No	Possible
Nystagmus	Yes	Yes
Horizontal	Yes	Yes
Rotary	Yes	Yes
Vertical	No	Yes
Positional	No	Yes
Spontaneous	Yes	Yes
Conjugate	Yes	Yes
Dysconjugate	No	Yes
Strabismus	Yes	Yes

likely candidate for the animal's presenting signs. A key component in the diagnosis of central vestibular disease is the presence of neurologic deficits that cannot be attributed to the peripheral nervous system (PNS) alone. Seizures, neck pain, tremors, and myasthenia gravis are often mistaken for vestibular disease. Animals with vestibular dysfunction will usually present with a primary complaint of head tilt, nystagmus, or ataxia (or combinations of all three). The key to differentiation between peripheral and central vestibular disease is to try to isolate the clinical signs to either involve only components of the peripheral vestibular system or include deficits that could only be explained by a central (brain) lesion. The deficits that may point the examiner in the direction of central vestibular disease include cranial nerve deficits (other than CN VII and VIII), vertical nystagmus, positional nystagmus, behavioral changes, mentation changes, seizures, and the presence of proprioceptive deficits (Table 11.1). Dogs with central vestibular disease are significantly more likely to have nonambulatory tetraparesis compared with those with peripheral vestibular disease. Clinical signs of resting nystagmus and veering or leaning to one side are significantly more common in dogs with peripheral vestibular disease.

A head tilt may be present with either peripheral or central vestibular disease. In the case of peripheral vestibular disease, the head tilt is always toward the side of the lesion. In the case of central vestibular disease, the head tilt may be toward or away from the side of the lesion (see discussion below of paradoxical vestibular disease).

Nystagmus that is either horizontal or rotary in nature can indicate either central or peripheral vestibular disease; however, the presence of a vertical nystagmus is highly suggestive of a central disease process. With peripheral vestibular disease, the fast phase of the nystagmus is away from the lesion. With central vestibular disease, the fast phase may be in either direction (toward or away from the lesion). The nystagmus is usually not positional with peripheral vestibular disease. Because animals are able to compensate rather well for peripheral vestibular disease, the nystagmus may only be present for a few days. With central lesions, the nystagmus is often positional, and it may change character (e.g. vertical to rotary) when the head position is altered. Another factor that may help with the differentiation between central and peripheral vestibular disease is the number of beats per minute (BPM) of resting nystagmus. It has been found that dogs with a resting nystagmus rate of ≥ 66 BPM are significantly more likely to have peripheral vestibular disease (median rate = 90 BPM), compared with those with central vestibular disease (median rate = 0 BPM). Additionally, the longer the clinical signs are present, the slower the rate of resting nystagmus (inverse correlation). With bilateral peripheral vestibular disease, a nystagmus (or head tilt) will often not be present. These animals will appear as if they are getting ready to collapse. They will walk very tentatively, with a low, crouched-down stance. Such patients may also display wide, side-to-side head excursions when ambulating.

The presence of strabismus is more of a "soft" finding when trying to differentiate peripheral from central vestibular disease. With peripheral lesions, the strabismus tends to be ventral or ventrolateral on the same side as the lesion (ipsilateral). Strabismus is often positional, regardless of whether the causative lesion is peripheral or central. Extending the patient's neck (moving the head dorsally) often elicits a ventral or ventrolateral strabismus in patients with vestibular dysfunction. With a lesion in the central vestibular system, the strabismus may be deviating in various directions. Dysconjugate strabismus describes a deviation of both eyes but in different directions. This is an uncommon finding and is usually associated with central vestibular disease.

The facial nerve (CN VII) enters the internal acoustic meatus of the petrosal bone and courses through the facial canal to the point where it exits the skull (stylomastoid foramen) dorsal to the tympanic bulla. Because of its intimate contact with the peripheral vestibular system, disease processes such as otitis may affect facial nerve function. This may be manifested as complete or partial facial nerve paralysis or spasm. The sympathetic innervation to the eye also passes in close contact with the structures of the middle and inner ear. Therefore, the sympathetic system may be affected by peripheral vestibular disease and clinical signs of ipsilateral Horner's syndrome (ptosis, enophthalmos, miosis, protrusion of the third eyelid) may be present. Deficits in facial nerve function or sympathetic innervation to the eye suggest a peripheral lesion, especially in the face of otitis or trauma to the same side and absence of conscious proprioceptive deficits.

The presence of cranial nerve deficits other than the facial or vestibulocochlear nerve is suggestive of a central problem. Alterations in mental status or level of consciousness may support a diagnosis of central vestibular disease based on the notion that vestibular projections to the reticular substance in the brain stem may be affected along with the neighboring ascending reticular activating system. The single strongest sign of central vestibular disease is the presence of conscious proprioceptive deficits. It is common to mistake ataxia for proprioceptive deficits. Ataxia may be present with both central and peripheral vestibular disease. Because the proprioceptive pathways do not come into contact with the peripheral vestibular system, alterations of conscious proprioception are consistent with a central lesion. Portions of the cerebellum add to the maintenance of posture; therefore, cerebellar signs, along with vestibular signs, suggest either brain stem and/or cerebellar dysfunction. Clinical signs attributed to the forebrain (e.g. seizures, vision loss, behavioral or mentation changes), along with vestibular signs, suggest a multifocal or diffuse disease process.

Paradoxical vestibular disease refers to lesions of the central vestibular system in which the head tilt is away from the lesion. The cerebellum normally sends inhibitory efferent projections through the caudal cerebellar peduncle to the ipsilateral vestibular nuclei. If there is a lack of inhibition to the vestibular nuclei on the same side as the cerebellar lesion, the vestibular nuclei will be disinhibited, and through a mechanism similar to that discussed previously, there will be greater facilitation of the extensors on the ipsilateral side and facilitation of the contralateral flexors. Therefore, the body will lean away from the side of the lesion, and the head tilt will be in the opposite direction. In these cases, the fast phase of any resulting nystagmus will be toward the lesion. In many cases there will also be asymmetric conscious proprioceptive deficits. The lesion can be localized to the same side as the worst conscious proprioceptive deficits. Paradoxical vestibular disease can be seen with lesions of the flocculonodular lobes of the cerebellum, the caudal cerebellar peduncles, and the rostral and medial vestibular nuclei in the medulla. Occasionally, abnormalities in the dorsal nerve roots of C1–C3 will produce a paradoxical head tilt, and, if present, conscious proprioceptive deficits will localize the lesion to the most severely affected side.

Clinical evaluation of the auditory system[34, 90, 116]

The ear canals of dogs and cats open within the second week of life; however, the complete maturation of the auditory system does not occur until 6–8 wks of age. Some estimates have put the maturation date at 4–8 wks. When assessing hearing in dogs and cats, it is better to err on the conservative side and wait for complete maturation of the auditory apparatus. The entire auditory pathway, including the cerebral portions, is probably not completely matured until 12 wks of age. The clinical assessment of a suspected deaf animal can be difficult. Bearing this in mind, it is important to remember that all animals may react to vibratory clues (slamming a book on a table or shutting a door) or visual cues (clapping hands). Therefore, one should endeavor to stay out of the animal's visual field when trying to elicit an auditory perceived response. Complete hearing loss can be a challenge to assess clinically, and partial or unilateral hearing loss is even more difficult to ascertain. Central deafness, or deafness due to an abnormality in the brain stem without concomitant signs of diffuse neurologic disease, is rare. Because there are multiple points along the auditory pathways from the cochlear nuclei to the thalamus that cross, the auditory pathways are well represented bilaterally within the brain stem. It would therefore take a severe injury or disease process in order to completely disrupt auditory function. A process of that degree would certainly manifest itself with other signs of severe brain-stem disease. Therefore, complete bilateral deafness is usually caused by an abnormality with the auditory receptor (the organ of Corti) and more specifically with the hair cells themselves. The history and signalment of an animal suspected of having auditory dysfunction is very important. Especially pertinent are the breed of the dog and the age of onset when the owner first suspected a problem. This may help differentiate congenital deafness from acquired deafness, which may affect breeding programs. Other signs of neurologic disease, especially vestibular disease, are important to document, as well as any history of trauma to the head or ears, use of potentially ototoxic drugs or compounds, and any previous or current clinical signs of irritation (such as head shaking, odor, or exudates from the external ear canal). There are two types of deafness in dogs and cats: conduction deafness and sensorineural deafness.

Conduction deafness

When the middle or external ear is responsible for hearing loss, such loss is due to a problem with the actual conduction or transmission of the sound waves from the external environment to the cochlea. Blockage of sound wave transmission may be due to occlusion of the external ear canal by ceruminous debris, tissue, or foreign bodies. These blockages may be congenital, as in the case of birth defects, or acquired. Conduction blockage in the middle ear may be due to rupture of the tympanic membrane, fluid or exudate, excessive tissue growth, foreign body, malformation of or damage to the ossicles, or stiffening of the ossicles with age.

Sensorineural deafness

If the inner ear auditory structures or auditory pathways are compromised, sensorineural deafness may result. Abnormalities of the cochlea, cochlear portion of the vestibulocochlear nerve, auditory pathways in the brain, thalamus, and cerebrum all have the potential to lead to a blockage of the auditory signal transmission and subsequent deafness. In all practicality, almost all cases of pure sensorineural deafness are due to a functional problem with the hair cells of the organ of Corti. There are no degenerative, congenital, or acquired conditions that specifically target the auditory pathways and projections in the brain.

Diseases affecting the peripheral vestibular system[4, 7, 9, 15, 19, 34, 36, 41, 48, 55, 61, 64–66, 68, 71, 80, 82, 83, 86, 92, 104, 105, 113, 119, 122, 128, 129, 137]

Degenerative/anomalous

Peripheral vestibular disease may be evident in young animals and attributed to a congenital malformation or degeneration of the inner ear structures. If the abnormality is bilateral, these animals may not have a head tilt or nystagmus; however, they will frequently have a symmetrical ataxia, a wide-based stance, and a side-to-side movement of the head in the horizontal plane. The vestibular disease may be present in association with deafness. The clinical signs will usually present when the animals begin to ambulate. They may consist of head tilt, nystagmus, strabismus, ataxia, circling, falling, rolling, and abnormal head movements. Clinical signs associated with the vestibular disease may resolve; however, a head tilt or head tilt that shifts from side to side may persist. Many of the reported animals with this congenital peripheral vestibular disease will compensate for the abnormalities in balance. It is thought that any compensation is centrally mediated, likely through visual mechanisms. If the animal is deaf, the hearing abnormality is permanent. The abnormality has been known to affect German Shepherds, English Cocker Spaniels, Doberman Pinschers, as well as Siamese and Burmese cats. In a report of Doberman Pinscher puppies affected from multiple litters from the same dam, a lymphocytic labyrinthitis was discovered on histological examination. An *in utero* viral infection was hypothesized to cause the degeneration. No other abnormalities have been documented in affected animals. There is no treatment for the condition.

Metabolic

Hypothyroid-associated neurologic dysfunction is well recognized. Specific involvement of the peripheral vestibular system may be the primary presenting clinical complaint. It is usually seen in older animals as an acute onset, nonprogressive presentation. Nearly all animals will have a head tilt and positional strabismus. Many animals also have decreased menace responses and decreased palpebral reflexes. More obvious signs of facial nerve paralysis may also be present. Other clinical signs may be an abnormal gait and circling. Brain-stem auditory evoked response (BAER) testing may be abnormal. There may be other clinical and clinicopathological signs of hypothyroidism (hypercholesterolemia, abnormal thyroid-stimulating hormone response). Hyperlipidemia may be a contributing factor. Labrador Retrievers with severe hyperlipidemia have been described with central and peripheral vestibular signs, tetraparesis, paraparesis, and facial nerve paralysis. Infarction may be an inciting or contributing factor. Other potential causes of vestibular disease must be ruled out, paying special attention to possible structural disease. Because the clinical signs associated with this disease may suggest central vestibular disease, the clinician should be certain a poor prognosis is not given to the owners of the animal without first evaluating and ruling out the possibility of hypothyroidism. The diagnosis may be challenging in that many animals are mistakenly thought to have euthyroid sick syndrome. With an adequate supplementation of levothyroxine, the majority of these animals will return to normal.

Neoplastic

Neoplastic processes affecting the PNS may result in peripheral vestibular disease by compression or invasion of the vestibulocochlear nerve. Peripheral nerve tumors (i.e. schwannomas) may initially present as peripheral vestibular dysfunction; however, with time they can invade the brain stem. Tumors of the ear (e.g. ceruminous gland adenocarcinoma) may invade the middle and inner ear and cause vestibular disturbances. Other tumors—such as chondrosarcoma, osteosarcoma, fibrosarcoma, and squamous cell carcinoma—have the potential to invade adjacent tissue, resulting in vestibular disease. Treatment is directed at the primary lesion. Supportive treatment for vestibular dysfunction may also be necessary.

Idiopathic (Video 19)

A condition of idiopathic vestibular disease is well recognized in dogs and cats. Cats of any age can be affected. Dogs tend to be older, and therefore the disease is often referred to as *idiopathic geriatric vestibular disease*. These vestibular episodes are often confused with vascular accidents (“strokes”) or seizures. The key to this diagnosis is the absence of any detectable structural, metabolic, or inflammatory disease, as well as lack of evidence of central vestibular disease. The onset is acute or peracute, and animals may present with signs of dysfunction ranging from a mild head tilt to severe imbalance and rolling. The clinical signs are usually unilateral, with a horizontal or rotary nystagmus (fast phase away from the side of the head tilt) and an asymmetrical ataxia. The ataxia may be confused with proprioceptive deficits. Animals with idiopathic vestibular disease maintain their strength and mental status. The vestibular signs can be so severe that the affected animals are often incapacitated, making the initial neurologic exam difficult, especially in cats. Most animals will improve rapidly, although complete recovery may take 2–3 wks in a typical case. Improvement is often appreciated within the first 72 hrs. In some animals, clinical signs may persist for up to 5 wks. Occasionally, a mild head tilt will persist after other clinical signs have resolved. The condition can be relapsing. It is thought that this syndrome may result from abnormalities with the endolymphatic fluid of the inner ear structures, a mild intoxication of the vestibular system, or autoimmune disease. There is no specific treatment for the disease. The use of corticosteroids has not resulted in more rapid clinical improvement. Care should be directed at supportive treatment, which may include sedatives, and therapy directed at relieving motion sickness. There is debate as to whether central signs (such as proprioceptive deficits) may be present with this clinical syndrome. Occasionally, in geriatric dogs with this disorder, pelvic limb conscious proprioceptive deficits will be demonstrated on neurologic examination. In many of these cases, the placing deficits are suspected to be due to chronic, subclinical disc protrusions unrelated to the vestibular disorder. However, until there is substantial improvement in vestibular function, or central nervous system (CNS) disease is ruled out, pelvic limb conscious proprioceptive deficits should be considered potential evidence of a central vestibular disorder.

Inflammatory/infectious (Video 20)

The most common cause of peripheral vestibular disease in dogs and cats is otitis media/interna. It has been associated with approximately 50% of the cases of peripheral vestibular disease in older animals. The incidence is much lower in cats. The etiology of this condition is multifactorial. Otitis media/interna may develop from extension of otitis externa across the tympanic membrane, from the nasopharynx via the Eustachian tube, or hematogenously. In most cases, otitis externa is thought to develop as a secondary complication of various disease processes; such disorders include hypersensitivities (e.g. atopy, contact allergy, food allergy), parasites (e.g. *Otodectes cynotis*, *Demodex canis*), foreign bodies, and tumors. The most common infectious agents are *Staphylococcus* spp., *Streptococcus* spp., *Pseudomonas* spp., *Proteus* spp., and *Malassezia pachydermatis*. *Herpes* virus infection has been associated with or suspected to be the underlying etiology in several human conditions causing vestibular dysfunction (Ménière's disease, Ramsay Hunt syndrome). Sensory ganglia are a site of viral latency with possible sources of infection being hematogenous, sensory nerve endings on the body surface, and through the meninges via the endolymphatic duct and cochlear aqueduct. A naturally occurring canine herpesvirus infection of the vestibular labyrinth and ganglion of dogs has been identified. Its role in the possible etiology of vestibular disease in dogs is unknown. However, its presence raises the possibility of it as a potential cause of the symptoms, similar to what is suspected for cases such as idiopathic facial nerve paresis/paralysis and trigeminal neuritis. In addition to infectious otitis media/interna, an apparently noninfectious form of otitis media has been described in Cavalier King Charles Spaniels. This disorder has been termed *primary secretory otitis media (PSOM)* and denotes the accumulation of a viscous mucus plug within one or both middle ear cavities. These dogs do not have evidence of otitis externa and display clinical signs of discomfort around the head and neck regions, as well as other indications of otitis media (e.g. head tilt, facial nerve dysfunction). Although the pathophysiology of PSOM is unknown, it has been theorized that an increased production of mucus within the middle ear cavity, a decreased drainage of this mucus via an abnormal Eustachian tube, or a combination of these two factors may be involved. A complete, deep otoscopic exam is imperative. Additionally, a myringotomy with associated histopathology, antimicrobial culture, and sensitivity will direct the clinician to a proper treatment regimen. Radiographs or advanced imaging, such as computed tomography (CT) or magnetic resonance (MR) imaging, may confirm involvement of middle and inner ear structures. Occasionally, cases of otitis media/interna may extend centrally. In these cases, advanced imaging techniques such as MR imaging may help the clinician to prognosticate, depending on the character of the lesion, and evaluate potential success of treatment (Fig. 11.8). A combination of surgery (ventral bulla osteotomy) and antibiotic treatment appears to be associated with a favorable prognosis in cases of bacterial otitis media/interna that extend into the brain in dogs and cats. If myringotomy samples are not successful in the diagnosis of an etiologic agent and the animal does not respond to broad-spectrum antimicrobials, a bulla osteotomy may be indicated both as a treatment modality and to arrive at a definitive diagnosis of the etiologic agent. Most cats with polyp-associated otitis media/interna will require a bulla osteotomy for resolution of clinical signs. General treatment of otitis media/interna consists of the removal of any offending foreign bodies, adequate control of parasites, and usually long-term antibiotics or antifungals specifically directed at the offending organism(s) for 3–6 wks or until resolution of clinical signs. Occasionally, animals may need to be treated with medications directed at improving signs associated with motion sickness (e.g. diphenhydramine, dimenhydrinate, maropitant). Any predisposing anatomic conditions may have to be addressed if the condition is chronic or relapsing (surgical resection or ablation of the ear canal). The prognosis for recovery is good if the damage to the receptor organs is not severe. Many animals will be able to centrally compensate for any residual vestibular deficits.

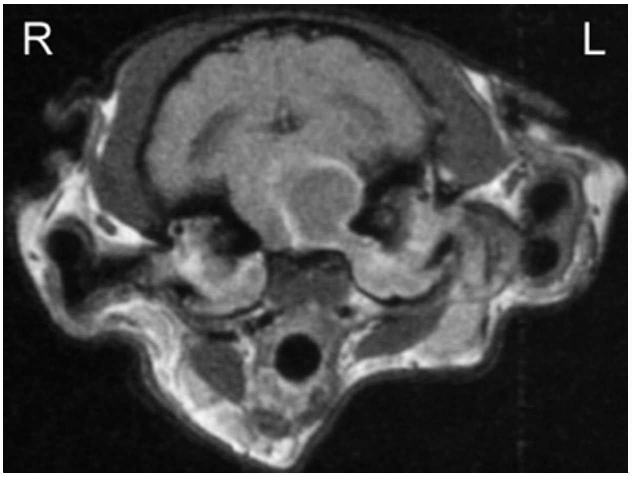

Figure 11.8 Transverse T1-weighted MRI (with contrast) of a cat with otitis media/interna that extended into the brain stem. (Sturges and Rosychuk 1994. Reproduced with permission from Elsevier.)[120]

Toxic

The same toxic substances that may result in hearing deficits will affect the labyrinthine receptors of the vestibular system (see the "Diseases affecting the auditory system" section below). Animals will usually present with signs of unilateral vestibular disease, although bilateral involvement is possible. The most common compounds are antimicrobials that belong to the family of aminoglycosides, loop diuretics (e.g. furosemide, ethacrynic acid), and ear-cleansing compounds. If toxicity is recognized early, and the offending compound is discontinued, vestibular signs may resolve.

Traumatic

Although uncommon, trauma to the petrous temporal bone may cause unilateral vestibular signs. Disruption of the bony and membranous labyrinth will predominate; however, if the injury is severe, other adjacent structures may be affected. It is much more common to have associated brain-stem, cerebellar, or supratentorial signs with trauma to this region of the skull. Ipsilateral facial nerve or trigeminal nerve dysfunction may also result. If the injury is mild or confined to the petrous temporal bone, or the animal heals from associated areas of trauma (brain stem or cerebellum), the prognosis for recovery from peripheral vestibular disease is good, providing central compensating mechanisms are adequate.

Diseases affecting the central vestibular system[4–6, 11–13, 15–18, 20, 24, 26, 28, 29, 32, 34–37, 42–44, 46–49, 54–57, 59–61, 64, 69, 70, 72, 73, 77, 79, 80, 83, 85–89, 91, 94, 97, 100, 101, 103, 104, 106, 112, 119, 121, 123, 124, 128, 129, 134, 136, 138, 139]

Any disease process involving the brain has the potential to manifest itself with vestibular dysfunction. Alterations of normal vestibular pathways as a direct result of ischemia, compression, or infiltration will be secondary to the primary offending lesion. There are no recognized diseases of the CNS that specifically target the vestibular pathways; however, some of the disease processes that affect the vestibular structures do so preferentially.

Neoplastic

Any neoplastic process, whether primary or secondary, may affect portions of the nervous system involved with vestibular functions. Ischemia, compression, and infiltration may all result from neoplasia. The clinical signs associated with the tumor may have an acute onset or be slowly progressive. They may result from a tumor in the immediate vicinity of the brain stem or supratentorial masses that compress the diencephalon and cause secondary compression of the brain stem (either directly from brain parenchyma or via herniation). Tumors of the fourth ventricle—such as choroid plexus papillomas, ependymal tumors, as well as epidermoid and dermoid cysts—may cause compression of adjacent brain-stem structures. Medulloblastomas originating from the cerebellum may affect the brain stem or the vestibulocerebellum. Oligodendrogliomas and astrocytomas may involve parenchyma directly associated with vestibular pathways. The most common brain tumors of dogs that affect vestibular function and associated brain-stem areas are meningiomas and choroid plexus tumors (Fig. 11.9). Meningiomas and lymphomas are common neoplastic lesions in cats. The prognosis depends on many factors, including the location, tumor type, size, and systemic status of the animal. Treatment options include glucocorticoids to alleviate any peritumoral edema, chemotherapy, surgery, radiation therapy, or a combination of all of these (see Chapter 7 for more details concerning brain tumors).

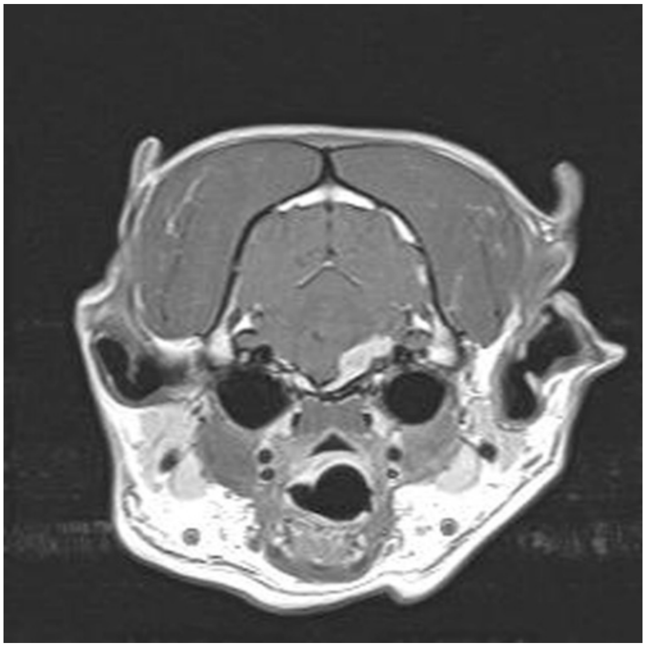

Figure 11.9 Transverse, T1-weighted MRI (with contrast) of a dog with a plaque-like meningioma involving the ventrolateral medulla.

Inflammatory/infectious (Video 8)

Canine distemper virus (CDV) may cause a distemper encephalomyelitis. Older dogs that develop distemper encephalomyelitis may present with an altered gait and vestibular disease. These dogs usually have an adequate vaccination history, and a diagnosis of canine distemper encephalomyelitis can be difficult. Cerebrospinal fluid (CSF) may be characterized by a moderate mononuclear pleocytosis that is positive for the antibody directed at the CDV. It is important to realize that a breakdown in the blood–brain barrier (BBB) may result in a false positive test result due to a leakage of systemic antibody into the CSF. More specific information regarding diagnostic testing for CDV infection can be found in Chapter 7. Young dogs affected with distemper encephalomyelitis may recover from their systemic disease. In these cases, the resolution of vestibular signs may follow. Cats infected with the feline infectious peritonitis (FIP) virus will often develop vestibular signs. Cats diagnosed with FIP usually have the dry form of the disease. A diagnosis is based on history, potential exposure, clinical signs, and the demonstration of a high CSF antibody titer directed at the feline coronavirus (see Chapter 7). There is no treatment for the disease, and the prognosis is poor if the clinical signs are severe.

Dogs infected with the rickettsial agents causing Rocky Mountain spotted fever (RMSF) or ehrlichiosis may, among other clinical signs, develop vestibular dysfunction. The diagnosis of rickettsial infection will be based on potential exposure to ticks, hematological and biochemical abnormalities, clinical signs consistent with rickettsial disease, a single high titer, and/or a rising titer. Most cases will present between April and October, with the highest incidence in the month of June. RMSF is typically an acute onset infectious disease. Characteristic abnormalities may include anorexia, lethargy, fever, cutaneous lesions, ocular lesions, leukocytosis, anemia, thrombocytopenia, and other signs referable to a vasculitis. Vestibular signs may include a horizontal nystagmus and ataxia. Early recognition and treatment with doxycycline will often result in the complete resolution of the disease and vestibular signs.

Meningoencephalomyelitis resulting from primary bacterial infections is an uncommon occurrence in dogs and cats. When suspected, a CSF tap followed by antimicrobial culture and sensitivity, is indicated. A combination of antimicrobials should provide broad-spectrum antimicrobial activity against most organisms if a specific etiology cannot be determined. Animals with an inflammatory CSF sample may benefit from low doses of prednisone (0.5 mg/kg bid). The anti-inflammatory activity of the prednisone may alleviate some of the inflammation responsible for the clinical signs. The dose is low enough that it should not severely inhibit the immune response and may be discontinued early in the course of treatment (see Chapter 7). Other infectious organisms such as *Toxoplasma gondii* and *Neospora caninum* can infect the nervous system and result in clinical signs that may include vestibular disease. Other clinical signs such as myalgia (due to myositis), paresis, and multifocal systemic involvement may predominate. Chapter 7 contains more information on the diagnosis and treatment of toxoplasmosis and neosporosis. Fungal infections involving the nervous system may be isolated to neural tissue; however, most animals will show other systemic signs of fungal disease, including cutaneous, ocular, respiratory, and gastrointestinal disease. The most common fungal organism to involve the nervous system of dogs and cats is *Cryptococcus neoformans*. Coccidioidomycosis may be suspected in dogs with recent respiratory signs. Animals will often recover from a mild respiratory tract infection. In order to make this diagnosis, the animal's history should indicate that it has been in the Southwest United States. Another fungal infection that usually affects multiple organs is blastomycosis. Multifocal disease, along with any indication for potential fungal infection (travel history, unresponsiveness to antimicrobials, etc.), should give the clinician cause to investigate a possible fungal infection with attempts at direct visualization of the organism from infected tissues, CSF analysis, and serology. The prognosis depends on the duration of the infection and the severity of clinical signs. Fluconazole is the antifungal of choice for cases of cryptococcosis and coccidioidomycosis. Very few animals show improvement with antifungal treatment for nervous system infection of blastomycosis. Disseminated protothecosis has been reported to cause vestibular signs in a dog. *Prototheca wickerhamii* and *Prototheca zopfii* have been identified as pathogenic species of algae. Although an uncommon infection, other clinical signs of multi-organ involvement are usually apparent. The prognosis for animals infected with protothecosis is poor.

It is thought that granulomatous meningoencephalomyelitis (GME) is a primary autoimmune disease. This disease may represent an immune response to an as yet unidentified organism. There are disseminated (multifocal), focal, and ocular forms of the disease. The distinction between autoimmune disease and neoplasia has been debated. This disease typically affects middle-aged, small-breed dogs. Brain-stem signs including vestibular dysfunction are the primary signs associated with the disease; however, clinical signs would be referable to that portion of the nervous system that is most severely affected. In the vast majority of cases, a definitive diagnosis of GME can only be made on a postmortem examination of affected tissue. The histologic lesions consist of perivascular granulomas comprising primarily dense accumulations of inflammatory cells. Accumulations of histiocytes, lymphocytes, and plasma cells in the nervous system result in compression and invasion of surrounding tissue. A presumptive diagnosis may be made based on CSF analysis, by ruling out infectious etiologies, and by a demonstration of focal or diffuse contrast-enhancing lesions on CT or MR examination. Lesions may not be evident on CT/MR images in GME cases. On CSF examination, there is usually a mixed, predominantly mononuclear, pleocytosis and moderately elevated protein. Most animals will initially show a response to systemic corticosteroids; however, the remission of disease is usually short-lived. Radiation therapy may provide an effective treatment option for dogs with focal GME. Improved survival times for GME have been obtained in recent years with the use of several new treatment options, including procarbazine, cyclosporine, and cytosine arabinoside (see Chapter 7).

Toxins

Metronidazole has been associated with vestibular disease. The onset is acute and usually occurs when animals receive high doses of the medication for a long duration. However, signs of metronidazole toxicity have been seen with treatment for as little as 1 wk and as long as 4–6 wks. There is much debate as to the toxic dose of metronidazole in the dog. Both dogs and cats are susceptible to metronidazole toxicity, and the toxicity is well recognized in humans. Clinical signs of metronidazole toxicity usually show up 7–12 days after continuous high doses (greater than 60 mg/kg/day), but they have also been reported to occur at lower doses. The exact mechanism of the toxicity is unknown. It has been hypothesized that it may interfere with RNA synthesis or possibly inhibit the actions of the primary inhibitory neurotransmitter in the cerebellum and vestibular systems; gamma-aminobutyric acid (GABA). The onset of clinical signs is likely dependent on the dose the animal is receiving. However, clinical signs can also develop after long-term, low-dose therapy. They may consist of generalized ataxia, nystagmus, anorexia, and vomiting. In severe cases, altered mental status, seizures, and opisthotonus may be present. Cats are typically affected by altered mental status and supratentorial dysfunction (seizures, blindness, and ataxia). Clinical signs will usually resolve within 1–2 wks after discontinuation of the drug. Clinical recovery has been shown to be more rapid in dogs that were treated with injectable and oral diazepam compared to those that were not treated. In a treated group, dogs receiving an average dose of 0.43 mg/kg of injectable or oral diazepam every 8 hrs for 3 days had an average recovery time of 38.7 hrs compared to an average recovery time of 11.6 days in those that were not treated. Some changes to the CNS may result in permanent neurologic deficits. Although a very effective antimicrobial, metronidazole is not innocuous. It is recommended that the dosage schedule be individualized for every animal, dependent upon the intended target of the drug. For most applications of metronidazole, a total daily dose of 30 mg/kg body weight (e.g. 10 mg/kg body weight, q 8 hrs) is sufficient.

Miscellaneous

Degenerative processes rarely specifically affect the central vestibular system. However, hereditary polioencephalomalacia results in degeneration of central vestibular pathways (thalamocortical pathway), such as the caudal colliculus, vestibular nuclei, and cerebellar nuclei, amongst other areas of the brain and cervical spine. Cases have been reported in Australian Cattle Dogs and a Shih Tzu. A heritable, rapidly progressive lethal necrotizing encephalopathy similar to human Leigh syndrome (a mitochondrial encephalopathy) has also been reported in related American Staffordshire Terrier dogs. These dogs presented at 6–8 wks of age with clinical signs of neurologic dysfunction referable to the central vestibular system (ataxia, head tilt, intention tremor, strabismus, and nystagmus). This disorder is distinct from another mitochondrial encephalopathy that affects this breed (L-2-hydroxyglutaric aciduria). Vestibular dysfunction may result secondary to ischemic changes or direct trauma to the vestibular pathways. Hydrocephalic animals may have vestibular deficits that are part of the constellation of clinical signs that are commonly present (see Chapter 7). Metabolic disturbances—such as hepatic encephalopathy, altered electrolyte balance, or renal disease—may also cause secondary vestibular signs; however, these abnormalities would not likely cause isolated alterations in vestibular function. Rather, they would result in multifocal signs, of which vestibular signs may be a part.

Thiamine deficiency is a nutritional disorder that can affect the vestibular system. The deficiency may result from a diet that is deficient in thiamine, an all-cooked diet, or a diet that contains large amounts of thiaminase (fish viscera). Thiamine is necessary for the completion of the citric acid cycle and therefore is particularly important in tissues that rely on glucose for energy (brain). Thiamine deficiency primarily results in bilaterally symmetrical areas of necrosis, spongiosis, and hemorrhage in the brain stem. In cats, the vestibular nuclei are often affected, resulting in vestibular signs. Cerebellar signs consisting of ataxia, tremors, and absent menace responses may also be seen. Because the heart is also very dependent upon glucose as a fuel source, it too may be affected. Bradycardia, tachycardia, and arrhythmias may be appreciated with thiamine deficiency. If diagnosed early, many animals will respond to parenteral administration of thiamine hydrochloride (vitamin B_1). Many animals will have a complete resolution of clinical signs if treated early.

Hypothyroidism has been associated with central vestibular dysfunction in a limited number (14) of dogs. Whether the pathophysiology of hypothyroid-related central vestibular dysfunction involves infarction, abnormal neurotransmitter release, or some combination of these and other factors is unknown. All dogs responded favorably to thyroid supplementation.

Intracranial epidermoid cysts, while technically tumors, are not neoplastic. They are commonly found at the cerebellomedullary junction but may also arise within the fourth ventricle. It is hypothesized that they arise from fragments of epidermoid tissue at an abnormal location due to a defect in neural tube closure. While the incident occurs around 3–5 wks of gestation, the clinical signs may not be apparent until adulthood. It may be challenging to differentiate intracranial epidermoid cysts from other intracranial cysts with advanced imaging; however, characteristics particular to cystic lesions in the brain with poor or no contrast enhancement in the area of the cerebellar medullary junction and fourth ventricle should be suspected. These lesions have also been described in other areas of the brain. There is one report of a fourth ventricular cholesterol granuloma in a dog.

Vascular disease is associated with central vestibular signs. Transient ischemic attacks (TIA) and cerebrovascular accidents (CVA) or strokes are widely recognized in the human population. MR imaging has aided greatly in the detection of CVA events in dogs, particularly in the region of the brain supplied by the paired rostral cerebellar artery and the paired caudal cerebellar artery, both of which arise from the basilar artery. The rostral cerebellar artery supplies the rostral portion of the cerebellar hemispheres, the vermis, and the dorsolateral brain stem. The caudal cerebellar artery provides blood supply to the caudoventral portion of the cerebellum and the lateral medulla oblongata. Ischemic events involving both these arteries have been documented in veterinary medicine. TIAs are a diagnostic challenge considering that even with advanced imaging techniques, such as diffusion-weighted imaging using MRI, the diagnosis is often presumptive based primarily on the time course of the clinical signs (usually less than 24 hrs in humans) and lack of MRI findings. Central vestibular signs may be paroxysmal and are more commonly observed in patients with hypertension, heart disease, hypercoagulable conditions, diabetes mellitus, and hypothyroidism. However, a significant number of documented CVAs have no underlying cause and are therefore defined as "cryptic" or "cryptogenic." Prognosis for complete recovery with TIAs is good to excellent, whereas that of CVAs is relatively good to excellent but significantly more dependent on the degree of damage to the affected portion of the brain. Time to recover and supportive care of the patient should be encouraged.

Diseases affecting the auditory system[1–3, 8, 14, 15, 19, 21, 23, 25, 29, 30, 33, 34, 36, 38–40, 48, 50–53, 58, 62, 63, 66, 69, 71, 75, 76, 78, 81–83, 85, 90, 93, 95, 96, 98, 99, 101, 102, 107–111, 114–118, 122, 125, 127, 131, 132]

Due to the close anatomical relationship between the auditory and vestibular receptors, abnormalities of hearing may be observed in conjunction with clinical signs of peripheral vestibular disease. As previously mentioned, a presumptive diagnosis of deafness is easier to make if bilateral disease is present.

A. Degenerative/anomalous

1. Congenital aplasia/hypoplasia of auditory receptors

   Loss of hearing receptors either *in utero* or shortly after birth is a very common cause of deafness in dogs and cats. This is a pure sensorineural deafness due to degeneration of the hair cells in the organ of Corti. It is thought that an abnormality of the stria vascularis leads to a secondary degeneration of the hair cells. Once lost, hair cells are gone forever. Dogs and cats can be either unilaterally or bilaterally affected with partial or complete hearing loss, respectively. This form of deafness often affects white-colored dogs and cats and merle or piebald-colored dogs. Non-white breeds of dogs, such as the Doberman Pinscher, can also be affected. High-incidence dog breeds include Dalmatian, English Cocker Spaniel, English Setter, Australian Shepherd, Australian Cattle Dog, and Bull Terrier. Deafness may also be associated with blue eye coloration. White cats that have two blue eyes have a 50% chance of being born either unilaterally or bilaterally deaf. The incidence of deafness in Dalmatians is reported to be nearly 30%. Congenital deafness has been reported in many breeds (Box 11.1), although not all have been shown to be hereditary. Because the degeneration of the organ of Corti may not take place until 3 wks after birth, it is important to delay testing young animals until their auditory apparatus has matured (6–8 wks). There is a syndrome of congenital deafness and vestibular dysfunction that has been reported in Beagles. Congenital deafness may also be the result of exposure to ototoxic drugs *in utero*.

2. Age-related hearing loss

   Older animals may be affected by slowly progressive hearing loss. This senile degeneration may affect the ossicles of the middle ear, resulting in conduction deafness, or the auditory receptor (organ of Corti), resulting in sensorineural deafness. This may be mistakenly interpreted as cognitive dysfunction syndrome (see Chapter 7). A BAER test will confirm the dysfunction, usually seen as an attenuation of all waveforms and increased latency from stimulus to appearance of wave I (hearing impairment) or the absence of waveforms (complete deafness). Senile ossicle or receptor dysfunction usually has a slow progression, and there is no treatment for the progression of the condition; however, hearing aids may be used in animals. The success of a hearing aid is dependent on the tolerance of the animal to having a foreign body constantly in its ear. Placing inexpensive foam earplugs in the animal's ear to see whether they are tolerated is a good way to test potential acceptance of a hearing aid.

Box 11.1 Dog and cat breeds reported to have congenital deafness.

Canine

Akita
American–Canadian Shepherd
American Eskimo dog
American Staffordshire terrier
Australian Blue Heeler
Australian Cattle dog
Australian Shepherd
Beagle
Bichon Frise
Border Collie
Borzoi
Boston Terrier
Boxer
Bull Terrier
Cardigan Welsh Corgi
Catahoula Leopard dog
Cavalier King Charles Spaniel
Chihuahua
Chow Chow
Cocker Spaniel
Collie
Dalmatian
Dapple Dachshund
Doberman Pinscher
Dogo Argentino
English Bulldog
English Cocker Spaniel
English Setter
Fox Hound
Fox Terrier
French Bulldog
German Shepherd
Great Dane
Great Pyrenees (Pyrenean Mountain dog)
Ibizan Hound
Italian Greyhound
Jack Russell Terrier
Kuvasz
Labrador Retriever
Maltese
Miniature Pinscher
Miniature Poodle
Mixed-breed dog
Norwegian Hound (Dunker)
Nova Scotia Duck Tolling Retriever
Old English Sheepdog
Papillon
Pit Bull Terrier
Pointer
Puli Rhodesian Ridgeback
Rottweiler
Saint Bernard
Schnauzer
Scottish Terrier
Sealyham Terrier
Shetland Sheepdog
Shropshire Terrier
Siberian Husky
Soft-coated Wheaten Terrier
Springer Spaniel
Sussex Spaniel
Tibetan Spaniel
Tibetan Terrier
Toy Poodle
Walker American Foxhound
West Highland White Terrier
Whippet
Yorkshire Terrier

Feline (associated with white coats)

European White
Foreign White
White American Shorthair
White British Shorthair
White Cornish Rex
White Devon Rex
White Exotic Shorthair
White Manx
White Oriental Shorthair
White Persian
White Scottish Fold
White Turkish Angora

3. Structural anomalies of the brain

   Hydrocephalus and other anomalous structural conditions that affect the brain may affect auditory function. These dogs may have difficulty localizing sound due to poor development of higher auditory centers. Structural brain anomalies are discussed in Chapter 7.

B. Inflammatory/infectious

Peripheral vestibular disease is often a result of otitis in dogs and cats. It is one of the most common conditions diagnosed as causing secondary vestibular disease. Otitis may affect the external ear (otitis externa), the middle ear (otitis media), the inner ear (otitis interna), or combinations of these three locations. A thorough otoscopic examination is essential for diagnosis. A normal otoscopic exam does not rule out otitis as a potential cause of either hearing loss or vestibular disease. Otitis externa or media may cause a conduction block, resulting in a hearing deficit of the affected ear. Otitis interna may be severe enough to cause sensorineural hearing deficits. Some of the more common isolates from the ear are *Streptococcus* spp., *Pseudomonas* spp., and *Staphylococcus* spp. Treatment should be based on results obtained from culture and sensitivity testing. Long-term (e.g. 4–6 wks) treatment with systemic antimicrobials is often necessary. In addition to systemic antibiotics, otitis externa may be treated with topical antimicrobial preparations and routine ear canal lavage. Occasionally, surgery is necessary in refractory cases. Surgical procedures include ear canal resection, total ear canal ablation, and bulla osteotomy. Nasopharyngeal polyps are often associated with otitis media in cats. These proliferative tissue growths originate from the lining of the tympanic cavity and often grow along the path of least resistance: the pharyngotympanic (Eustachian) tube. They can often be seen within the nasopharynx. Cats will usually have clinical signs referable to a nasopharyngeal mass (e.g. sneezing, gagging) in addition to hearing loss, vestibular dysfunction, and possibly ipsilateral Horner's syndrome. They may be plucked from the nasopharynx or, preferably, removed surgically via a ventral bulla osteotomy. Nasopharyngeal polyps are much less likely to recur if removed via ventral bulla osteotomy.

C. Toxic

There are numerous known and suspected ototoxic agents that may cause vestibular signs and deafness. Often, the vestibular dysfunction is reversible upon withdrawal of the compound; however, deafness is usually permanent. The most commonly incriminated compounds are the aminoglycoside antimicrobials and ear-cleaning solutions. Many of the suspected ototoxicities are anecdotal. Ototoxic substances may gain exposure to the inner ear via a ruptured tympanic membrane when applied topically or hematogenously. Once in the middle ear, the substance enters the inner ear through the oval or round window. Toxin-mediated destruction may involve the cochlea, the semicircular canals, or the vestibule and typically affects the hair cells either directly or indirectly via alteration of the stria vascularis. Many commonly used ear-cleaning solutions may be ototoxic if applied in an ear with a ruptured tympanic membrane. Possible substitutions for ceruminolytic agents are dilute acetic acid (white vinegar) and saline at a 1:3 ratio or saline alone. If hearing loss or vestibular disease is suspected due to a potential ototoxic agent, the use of the compound should be discontinued immediately. Prognosis for recovery will depend on the age, species, breed, and general health status of the animal and time and application of use.

D. Traumatic

Unilateral deafness secondary to trauma is possible. Trauma rarely results in complete deafness. The petrous temporal bone may fracture and injure the vestibulocochlear nerve. The higher auditory centers may also be affected by cranial trauma; in these cases there would likely be signs of diffuse and severe neurologic impairment (see Chapter 8).

E. Miscellaneous

A rare condition called otoacoustic emission (OAE) has been reported in several dogs and one cat. This disorder is similar to tinnitus of people. In addition to their normal function of converting sound waves to mechanical vibrations, the outer hair cells of the cochlea are apparently able to generate sound by vibrating. The etiology of OAE is unknown. Typically, a continuous high-frequency ringing tone can be heard emanating from the affected ear. Behavioral responses to sound are normal in affected patients, as are BAER tests. There is no known effective treatment for OAE, but the disorder does not appear to pose any adverse effects on health.

Diagnostic tests[3, 4, 6, 13, 15, 19, 34, 44, 50, 62, 71, 75, 78, 82, 84, 107, 108, 115, 117–119, 123, 128, 130, 133, 135]

Peripheral disease

When a suspected peripheral nerve disease is presented, a thorough otoscopic exam should be performed to completely evaluate the outer ear. An otoscopic exam may also give clues to the examiner regarding the integrity of the middle ear. A bulging, discolored tympanic membrane may be indicative of otitis media. If so equipped, an otoscope with a side port may be used to subjectively test the compliance of the tympanic membrane with a gentle puff of air. The authors use a short piece of rubber tubing attached to the port on the head of the otoscope. While visualizing the tympanic membrane, a gentle puff of air is blown into the tubing and the tympanic membrane is observed to see how much deformation occurs. If the middle ear is fluid filled or occluded by tissue, the compliance of the tympanic membrane will be decreased. A thorough otoscopic exam almost always requires general anesthesia. This examination can be performed in conjunction with other diagnostic tests that require general anesthesia (e.g. radiographs, CT, MRI, CSF tap).

Indirect evaluation of the auditory system is possible using electrodiagnostics. The BAER test (see Chapter 5) is one method of evaluating the auditory pathways. This test is usually performed on awake dogs and cats; however, it can also be performed with mild sedation or anesthesia, if necessary. The potentials that are measured result from a far field recording of an evoked response. To perform this test, clicks or tones are generated in the ear of the animal, and the response of the brain stem and auditory pathways is recorded using needle electrodes placed on the scalp and near the ear. The test generates an early-latency waveform within 1–10 ms, indicating various activities within the brain. With peripheral disease, there would be attenuated or absent waveforms. This does not differentiate between conduction block and sensorineural block. However, a bone resonator may be used to stimulate the cochlea directly by placing it on the mastoid process of the temporal bone (junction of the nuchal crest and the caudal aspect of the zygomatic arch). A conduction block may be differentiated from sensorineural block because the mechanical vibrations generated by the resonator will themselves activate the receptor organ directly, effectively bypassing the external and middle ear cavities. The BAER is able to evaluate both ears. Most animals with bilateral deafness can be diagnosed with confidence based on a thorough physical and neurologic exam. An animal with unilateral deafness will often appear normal clinically and therefore can only reliably be diagnosed by performing a BAER test.

Some less-frequently performed diagnostic tests include impedance audiometry-tympanometry and testing of the acoustic reflex. Tympanometry can be used to evaluate the size of the internal ear, the integrity and compliance of the tympanic membrane, and the function of the middle ear components (ossicles and muscles). In this test, a tube is inserted into the external auditory canal that delivers both an auditory stimulus and pressure changes. The ear canal is sealed, and the changes in pressure reflected back from the tympanic membrane inside the sealed cavity are measured. The curve of the tympanogram will tell the examiner information about the compliance of the tympanic membrane. An abnormally high compliance (flabby tympanic membrane) would result from damage to the ossicles. An abnormally low compliance (stiff tympanic membrane) may result from otosclerosis. The acoustic reflex is a protective mechanism to prevent damage to middle and inner ear structures. The reflex is mediated through the afferent arm of the cochlear nerve. The efferent portion is generated via both the facial nerve, which innervates the stapedius muscle, and the trigeminal nerve, which innervates the tensor tympani muscle. When a loud noise is received by the inner ear, the reflex contraction of the middle ear muscles prevents excessive displacement of the ossicles, which could damage the ear. Of course, there is a delay in the reflex; very loud, sudden noises may cause significant damage.

Imaging techniques for evaluating the peripheral vestibular system and auditory components are rather limited. Radiographs of the skull may provide the clinician with the "footprints" of disease, such as sclerosis of the external acoustic meatus and bulla. These may prompt the examiner to take a closer look at the problem; however, lack of evidence of bony changes does not rule out the possibility of disease. CT greatly enhances the evaluation of the bony components of the PNS by providing transverse images through the area of interest. MR imaging can be performed and provides the ability to look at changes in the bulla, allowing the clinician to distinguish between fluid and soft-tissue abnormalities (including the presence of polyps). On MR imaging, the air-filled bulla would appear hypointense (black). Refer to Chapter 6 for more information concerning MR imaging.

If a case of otitis media/interna is suspected, a myringotomy may be performed. This diagnostic test requires general anesthesia. A needle is used to puncture the tympanic membrane, and fluid, if present, is aspirated and evaluated through cytology, culture, and antimicrobial sensitivity. The tympanic membrane will heal from this procedure, if it is performed correctly.

Central disease

The BAER test can be helpful in differentiating central from peripheral vestibular disease. If the sound waves can get to the organ of Corti, and the animal is not deaf, then the evoked response should be visible as a series of waves that represent brain-stem activity. The exact locations of the generation of the waves in the brain are not completely known. It is agreed that the generator of the first wave is the vestibulocochlear nerve. The other waves typically visualized (waves II–V) represent various nuclei and pathways for auditory function in the brain (see Chapter 5). The latencies (time necessary for the generation of the wave following a stimulus), amplitude, and morphology (right vs. left) of the waves are evaluated. The first wave will often be present, followed by abnormal waves and increased interwave intervals (latencies), in cases of central vestibular disease. The BAER test has also been used to evaluate brain death, often in conjunction with electroencephalography.

Radiographs may be of benefit when evaluating an animal for suspected skull trauma. Because of anatomic variations and difficulty with correct positioning and interpretation, skull radiographs do not provide a high level of diagnostic information regarding central vestibular disease. CT will allow the clinician to evaluate the skull and brain in the transverse (axial) plane. Contrast may be added to demonstrate any break in the BBB. CT may be a better diagnostic tool for evaluating bone; however, an MR exam will allow for an adequate evaluation of bone and a superior evaluation of soft tissue, and it will potentially save the animal from undergoing a second anesthetization if no abnormalities are seen on CT examination. It is the best test for the evaluation of structural brain disease. MR imaging will give a multiplanar evaluation of brain structures, is noninvasive, and is rapidly performed in the hands of a skilled technician. The drawbacks to MR examination are both a paucity of facilities in which the test can be performed and the limited access to personnel adequate in their evaluation. Most major cities and universities will have access to animal-dedicated MR facilities. A diagnosis of inflammatory brain disease can only be made with CSF analysis. The authors typically perform this test following MR evaluation of the brain. It has been hypothesized that in the face of increased intracranial pressure a cisternal tap may alter the homeostasis of pressure relationships in the brain, which may lead to secondary brain-stem herniation (transtentorial or foraminal). In cases of large structural abnormalities (mass effect), a lumbar tap may decrease the chances of herniation (although it is not eliminated). This potential advantage of performing a lumbar versus cisternal CSF tap remains to be proved. Although many cisternal taps have been performed with no complications in the face of large, compressive brain masses, caution should be used. Analysis of CSF is discussed in Chapter 5.

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Video Resources

Video resources are available on the companion website: www.wiley.com/go/dewey/neurology

See videos 8, 19 and 20.

CHAPTER 12

Cerebellar Diseases and Tremor Syndromes

Sean G. Sanders

Cerebellar disorders

Introduction[3, 15, 18, 28, 59, 86, 100, 114, 139, 152, 175]

The cerebellum is unique both structurally and functionally within the central nervous system (CNS). Although only occupying approximately 10% of brain parenchyma in dogs and cats, it is primarily responsible for the efficient and accurate processing of motor function. The cerebellum is also recognized as having a multifunctional role in several integrative functions, including behavior processing, memory, associative learning functions, and nociceptive processing (pain). A basic understanding of the cerebellum's role in the nervous system is helpful when considering how pathology within the cerebellum affects clinical functions. The cerebellum is responsible for the modification, rather than the initiation, of movement. The cerebellum functions to coordinate segmental movements so they are fluid in nature and to aid in ensuring movements are performed in an efficient manner. The cerebellum helps to regulate posture, unconscious proprioception (the position of the body in space), and muscle tone. The cerebellum is also believed to influence conscious thought processes, such as judging the timing of events and solving spatial and perceptual reasoning problems.

Divisions of the cerebellum[15, 35, 59, 86, 100, 114, 138, 210]

The cerebellum can be conceptually divided in numerous ways, according to developmental, anatomical, and functional features. Depending upon the clinical situation and clinician preference, an understanding of the cerebellum can be framed in the context of these different categorization schemes.

Phylogenetically, the cerebellum can be divided into three parts. The archicerebellum is the oldest part and is composed of the flocculonodular lobe. The paleocerebellum is next in line and consists of the most rostral portion of the cerebellum, rostral to the primary fissure. Finally, the neocerebellum is the newest and largest portion of the cerebellum and is composed of the hemispheres and paravermal portion caudal to the primary fissure.

Anatomically, the structure of the cerebellum contains the two lateral hemispheres, a median portion (the vermis), and a small ventral portion (the flocculonodular lobe). The superficial surface folds of the cerebellum are known as folia (Fig. 12.1). On the cut section, the cerebellum has many branching, infolded sections known as arbor vitae (meaning "tree of life"). Embedded within the deep white matter are the three paired "roof" nuclei. From medial to lateral, these are known as the *fastigial*, *interposital*, and *dentate* nuclei (Fig. 12.2). The dentate nucleus is also referred to as the *lateral nucleus* in some texts. These nuclei are synaptic centers for both afferent and efferent information. The cerebellum makes up the dorsal half of the metencephalon, with the pons comprising the ventral half. The cerebellum is attached to the brain stem by the three paired cerebellar peduncles, which act as conduits for both afferent and efferent information related to cerebellar function.

Finally, and probably most importantly, the cerebellum can be functionally divided into the cerebrocerebellum, spinocerebellum, and vestibulocerebellum. Each functional division is related to its associated anatomical structures (Fig. 12.3). The cerebrocerebellum consists of the cerebellar hemispheres, is associated with the dentate nucleus, and is primarily responsible for limb movements. This portion of the cerebellum is necessary for the coordinated implementation of voluntary, planned, multijoint movements. Additionally, the cerebrocerebellum is involved in the cognitive process of the intention to move. Studies have shown that neurons of the dentate nucleus fire before the onset of movement and before the neurons in the cerebral motor cortex responsible for that particular movement. In general, the cerebrocerebellum is required for the control of movement direction, timing, and force. It accomplishes this function through influencing the cerebral cortex motor output.

The spinocerebellum is composed of the vermis and the intermediate zone (medial portions of the hemispheres). It receives

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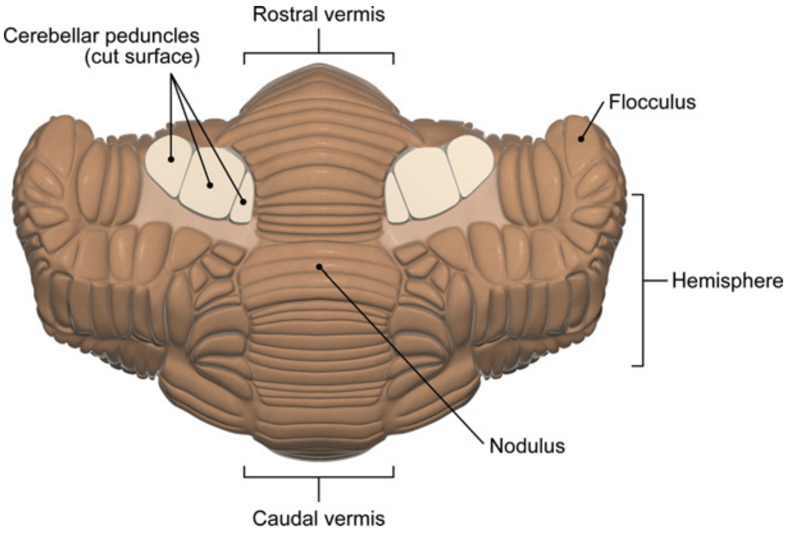

Figure 12.1 Gross anatomy of the cerebellum, ventral aspect. (The Ohio State University. Reproduced with permission.)

somatosensory information from the spinal cord. This division of the cerebellum is associated with the fastigial and interposital nuclei. It is primarily responsible for regulating muscle tone and unconscious motor movements necessary for posture and gait.

The vestibulocerebellum is made up of the flocculonodular lobe (the nodulus and two flocculi) and the fastigial nuclei. This portion of the cerebellum primarily projects to the vestibular nuclei of the brain stem. It is principally responsible for the maintenance of equilibrium and coordinating movements of the head and eyes.

Microscopic anatomy of the cerebellum[15, 35, 59, 86, 89, 210, 211]

The inner portion of the cerebellum is the medullary substance. It contains the deep cerebellar nuclei (i.e. fastigial, interposital, dentate nuclei). The outer portion is the cerebellar cortex. The cerebellar cortex is made up of three distinct layers. From outer to inner, these are the molecular cell layer, the Purkinje cell layer, and the granular layer (Fig. 12.4). The sophisticated arrangement of the cells that make up these layers allows the cerebellum to distinguish between errors in movement and the intended movement. The complex interactions of the distinct synapses allow the cerebellum to recognize both temporal and spatial events.

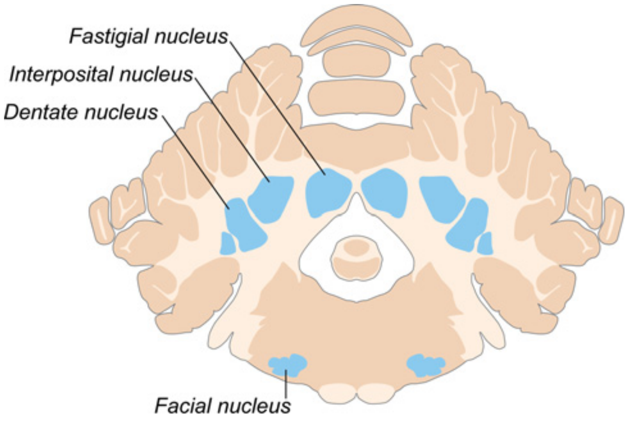

Figure 12.2 Cut section of cerebellum. Deep cerebellar nuclei are from medial to lateral fastigial, interposital, and dentate. Facial nucleus at level of cerebellomedullary junction. (The Ohio State University. Reproduced with permission.)

The molecular layer is a comparatively cell-free area. It contains two distinct cell types and the axons of neurons from the granular layer that send their projections to the molecular layer (parallel fibers). The cells are known as *basket cells* and *stellate cells*. Both cell types are inhibitory. The axons of basket cells descend to the Purkinje cell layer and make terminal arborizations with Purkinje cell bodies. The stellate cells make synaptic contacts with Purkinje cell dendrites that extend into the molecular layer.

The Purkinje cell layer contains the highly ordered and uniformly arranged large cell bodies of the Purkinje cells. This layer, located between the molecular layer and the granular layer, contains the cells responsible for the output of the cerebellum. Purkinje cells are large, highly metabolically active, and therefore very susceptible to ischemic or toxic damage. These inhibitory neurons utilize gamma-aminobutyric acid (GABA) as their neurotransmitter. The myelinated axons of Purkinje cells leave the cerebellar cortex to synapse on the deep cerebellar nuclei. Along the way, these axons will send collateral projections off in the granular layer to synapse on neurons located there. Additionally, the Purkinje cells will send fanlike dendritic processes into the molecular layer. These projections run perpendicular to the parallel fibers in the molecular layer. The parallel fibers run through the dendritic processes of the Purkinje cells much like electrical wires running through a bushy tree, making cross synapses with the Purkinje dendrites as they travel throughout the molecular layer.

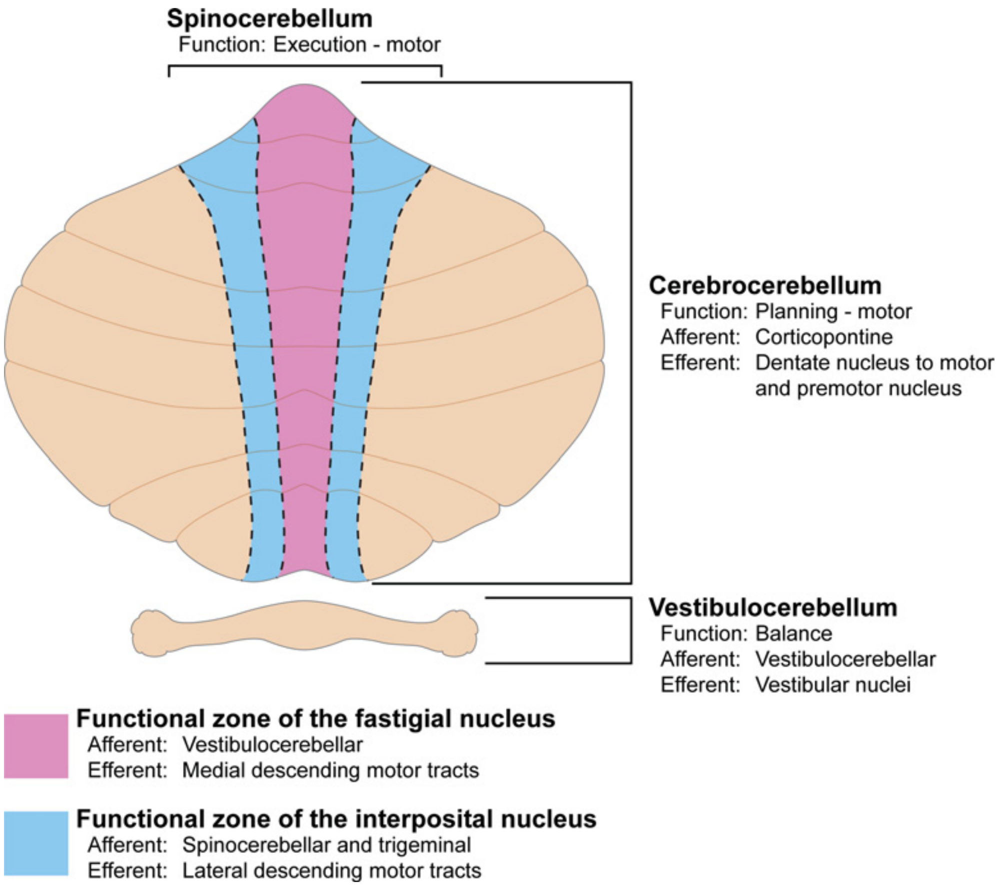
Spinocerebellum
Function: Execution - motor
Cerebrocerebellum
Function: Planning - motor
Afferent: Corticopontine
Efferent: Dentate nucleus to motor and premotor nucleus
Vestibulocerebellum
Function: Balance
Afferent: Vestibulocerebellar
Efferent: Vestibular nuclei
Functional zone of the fastigial nucleus
Afferent: Vestibulocerebellar
Efferent: Medial descending motor tracts
Functional zone of the interpositial nucleus
Afferent: Spinocerebellar and trigeminal
Efferent: Lateral descending motor tracts

Figure 12.3 Functional divisions of the cerebellum. (The Ohio State University. Reproduced with permission.)

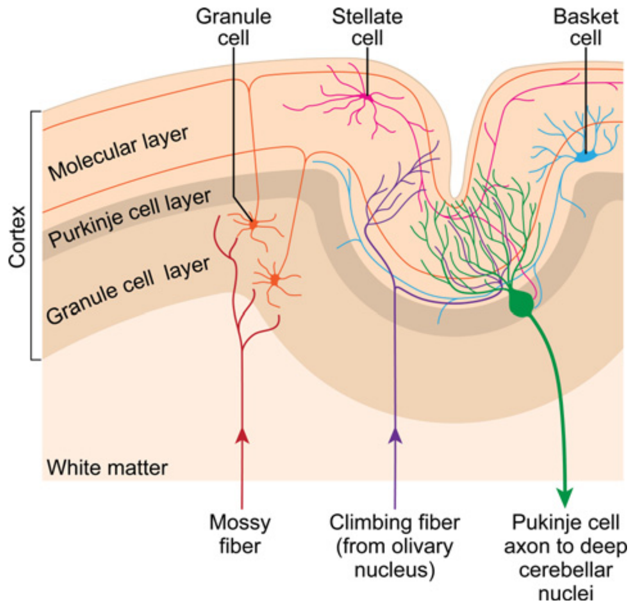
Granule cell
Stellate cell
Basket cell
Cortex
Molecular layer
Purkinje cell layer
Granule cell layer
White matter
Mossy fiber
Climbing fiber (from olivary nucleus)
Pukinje cell axon to deep cerebellar nuclei

Figure 12.4 Cellular arrangement of the cerebellar cortex. (The Ohio State University. Reproduced with permission.)

The deepest layer of the cerebellar cortex is the granular layer. Two types of neurons are present there: the granule cells and the Golgi cells. This layer is filled with densely packed cells that look like lymphocytes when Nissl stained. The granule cells have unmyelinated axons that ascend to the molecular layer where they function as parallel fibers making cross synapses with the Purkinje dendrites (the electrical wires through the bushy trees). Golgi cells are located in the upper portion of the granular layer. They are inhibitory neurons that utilize GABA as their neurotransmitter. Dendrites from the Golgi cells extend throughout all layers of the cerebellar cortex. Their axons form specialized synapses at the cerebellar glomeruli. The glomeruli are chiefly made up of axonal endings of mossy fibers (one of the two types of afferent projections into the cerebellum). Dendrites and axons from the Golgi cells, as well as dendrites from the granule cells, will synapse in the cerebellar glomeruli.

Afferent projections to the cerebellum[15, 18, 35, 59, 86, 89, 161, 210, 211]

The cerebellum receives sensory information from the entire nervous system yet projects its regulatory information to specific

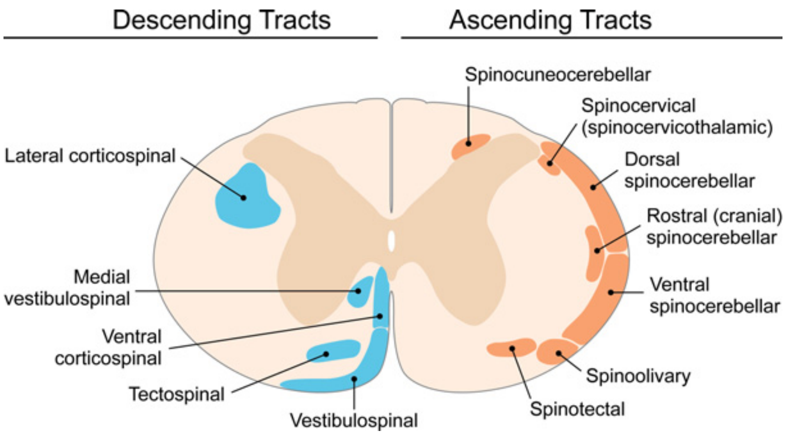

Figure 12.5 Transverse section through the spinal cord (second spinal cord segment) showing the descending and ascending spinal tracts related to the cerebellum. (The Ohio State University. Reproduced with permission.)

areas of the brain and spinal cord. The ascending and descending spinal cord tract related to cerebellar function are summarized in Fig. 12.5. The three different functional subdivisions of the cerebellum each receive primary information from specific portions of the nervous system (Fig. 12.3). The main contributions to each subdivision will be discussed; however, it is important to realize that afferent information to the cerebellum is distributed to all subdivisions in varying degrees. The cerebrocerebellum (hemispheres) receives input from the cerebral cortex via the pons (corticopontine fibers). Axons of the corticopontine fibers originate from the cerebral cortex, synapse on the deep pontine nuclei, cross midline as the transverse fibers of the pons, and ascend through the middle cerebellar peduncle. This information assists the cerebrocerebellum with motor planning.

The vestibulocerebellum (flocculonodular lobe) primarily receives afferent projections from the vestibular labyrinth indirectly via the vestibular nuclei in the medulla and directly via connections from the vestibulocochlear nerve (cranial nerve [CN] VIII). It also receives information from the lateral geniculate nuclei and rostral colliculi via the pontine nuclei (corticopontine tracts). All information entering the cerebellum from the pontine nuclei ascends through the middle cerebellar peduncle. This information will help the cerebellum with balance (both while standing and ambulating) and eye movements.

The spinocerebellum (vermis and intermediate zone) receives afferent information regarding joint position and lower motor neuron (LMN) status from the spinal cord (spino-olivary tracts, spinocerebellar tracts, cuneocerebellar tracts).

The neural pathways' names are a combination of their place of origination in the nervous system and their place of termination. For example, the spinocerebellar tracts originate in the spinal cord and terminate in the cerebellum; therefore, they are termed *spinocerebellar*. In general, the spinocerebellar tracts convey information from the limbs and body to the ipsilateral cerebellum. Proprioceptive information from the lower body and pelvic limbs is conveyed to the cerebellum via the dorsal and ventral spinocerebellar tracts (Fig. 12.6), whereas such information from the cervical region and thoracic limbs is conveyed to the cerebellum primarily via the cuneocerebellar (spinocuneocerebellar) and rostral (cranial) spinocerebellar tracts (Fig. 12.7). The dorsal spinocerebellar tract sends information from cutaneous, muscle, and joint receptors regarding proprioception from the pelvic limbs and caudal region of the body. This tract is located in the dorsal portion of the lateral funiculus. The information is projected to the ipsilateral cerebellum and enters via the caudal cerebellar peduncle. The ventral spinocerebellar tract, which also conveys information from the pelvic limbs and caudal body region, is also located in the lateral funiculus, ventral to the dorsal spinocerebellar tract. It sends information from muscle receptors and Golgi tendon organs, which ultimately reaches the ipsilateral cerebellum (after crossing midline twice) via the rostral cerebellar peduncle. The spinocuneocerebellar tract (cuneocerebellar tract), located in the lateral portion of the dorsal funiculus (fasciculus cuneatus), primarily sends proprioceptive information from cutaneous, muscle, and joint receptors from the ipsilateral thoracic limb and cranial part of the body. It projects to the cerebellum via the caudal cerebellar peduncle. It is named by its synaptic connections with the lateral cuneate nucleus in the medulla (rostrolateral to the medial cuneate nucleus), where spinal projections synapse prior to entering the cerebellum. The rostral spinocerebellar tract (medial to the ventral spinocerebellar tract) also conveys information from the thoracic limbs and cranial aspect of the body. Axons of this tract enter the ipsilateral rostral and caudal cerebellar peduncles. The cervicospinocerebellar tract is a pathway conveying proprioceptive information from the neck region (first four cervical spinal cord segments) to the contralateral caudal cerebellar peduncle. The axons of this tract synapse in the rostral vermis. The cerebellum indirectly (via the pontine nuclei) receives visual and auditory information through the collicular nuclei via the middle cerebellar peduncle and vestibular input from the vestibular nuclei via the caudal cerebellar peduncle. This information is organized somatotopically and represents entire maps of the body projected in the region of the vermis and intermediate zone of the cerebellar hemispheres.

All of the projections to the cerebellum are either mossy fibers or climbing fibers (Fig. 12.4). These excitatory fibers alone

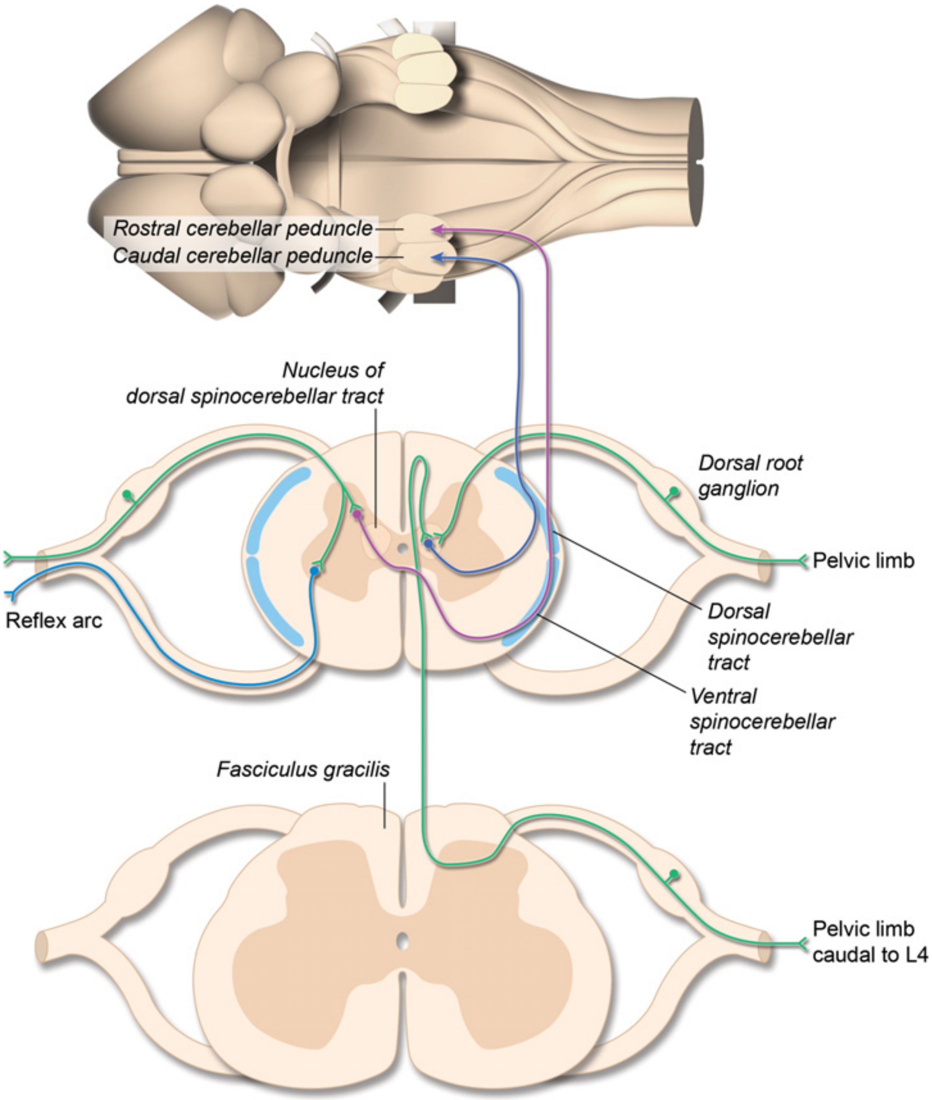
Rostral cerebellar peduncle
Caudal cerebellar peduncle
Nucleus of dorsal spinocerebellar tract
Dorsal root ganglion
Pelvic limb
Reflex arc
Dorsal spinocerebellar tract
Ventral spinocerebellar tract
Fasciculus gracilis
Pelvic limb caudal to L4

Figure 12.6 Schematic illustration of the ascending proprioceptive tracts to the cerebellum from the lower body and pelvic limbs—the dorsal and ventral spinocerebellar tracts. (The Ohio State University. Reproduced with permission.)

control the activity and therefore the output of the Purkinje cells. For the most part, afferent axons enter the cerebellum through either the caudal or middle cerebellar peduncles. In general, information from the pons (metencephalon) enters the cerebellum through the middle cerebellar peduncle and information from the medulla (myelencephalon) enters through the caudal cerebellar peduncle. Exceptions include the ascending proprioceptive information from the pelvic limbs coursing in the ventral spinocerebellar tract and a portion of the ascending information from the thoracic limbs conveyed by the rostral spinocerebellar tract. These axons enter the cerebellum through the rostral cerebellar peduncle.

Mossy fibers primarily originate from the spinal cord, reticular formation, vestibular nuclei, and pontine nuclei. They indirectly influence the firing of Purkinje neurons through their interactions with granule cells in the granular layer. The granule cells are excitatory interneurons. The interaction of mossy fibers and granule cells occurs at the cerebellar glomeruli, where mossy fiber terminals come into contact with Golgi cell axons and granule cell dendrites. A single mossy fiber will typically activate a cluster of granule cells, the axons of which will ascend into the molecular layer. Along the way, the granule cell axons will send off collaterals to Purkinje cells. Once in the molecule layer, these granule cell axons will become parallel fibers where they then again have the opportunity to interact at cross synapses with the Purkinje dendrites that extend into the molecular layer.

Three additional fiber types innervate all areas of the cerebellar cortex. All of these fibers enter the cerebellum as mossy fibers. One of the fiber types originates from the locus ceruleus and releases norepinephrine. These fibers interact directly with Purkinje cells. The second fiber type originates from the raphe nuclei and contains serotonin. These fibers do not synapse on

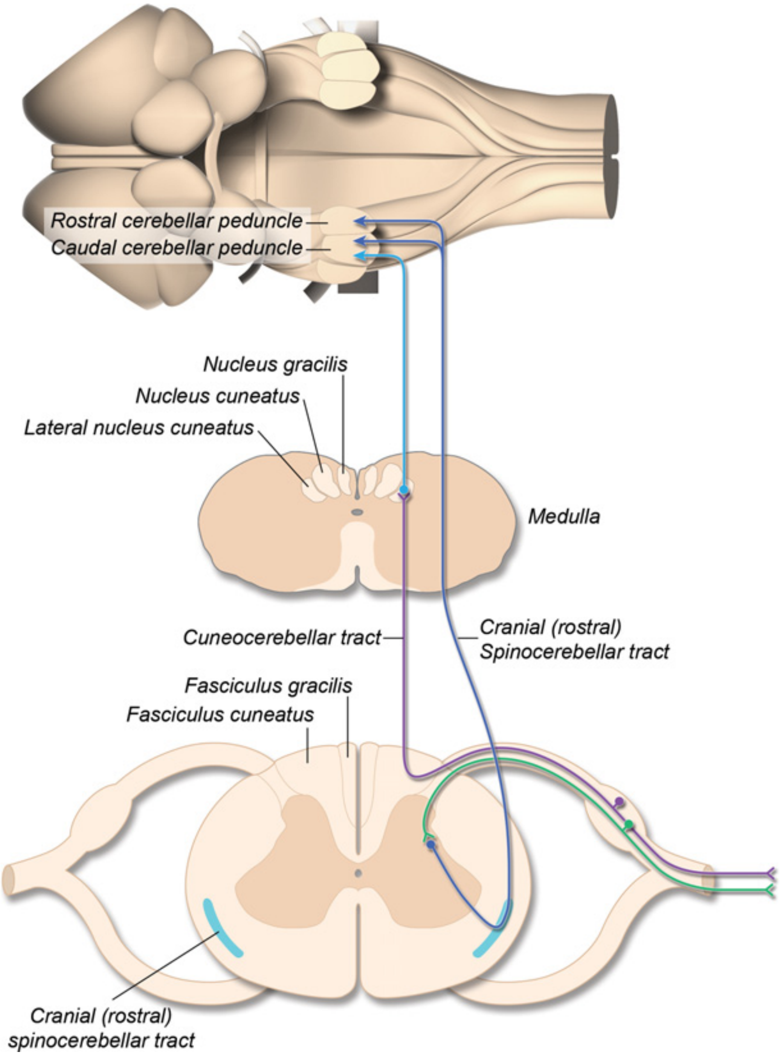
Rostral cerebellar peduncle
Caudal cerebellar peduncle
Nucleus gracilis
Nucleus cuneatus
Lateral nucleus cuneatus
Medulla
Cuneocerebellar tract
Cranial (rostral) Spinocerebellar tract
Fasciculus gracilis
Fasciculus cuneatus
Cranial (rostral) spinocerebellar tract

Figure 12.7 Schematic illustration of the ascending proprioceptive tracts to the cerebellum from the cervical region and thoracic limbs—the cuneocerebellar and rostral spinocerebellar tracts. (The Ohio State University. Reproduced with permission.)

Purkinje cells. Both of these fibers are thought to possibly play a role in emotional states and cerebellar function. A third fiber type originates from undefined brain-stem nuclei and releases acetylcholine.

Climbing fibers originate from a single source: the olivary nucleus (rostral myelencephalon). The olive receives descending input from the cerebral cortex and brain-stem upper motor neuron centers, as well as ascending input from the ventral spinocerebellar tract. Information from the olivary nucleus projects to the cerebellum, sending off collaterals to the cerebellar nuclei, and continues into the Purkinje cell layer to form direct excitatory contact with Purkinje neurons. A Purkinje neuron receives input from a single climbing fiber, and a single climbing fiber will interact with several Purkinje neurons. Of all the excitatory synapses in the CNS, the climbing fiber's interaction with the Purkinje neuron is one of the most powerful. An action potential from a climbing fiber will produce a prolonged depolarization of the target Purkinje cell. While mossy fibers rely on temporal and spatial summation to excite a Purkinje neuron, the climbing fiber can accomplish this with a single action potential.

Efferent projections from the cerebellum[3, 15, 18, 35, 59, 86, 91]

As stated previously, the only output of the cerebellar cortex is via Purkinje axons. The Purkinje neurons exert an inhibitory influence on the tonically active deep cerebellar nuclei. As with the afferent organization, the efferent projections from the cerebellum can be categorized based upon the three major subdivisions (Fig. 12.3). Purkinje neurons from the most lateral subdivision, the cerebrocerebellum, project to the most lateral cerebellar nuclei: the dentate nuclei. From the dentate nucleus, fibers descend through the contralateral rostral cerebellar peduncle to the ventral lateral nucleus of the thalamus. By crossing back to the contralateral rostral peduncle, the cerebrocerebellar projections will project to the ipsilateral cerebral cortex. As described earlier, the corticopontine fibers, which project to the cerebrocerebellum, cross in the pons to project to the contralateral cerebrocerebellum; the efferent projections cross back to maintain an ipsilateral circuit. The thalamic projections influence the motor and premotor areas of the cortex. Additionally, the dentate nucleus sends projections to the red nucleus in the mesencephalon. These projections form a complex feedback circuit back to the cerebellum through the olivary nucleus. They do not make up any portion of the rubrospinal tract (a descending spinal projection that originates from the red nucleus). The efferent projections of the cerebrocerebellum are responsible for the coordination and planning of limb movements. Some of the vestibulocerebellum's Purkinje neurons project directly to the vestibular nuclei in the medulla. These arise primarily from the flocculonodular lobe. Neurons of the fastigial nucleus also project to the vestibular nuclei. The vestibular nuclei give rise to the lateral and medial vestibulospinal tracts, which run in the ventral funiculi of the spinal cord white matter (Fig. 12.5). The main output is necessary for the control of axial and proximal limb muscles in order to maintain balance. Vestibulocerebellar projections are also responsible for coordinated eye and head movements, as well as vestibular reflexes.

The spinocerebellum's output is projected through the fastigial and the interposital nuclei. The fastigial nucleus receives output from the vermis. Some of these fibers ascend to the cerebral cortex; however, most efferents descend to the vestibular nuclei and the reticular formation, both of which contribute fibers to the medial descending motor systems. The interposital nucleus receives output from the intermediate zone (medial hemispheres). Axons of the interposital nuclei continue on to influence lateral descending motor tracts. The areas of the cerebellum contributing to the medial descending motor pathways are responsible for the regulation of axial and proximal musculature. Axons from the interposital nuclei descend through the rostral cerebellar peduncle to the contralateral red nucleus. They continue to the ventral lateral nucleus of the thalamus and eventually the cerebral motor cortex. These projections help to regulate the function of distal limb muscles by exerting their influence on both the corticospinal and the rubrospinal tracts, which are two of the lateral descending motor pathways. Efferents of the spinocerebellum coordinate the actions of axial and limb muscles to smooth out intended movements and dampen oscillations of ongoing movements.

Functions of the cerebellum[3, 12, 15, 18, 23, 24, 28, 48, 56, 59, 102, 107, 114, 132–137, 147, 152, 157, 216]

The cerebellum has traditionally been thought of as a modulator or regulator of movement initiated by the cerebrum. Experiments have shown that neurons in the dentate nucleus (cerebrocerebellum) actually begin firing before neurons in the cerebral motor cortex that are responsible for the intended movement. Neurons in the fastigial and interposital nuclei (spinocerebellum) fire after the movement has begun, and their activity is directly related to the velocity and force of the movement. This suggests that the cerebrocerebellum is actually involved with the intention to move and therefore linked to cognitive function at some level, whereas the spinocerebellum monitors the consequences of the evolving movement. It is well accepted that the cerebellum plays a much greater role in an animal's cognitive awareness and output related to its environment.

The roles of the cerebrocerebellum and spinocerebellum in the initiation and execution of movement can be hypothetically mapped out (Fig. 12.8). The upper loop involves the cerebrocerebellum, which, along with the premotor cortex, is important for the programming of future movements. The lower loop involves the spinocerebellum, which, along with the cerebral motor cortex, regulates evolving movements.

The cerebellum is responsible for the optimization of motor performance. To that end, it plays an important role in "learning" the most efficient method for the initiation, execution, and modification of conscious and unconscious movements. The firing of Purkinje neurons is modified indirectly through the action of mossy fibers on climbing fibers so that, in a sense, the climbing fibers are "teaching" the Purkinje neurons to generate a new response.

Clinical signs of cerebellar dysfunction[3, 15, 18, 59, 86, 100, 119, 155] (Video 9)

Clinical signs of cerebellar dysfunction can generally be referred to as abnormalities in the rate, range, direction, and force of motor movements. Lesions of the cerebellum typically result in ipsilateral deficits. This physiological phenomenon is due to the fact that output through the rostral cerebellar peduncle is crossed and primarily acts to modify movement generated through the corticospinal and rubrospinal tracts, which are also crossed. Pure cerebellar disease does not result in paresis (weakness). There are usually no conscious proprioceptive deficits with lesions restricted to the cerebellum; however, during a neurologic evaluation, it is important to consider that a specific lesion may involve multiple areas of the nervous system. For example, a cervical lesion may affect the ascending spinocerebellar tracts, leading to signs of cerebellar dysfunction, while at the same time affecting conscious proprioceptive pathways, resulting in apparent proprioceptive deficits (such as articular-process (facet)-associated cervical vertebral spondylomyelopathy in young, large-breed dogs). Disorders of cerebellar function may result in specific alterations in motor function. These deficits may exhibit themselves as hypermetria or hypometria, ataxia, dysmetria, and tremors.

It is more common for dogs and cats with cerebellar disease to exhibit signs of hypermetria. This results from the delay in the cessation of the intended movement and typically manifests itself at gait as the animal takes on a "toy soldier"

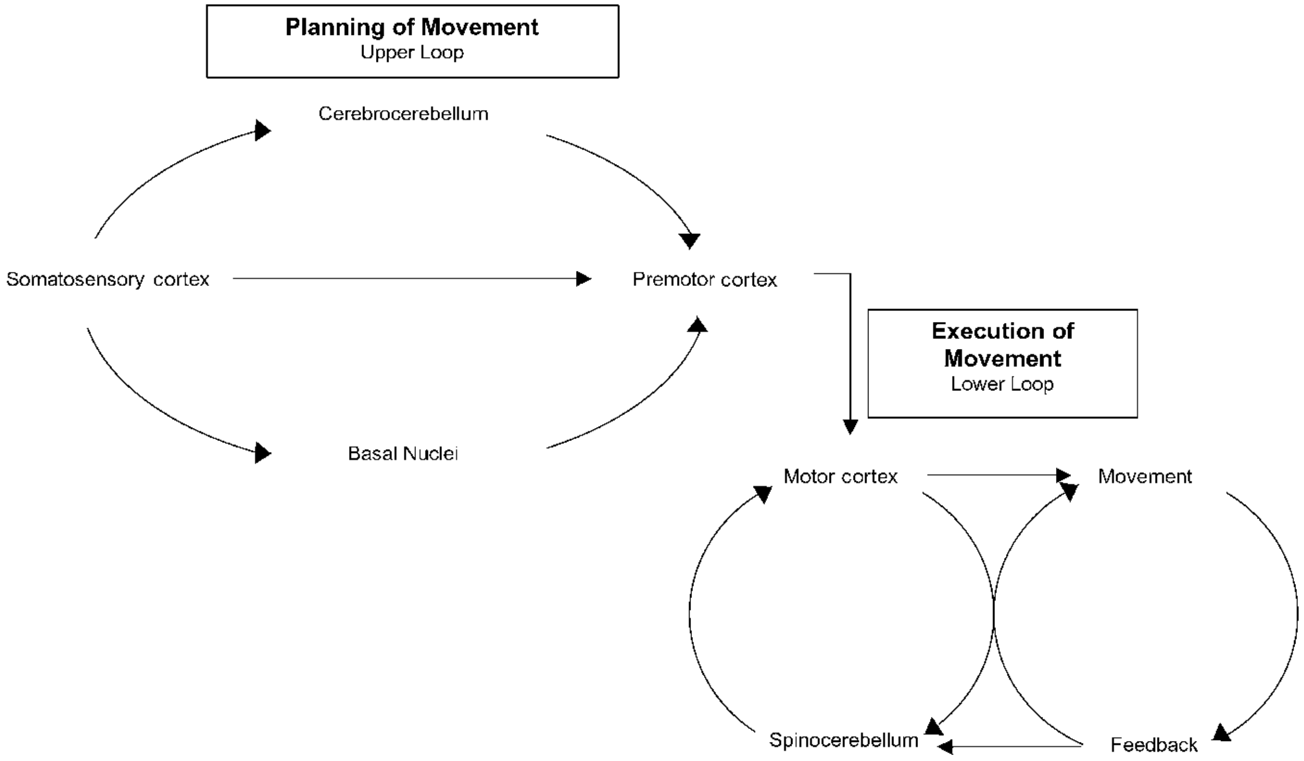

Figure 12.8 Hypothetical map of cerebrocerebellar and spinocerebellar involvement in the planning and execution of movement.

appearance. The limbs are stiff and frequently overreaching. There is usually a broad-based stance, and the intended movement will overshoot the goal with an excessive rebound. Ataxia can be thought of as the manifestation of a constellation of signs resulting from hypermetria, dysmetria, and asynergia. Dysmetria refers to abnormalities in the rate and force of movement. Asynergia is the lack of coordination in the execution of multisegmental movements. Since the cerebellum is usually affected in a diffuse manner, the clinical sign of ataxia is a common one. The word *ataxia* comes from the Greek and means "without order." When considered in this manner, it is easy to see how ataxia can be one of the primary manifestations of cerebellar disease. The clinician will recognize the animal having a "drunken" gait or the "lack of an axis." This may be thought of as movement away from the axis of the body (a straight line drawn from the nose to the tail). The animals will have a broad-based stance and sway from side to side at gait. The head will often oscillate, as the vestibulocerebellar function is also affected. Affected patients tend to have difficulty maintaining their balance and are easily tipped over.

Since the spinocerebellum is somatotopically organized, a lesion of the vermis or fastigial nucleus will produce titubation. *Titubation* is a shaking of the trunk and head while sitting or standing, which is commonly observed as forward and backward oscillations of the body. Tremors of cerebellar origin are referred to as intention tremors. These tremors are manifested when the animal initiates voluntary movement. They typically appear as the to-and-fro movements or oscillations of the head and neck, which become more severe as the animal begins to reach the goal (such as a food bowl). Intention tremors imply a lesion of the cerebrocerebellum, the more lateral areas of the cerebellar hemispheres, or the dentate nucleus. This is the area of the cerebellum primarily influencing the application of voluntary movement. Lesions of the vestibulocerebellum (flocculonodular lobe), vestibular nuclei, or fastigial nucleus may cause nystagmus, strabismus, loss of balance, and a head tilt either toward or away from (paradoxical) the side of the lesion.

Lesions of the rostral cerebellar peduncles and deep cerebellar nuclei produce the most severe clinical signs. An abnormality in the region of the fastigial nucleus in cats may produce contralateral pupillary dilation. The affected pupil will not be completely responsive to light (miosis), and there will be partial protrusion of the ipsilateral third eyelid. With lesions of the interposital nucleus, the same pupillary light abnormalities will occur as in a fastigial nucleus lesion; however, the affected pupil is ipsilateral to the lesion.

Paradoxical vestibular syndrome and decerebellate rigidity are two classic signs of cerebellar disease. Occasionally, animals will present with a head tilt and paresis on the opposite side of the head tilt, and they may or may not have other signs of cerebellar dysfunction (e.g. nystagmus or tremor). Lesions of the flocculonodular lobe or caudal cerebellar peduncles will produce these signs. In these cases the head tilt is paradoxical in that it is away from the side of the lesion. The lesion can be localized to the same side as the most severe conscious proprioceptive deficits. This paradoxical vestibular syndrome is likely due to an abnormality in the vestibulocerebellum, which contains many crossed and uncrossed pathways and, depending on the location and severity of the lesion, may result in the contralateral head tilt (see Chapter 11). Decerebellate rigidity is seen with severe cerebellar abnormalities. It is characterized by a rigid extension of the forelimbs, alternating flexed or extended hind limbs, and opisthotonus. If damage is confined to the cerebellum, consciousness is maintained. The classic differentiation therefore, between an animal with decerebrate posturing and decerebellate posturing is the animal's level of consciousness. A decerebrate animal will be stuporous or comatose.

Occasionally, animals with cerebellar disease will have absent or decreased menace responses ipsilateral to the lesion. The menace deficit is observed despite normal visual pathways and facial nerve function. The cerebellum is known to play a role in the inhibition of micturition, and diseases of the cerebellum may therefore play a part in disorders of micturition (see Chapter 16).

Disorders of the cerebellum[1–4, 6–8, 10, 13–22, 25, 27–34, 36, 37, 39–43, 45–47, 49–52, 57–62, 64, 66–71, 73–77, 79–82, 84–88, 92, 95–101, 103–106, 108–113, 115–120, 122–128, 130, 140, 141, 143–146, 148–152, 154, 156, 158, 163–170, 172–174, 176–187, 189, 190, 192–199, 202–204, 209, 211, 213, 218–220]

A. Degenerative/anomalous

1. Cerebellar cortical abiotrophy

This group of diseases specifically refers to the degeneration of normal neuronal cell populations within the cerebellar cortex after birth. Additionally, deep cerebellar nuclei and the terminal fields of cerebellar projections may be affected. Many of these diseases are genetically transmitted; most are suspected to be autosomal recessive traits. The etiology for this group of disorders is unknown. Lack of a metabolic component necessary for cellular survival may be involved. Some of these abiotrophies may represent inappropriate programmed cell death of cerebellar neurons (apoptosis).

A genetically transmitted autoimmune process was suspected in a group of young (8-wk-old) Coton de Tuléar dogs with granule cell degeneration. An apoptotic process was suspected in a separate, younger (2-wk-old) group of Coton de Tuléar dogs with granular cell loss. Purkinje neurons are the most commonly affected cell population in cerebellar abiotrophy cases (Fig. 12.9 and Fig. 12.10). However, granule cells, medullary nuclear cells (e.g. cuneate, gracile, olivary nuclei), and motor neurons in the spinal cord have also been affected. A condition of concurrent cerebellar (Purkinje cell) and hepatocellular degeneration was reported in several litters of Bernese Mountain dog puppies. Cerebellar cortical abiotrophy has been primarily reported in dogs, with only sporadic feline reports. The onset and rate of the progression of clinical signs varies with the breed affected (Table 12.1). Most breeds show an onset of clinical signs when the animals begin to ambulate and slightly later (3–12 wks). The course of the disease can be rapid (several weeks)

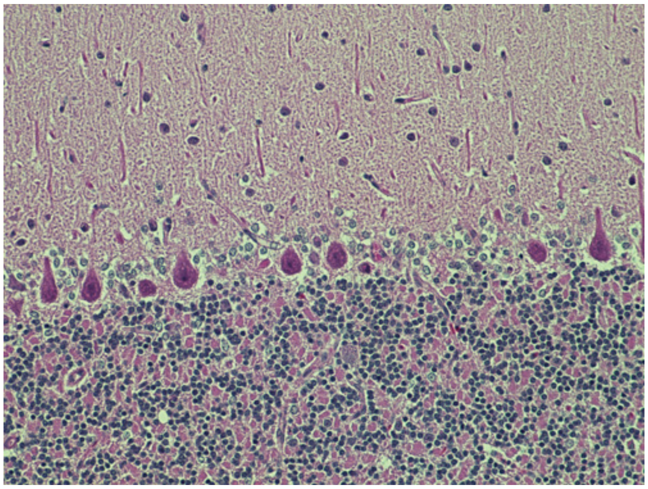

Figure 12.9 Normal section of cerebellum. Note molecular layer (M), Purkinje cell layer (P), and granular layer (G). Hematoxylin and eosin stain. Bar 5, 200 mm. (Kevin Lahmers, Washington State University, Pullman, WA, USA, 2014. Reproduced with permission from Kevin Lahmers.)

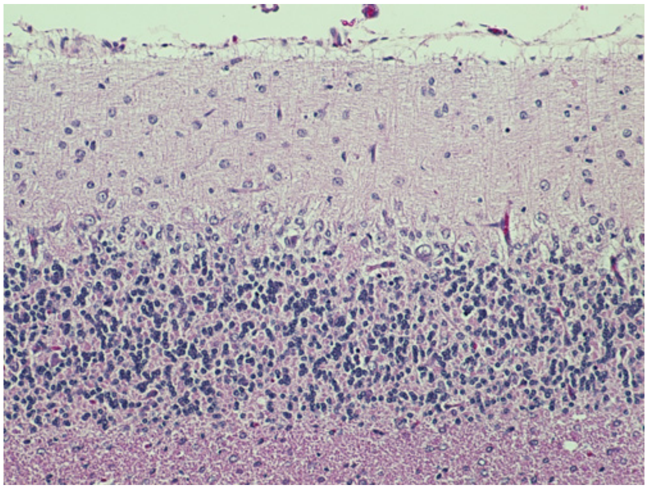

Figure 12.10 Cerebellar abiotrophy. Notice the lack of Purkinje cells in the Purkinje cell layer (P) and the thinning of the granular cell layer (G). Hematoxylin and eosin stain. Bar 5, 200 mm. (Kevin Lahmers, Washington State University, Pullman, WA, USA, 2014. Reproduced with permission from Kevin Lahmers.)

Table 12.1 Breeds of dogs and cats recognized to have cerebellar abiotrophy.

Breed	Age of onset	Progressive or stable
Dogs		
Airedale Terrier	< 6 mos	Progressive
American Staffordshire Terrier	18 mos to 9 yrs	Slowly progressive
Australian Kelpie	6–12 yrs	Progressive
Bavarian Mountain dog	3–7 mos	Slowly progressive
Beagle	3 wks	Progressive
Bernese Mountain dog	4–6 wks	Progressive
Border Collie	6–16 wks	Progressive
Brittany Spaniel	7–13 yrs	Slowly progressive
Bull Mastiff	4–28 wks	Progressive
Chinese Crested[a]	3–6 mos	Slowly progressive
Coton de Tulear[b]	8 wks/2 wks	Progressive/Nonprogressive
English Bulldog	8–12 mos	Slowly progressive
Finnish Harrier	< 6 mos	Progressive
Gordon Setter	6–10 mos	Slowly progressive
Irish Setter	3–10 days	Progressive
Jack Russell Terrier	2 wks	Progressive
Kerry Blue Terrier	8–16 wks	Progressive
Labrador Retriever	12 wks	Rapidly progressive
Lagotto Romagnolo	10–15 wks	Rapidly progressive
Miniature Poodle	3–4 wks	Unknown
Rhodesian Ridgeback	Birth	Progressive
Rough Coated Collie	4–8 wks	May stabilize
Samoyed	Birth to 6 mos	Slowly progressive
Cats		
Domestic Shorthair	> 1 yr	Slowly progressive
Mixed breed	6–8 wks	Progressive
Persian	7 yrs	Slowly progressive
Siamese	> 1 yr	Slowly progressive

Note: Other isolated cases: Akita, Boxer, Brittany Spaniel, Cairn Terrier, Clumber Spaniel, Cocker Spaniel, English Spaniel, Fox Terrier, German Shepherd, Golden Retriever, Great Dane, Italian Hound, Miniature Schnauzer, Papillion, Mixed Breed, Pit Bull Terrier, Portuguese Podengo, and Scottish Terrier.

[a] Chinese Crested dogs expressing the hairless phenotype (canine ectodermal dysplasia [CED] mutation) are affected through an autosomal dominant transmission. Homozygotes for CED are not viable.

[b] There are two forms of abiotrophy reported in this breed; one appears to be progressive and the other nonprogressive.

or slowly progressive (several years). In certain cases, the clinical signs will plateau, and the animal will remain stable.

In some breeds, clinical manifestations of cerebellar dysfunction occur near or during adulthood. In the cerebellar abiotrophy of Gordon Setters, clinical signs usually begin at about 6–10 mos of age and progress steadily over 9–18 mos. There is a late-onset cerebellar degeneration in Brittany Spaniels. These dogs are typically affected between 7 and 13 yrs of age. A slowly progressive late–onset form of cerebellar cortical degeneration has been characterized in American Staffordshire Terriers. Sixty-three dogs were examined. Onset of clinical signs began between 18 mos and 9 yrs. An autosomal recessive mode of transmission is most consistent with the inheritance. The slow progression of clinical signs to the development of an inability to walk and falling repeatedly was observed. In one report of eight Brittany Spaniels, the time from onset of cerebellar dysfunction to euthanasia varied from 6 mos to 4 yrs. A late-onset cerebellar abiotrophy disorder has been described in Old English Sheepdogs. These dogs exhibited primarily gait abnormalities (beginning between 6 and 40 mos of age) that were mild and slowly progressive. A hereditary cerebellar degeneration has also been described in Scottish Terriers, characterized histopathologically by a loss of Purkinje cells and an accumulation of polyglucosan bodies primarily in the molecular layer. The onset of clinical signs is similar to that of the Gordon Setter and Old English Sheepdog. Clinical signs are typically observed between 6 and 40 mos and are slowly progressive. This condition may have been present for some time although not recognized due to possible confusion with the hereditary disorders known as *Scotty cramp* and *central axonopathy of Scottish Terriers*. The episodic nature of Scotty cramp and the early onset with rapid progression of clinical signs associated with central axonopathy of Scottish Terriers would be differentiating signs between the conditions. An autosomal recessive mode of inheritance has been confirmed. A late-onset (more than 1 yr of age) cerebellar abiotrophy has also been reported in a number of cats, including two feral cats, a Persian cat, a Siamese cat, and a domestic shorthaired cat. The latter cat also exhibited retinal degeneration.

Clinical signs of cerebellar abiotrophy represent the cerebellar syndrome and may include ataxia, intention tremors, nystagmus, poor menace responses with normal vision, opisthotonus, behavioral abnormalities, and depression. Many cases of cerebellar degeneration/abiotrophy are also noted to have contralateral or ipsilateral conscious proprioceptive abnormalities that are believed not to occur with pure cerebellar disease. In a described case of slowly progressive disease in a Papillon, clinical signs developed at 5 mos and progressed slowly over 2 yrs. The dog initially presented with a cerebellar syndrome. Clinical signs progressed to generalized paresis by 1.5 yrs and the inability to stand by 2 yrs of age. The dog was observed to have difficulty swallowing and unilateral facial nerve paralysis followed by death due to aspiration pneumonia by 2 yrs and 9 mos of age. Immunohistochemistry of the cerebellum identified activation of the apoptotic pathway via identification of caspase-3 positive cells without inflammation in the granule and Purkinje cell layers.

Neurodiagnostics have generally not been beneficial in the antemortem diagnosis of this condition; however, in several breeds there are gross structural abnormalities of the cerebellum (hypoplasia and focal signal changes) that may be detectable with magnetic resonance imaging

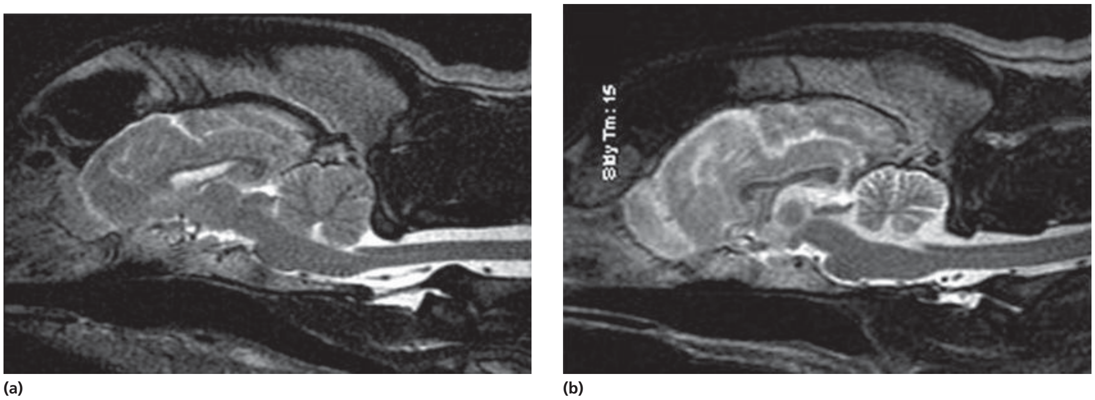

Figure 12.11 T2-weighted, midsagittal MR brain images of a normal dog (A) and an American Staffordshire Terrier with abiotrophy (B). Note the increased amount of cerebrospinal fluid within and between the folia and surrounding the cerebellum compared with the control dog's image. (Olby *et al.*, 2004. Reproduced with permission from Wiley.)[151]

(MRI; Fig. 12.11). Recently, computer-assisted MR image measurements have been shown to be very sensitive and specific in diagnosing cerebellar abiotrophy in the American Staffordshire Terrier breed. In addition, brain-stem auditory evoked response (BAER) testing (see Chapter 5) has been shown to be a useful diagnostic tool in American Staffordshire Terriers with cerebellar abiotrophy. There are no effective treatments for this group of disorders.

2. Neuroaxonal dystrophy

This disease has been reported in dogs and cats and is characterized histologically by swellings at the terminal ends of axons referred to as *spheroids*. In the *physiologic* form, it is considered a normal part of aging. The *primary* form is associated with the development of neuroaxonal swelling as the main pathological feature associated with the disease in young animals. This is also the name of a condition *secondary* to the accumulation of metabolic by-products in storage diseases, where the disease results in a neuroaxonal dystrophy. There is one report of neuroaxonal dystrophy in English Cocker Spaniels associated with primary metabolic vitamin E deficiency. Most cases of neuroaxonal dystrophy, however, are thought to represent primary, inherited disorders of axonal transport mechanisms. Axons in the cerebellum and its related pathways are affected, and cerebellar dysfunction often predominates early in the disease course. It is thought that a defect in axonal transport leads to the accumulation of transportable products in the distal ends of the affected axons. The disease is genetically transmitted in cats and is thought to be hereditary in dogs as well. An autosomal recessive mode of inheritance is suspected. The onset of clinical signs relating to the cerebellar syndrome is typically within the first few months of life in the Chihuahua, Collie, Papillon, Jack Russell Terrier, as well as the Siamese and domestic shorthaired cat. Boxers may be affected between 1 and 7 mos of age. The Rottweiler is affected within 1 to 2 yrs, and the German Shepherd may be affected at around 15 mos. In the case of the Rottweiler, there may be severe degeneration of the dorsal columns of the cervical spinal cord. These dogs often have conscious proprioceptive deficits, as well as cerebellar dysfunction. In a report of four Papillon puppies diagnosed with neuroaxonal dystrophy, histopathological evidence of disease was present in nearly all examined areas of the brain, affecting gray and white matter (cerebrum, cerebellum, pons, caudate, basal ganglia, etc.). Lesions were also present within the gray matter and all funiculi of the cervical, thoracic, and lumbar spinal cord. Peripheral nerves may also be affected but less commonly than the brain and spine. Wallerian degeneration was a prominent finding as well. The presence of LMN signs (such as reduced to absent patella reflexes) may result in a multifocal localization. Therefore, the diffuse distribution of the pathology warrants consideration of this disease in patients where cerebellar signs are not the only clinical presenting complaint. Neuroaxonal dystrophy may progress rapidly or slowly in the primary forms and is generally a slow progression in its physiologic (age-related degeneration) form, ultimately leading to multifocal CNS dysfunction. Early in the course of the disease, MRI has been reported as normal. However, if allowed to progress, MRI findings of diffuse brain atrophy have been reported with subsequent imaging studies. The value of high-field MRI examination has not yet been determined in the earlier stages of the disease. There is no treatment.

3. Cerebellar malformation

It is thought that a genetically transmitted condition of cerebellar hypoplasia exists. This condition has been reported in Chow Chows, Boston Terriers, Airedale Terriers, Irish Setters, Wire-haired Fox Terriers, and Bull Terriers. The reported malformations vary from complete absence of the cerebellum or parts of the cerebellum (agenesis), abnormal development of the cerebellum with no differentiation of tissue (aplasia), to abnormal

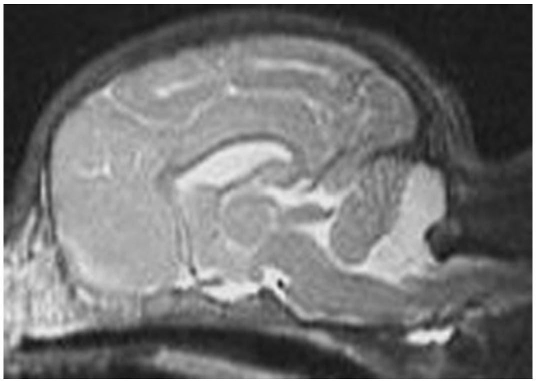

Figure 12.12 Sagittal T2-weighted MR image from a dog with cerebellar vermis hypoplasia, a characteristic feature of Dandy–Walker syndrome. (Dr. Gena Silver, 2014. Reproduced with permission from Dr. Gena Silver.)

development of the cerebellum with some differentiation of tissue (hypoplasia). The condition is present at birth and likely represents the failure of normal cerebellar development. The condition is not progressive, and clinical signs may improve as the animal matures.

4. Dandy–Walker syndrome
Dandy–Walker syndrome is a rare congenital malformation that shares similarities with the human form of the disease. It consists of a triad of congenital anomalies, including cerebellar vermis hypoplasia (Fig. 12.12), a communicating hydrocephalus, and the presence of a fluid-filled cyst (syrinx) within the posterior fossa. In humans, Dandy–Walker syndrome is one of several congenital syndromes typified by cerebellar vermis hypoplasia. It has been reported in several dogs with no breed or sex predilection and in a kitten. The clinical signs are typical of cerebellar disease (ataxia, hypermetria, absent menace, and tremors). Some dogs have also displayed a head tilt and circling. It is unknown whether the vestibular signs are due to the cerebellar disease or manifestations of the other developmental abnormalities. The clinical signs are typically not progressive, therefore surgical intervention may not be rewarding. Affected animals usually present early in life, at around 3 mos of age. There is no treatment.

5. Foramen magnum-associated malformations
Malformation of the caudal aspect of the skull, similar to Chiari type I disorder of people, has been described in small-breed dogs. These "Chiari-like" malformations (CLM), also termed *caudal occipital malformation syndrome* (see Chapter 7), are best appreciated on sagittal MRIs and usually include rostral displacement of the caudal aspect of the occipital bone, with caudal displacement of the caudoventral aspect of the cerebellum into or through the foramen magnum. Additionally, small-breed dogs may be affected by atlanto-occipital overlapping (AOO), either alone or in conjunction with Chiari-like malformation; AOO can result in cerebellar compression due to displacement of the C1 dorsal arch. In humans, the presence of this *basilar invagination* in conjunction with other aspects of cranial–cervical junction abnormalities results in treatment modification for the most successful outcome. There may be meningeal fibrosis at the cervicomedullary junction in dogs with these malformations. Overcrowding of the caudal fossa region is believed to lead to syringomyelia, especially in the cervical spinal cord region. Concurrent hydrocephalus may also be present. In the Cavalier King Charles Spaniel there is an association between increased cerebellar volume and syringomyelia. The malformation is estimated to be present in 70% of nonclinical Cavalier King Charles Spaniels by the age of 6 yrs, whereas if evaluated at 1 yr of age, only 25% of Cavalier King Charles Spaniels have MRI evidence of the malformation. Some patients with Chiari-like malformations may display evidence of cerebellovestibular dysfunction. Medical therapy (e.g. low doses of prednisone, gabapentin, diuretics) may be successful in some cases of Chiari-like malformations. Foramen magnum decompression (FMD) is usually successful in people with the disorder, and the author has had some success in dogs treated similarly. The presence of atlanto-occipital overriding and other aspects of the malformation is thought to result in a more guarded prognosis in dogs with this condition.

Occipital dysplasia is a controversial anatomical abnormality of the occipital bone. The controversy centers primarily on whether occipital dysplasia simply represents anatomic skull variation or is an actual disease state. This condition also primarily affects small-breed dogs. In cases of occipital dysplasia, the region of the occipital bone comprising the dorsal boundary of the foramen magnum (supraoccipital bone) is malformed and replaced by a membranous band of tissue. This abnormality can vary from a small notch leading to a keyhole-shaped foramen magnum to a large midline defect dorsal to the foramen magnum. Often, the caudal aspect of the cerebellum and the dorsal aspect of the cranial cervical spinal cord–caudal brain stem are exposed. It has been proposed that fluid-filled cavities in the brain stem and cranial cervical spinal cord seen on MR examination of dogs with this condition are secondary to abnormal pulsation of cerebrospinal fluid (CSF) through the foramen magnum. However, concurrent Chiari-like malformation and occipital dysplasia have been documented in dogs. In addition to the possibility that occipital dysplasia, by itself, does not represent a disease entity, it has been suggested that the decompressive effect of this defect may actually delay the development of clinical signs related to CLM in dogs that have both abnormalities present. The author has surgically removed this band of tissue in several dogs and has seen an improvement in clinical signs relating to ataxia and cerebellovestibular disease.

6. Episodic ataxia

A single case report of a 4-yr-old, male neutered Bichon Frise dog with presumed episodic cerebellar ataxia has been reported. Clinical signs manifested when the dog was 4 mos old. The episode were described as often being preceded by vomiting and ptyalism and lasting 6–24 hrs up to 2–4 times a week at their most frequent and intense point. During the episodes, the dog would exhibit stiffness in all four limbs, tetraparesis, reluctance to move, a wide-based stance, exaggerated jerky movements, frequent falling, and the development of a head bob. The dog would be mentally appropriate during the episodes. Diagnostic testing including complete blood count, biochemical profile, urinalysis, thyroid profile, bile acids, profile, thoracic radiographs, abdominal ultrasound, MRI, CSF analysis, and urine organic acid profile were considered normal. The dog responded to treatment with 4-aminopyridine, a potassium channel blocker that is used to treat a similar condition in humans. The clinical signs would usually resolve within an hour of taking the medication, and by 24 mos post treatment, the dog was normal with only occasional episodes occurring 2–3 times a year and being associated with vigorous exercise or long car rides. 4-aminopyridine is a voltage-gated, fast potassium channel blocker that has been shown to improve axonal conduction of demyelinated fibers. The cause of episodic ataxia in humans is unknown; however, it is suspected to be a disorder of irregular firing Purkinje cells. 4-aminopyridine has its greatest affinity for the Kv1.5 potassium channel and it is suspected that its mechanism of action is in restoring the normal pacemaking activity of Purkinje cells. It is used with caution in people due to its potential epileptogenic properties. A more specific blocker of the Kv1.5 potassium channel is hypothesized to be a more effective treatment with fewer potential side effects.

7. Spongy degeneration

A presumably autosomal recessive disorder affecting purebred male and female Malinois puppies, resulting in spongy degeneration of the cerebellar nuclei, has been described (13 puppies from five different litters). Clinical signs of cerebellar ataxia arise by 4–7 wks and affected multiple pups in five litters. Most dogs presented with varying degrees of cerebellar ataxia, wide-based stance, hypermetria, stumbling, or falling. MRI and computed tomography (CT) examination did not reveal any gross abnormalities of the brain in the patients that were scanned. The primary histopathological abnormality was severe bilaterally symmetrical vacuolization of the neuropil of the cerebellar nuclei and, to a lesser extent, similar vacuolization of the cerebellar granular cell layer and white matter of the cerebellar folia. Some puppies also demonstrated additional vacuoles in the brain-stem nuclei and the white matter of the brain stem and spinal cord. Because all puppies were euthanized by the age of 13 wks or before, it is difficult to say whether the clinical signs would have been progressive or stabilized.

B. Neoplasia

1. Primary brain tumors

Numerous primary neoplasms can affect the cerebellum. Typically, adjacent structures such as the brain stem and associated cranial nerves are affected as well. Not all neoplastic processes may be histologically considered invasive or malignant; however, because of the limited space for expansion, they are not considered benign, from a clinical point of view. Meningiomas are the most common brain tumor of dogs and cats. Unlike the meningiomas of humans and cats, dog meningiomas tend to be invasive to surrounding tissue and therefore difficult to remove entirely surgically. They usually form at the cerebellopontine or cerebellomedullary junction and grow along the path of least resistance, which is typically into the fourth ventricle. For this reason, they can be mistaken for choroid plexus tumors, which arise from the ventricles. They may also arise from the dural covering adjacent to the tentorium cerebelli. Advanced imaging techniques such as CT or MR imaging are necessary to aid in accurate diagnosis. The CT and MRI features of meningiomas have been described (see Chapter 5 and Chapter 6). Briefly, they are strongly contrast-enhancing, well-circumscribed masses that arise from the covering of the brain and, therefore, have a broad-based appearance (Fig. 12.13). There can often be a thickening of the bone adjacent to the tumor (hyperostosis). Choroid plexus tumors are also strongly contrast enhancing; however, these tumors lack the broad-based appearance of meningiomas. Cystic meningiomas have been reported in the dog. A broad-based, contrast-enhancing rim of tissue, filled with fluid, characterizes these tumors (Fig. 12.14). Feline

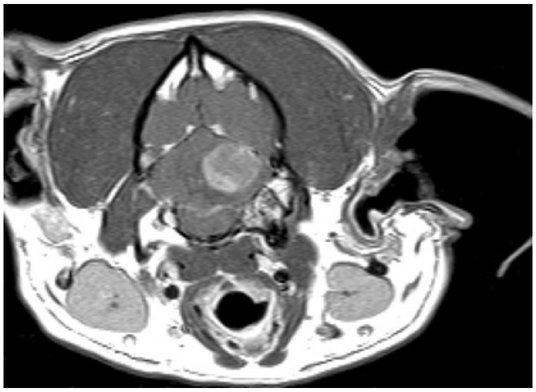

Figure 12.13 Transverse MRI of a dog's brain demonstrating a large, contrast-enhancing cerebellomedullary mass, consistent with a diagnosis of meningioma.

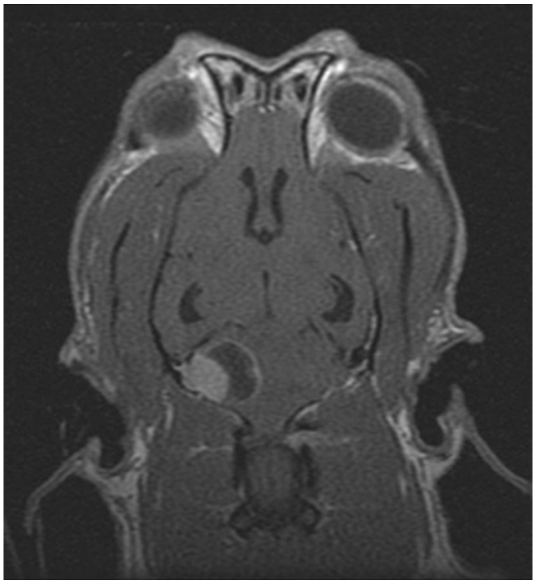

Figure 12.14 Dorsal T1-weighted MR image (with contrast), demonstrating a cystic meningioma in a dog's cerebellum.

intracranial meningiomas are most often benign growths in that they do not invade surrounding tissue. They are usually well encapsulated and therefore are good candidates for surgical resection (Fig. 12.15). When meningiomas extend into the fourth ventricle, they can be more difficult to remove.

Gliomas are neoplasms that originate from the supporting cells of the CNS (astrocytes and oligodendrocytes). Astrocytomas may be benign or malignant histologically; however, their presence in a confined space (the caudal fossa) compresses surrounding brain structures. They are usually slow growing, have poorly defined margins, and have a heterogeneously contrast-enhancing pattern that may also have ring enhancement. Oligodendrogliomas are round-cell tumors that invade surrounding tissue and are highly destructive. Similar to astrocytomas, oligodendrogliomas have nonuniform contrast enhancement. There are no specific features which allow the differentiation between astrocytomas and oligodendrogliomas on MRI examination. However, oligodendrogliomas are more likely to contact the meninges at least in the prosencephalon. In the case of prosencephalon oligodendrogliomas or astrocytomas, the contrast enhancement of tumors is associated with a higher tumor grade. The incidence of gliomas is greatest in brachycephalic dogs.

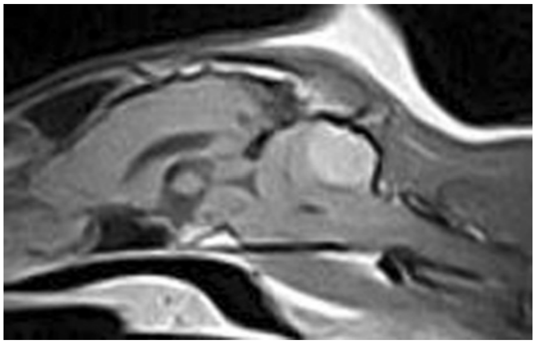

Figure 12.15 Sagittal T1-weighted MRI (with contrast) of a cat's brain, demonstrating a large cerebellar meningioma, which was successfully removed.

Choroid plexus tumors and ependymal tumors arise within the ventricles. These tissues are related embryologically and function in the production and movement of CSF. Tumors of ependymal origin are rare. The fourth ventricle is a common site for choroid plexus tumors. The choroid plexus is a very vascular tissue and therefore strongly contrast enhances on MR examination. Both of these tumor types can shed cells into the normal CSF pathways, and therefore a multifocal neuroanatomic localization is possible. Metastases of these tumors via CSF pathways are referred to as "drop" metastases (drop mets).

Medulloblastomas are highly metastatic brain tumors, typically occurring in the cerebellum of dogs and cats, usually between 3 and 10 yrs of age. These tumors share many characteristics with the same tumor type in people. They are classified as primitive neuroectodermal tumors. They arise from a population of cells thought to be present during the development of the cerebellum. Animals may present early or later in life with signs of cerebellar disease and possibly signs of brain-stem compression. As the tumors grow into the fourth ventricle, they will often cause obstructive hydrocephalus. Tumor cells will invade the adjacent meninges. Metastasis along CSF pathways is also common.

Epidermoid and dermoid cysts are structural abnormalities that may result in cerebellar dysfunction. These masses of tissue are not technically classified as neoplasia; however, because of their location, they create similar clinical signs. It is thought that they arise from an embryological invagination of neuroectoderm. During embryological development, portions of ectoderm destined to become skin become entrapped in the closing neural tube. Because the neural canal closes from a caudal to cranial direction, the fourth ventricle and cerebellomedullary junction is a common site for these abnormalities. They are present at birth; however, the onset of clinical signs usually occurs later in life. Because they are invaginations of tissue destined to become skin, they are filled with keratin and desquamated epithelial cells. They cause cerebellar signs due to the slow compression of surrounding structures. More information on primary brain tumors and epidermoid/dermoid cysts may be found in Chapter 7.

A cerebellar vascular hamartoma has been reported in a cat. The cat presented at 16 mos old with a history of cerebellar signs and a localization consistent with cerebellar syndrome. MR imaging of the cat identified a cerebellar mass with poor definition between the mass and normal cerebellar parenchyma. The mass was hyperintense on T2-weighted (T2-W) images and possessed both hyperintense and isointense region on T1-weighted (T1-W) precontrast images. On T1-W post contrast images, there was heterogeneous contrast enhancement with peculiar smaller, isointense, ring-enhancing areas within the mass. A histopathological examination of the mass identified multiple, proliferative endothelial-lined cavities containing thrombi and multiple foci of mineralization.

2. Secondary brain tumors

The CNS is a common site of metastatic tumors. The cerebellum may be affected through hematogenous spread or spread through the CSF pathways. The extent and nature of cerebellar dysfunction will be referable to the site of the metastatic tumor (i.e. it may involve other surrounding structures). Common metastatic tumors include mammary adenocarcinoma, prostatic adenocarcinoma, pancreatic adenocarcinoma, pulmonary adenocarcinoma, melanoma, hemangiosarcoma, and lymphoma.

Tumors of surrounding structures of the CNS may also compress the cerebellum. These include tumors of the skull, such as osteosarcoma, chondrosarcoma, and multilobular osteochondrosarcoma. More information regarding secondary brain tumors may be found in Chapter 7.

3. Paraneoplastic cerebellar degeneration (PCD)

Although relatively rare in humans, there are multiple reports of paraneoplastic cerebellar degeneration in people, and this is the most common paraneoplastic disorder of this species that affects the brain. The immunopathogenesis of this phenomenon is complex, but it generally involves aberrant peripheral (i.e. not CNS) tumor expression of neuronal antigens (usually of Purkinje cells), antigens that normally are sequestered from the immune system via the blood–brain barrier. The resultant autoimmune response against these tumor antigens leads to a secondary autoimmune degeneration of cerebellar neurons (primarily Purkinje cells). Cerebellar dysfunction in such cases is typically acute or subacute in onset and precedes detection of an obvious neoplasm in up to two-thirds of cases. A wide variety of tumors have been associated with PCD in people, but the most commonly reported are small cell lung carcinoma, ovarian carcinoma, breast carcinoma, and Hodgkin's lymphoma. Diagnosis can be very challenging, especially in the absence of a detectable neoplasm. Brain imaging is often normal, though evidence of cerebellar degeneration may be appreciated. CSF analysis may also be normal, though a mild pleocytosis may be evident. Definitive diagnosis depends upon the identification of serum and/or CSF antibodies directed against specific neuronal antigens (e.g. anti-Yo, anti-Hu antibodies). These antibody tests are not available for dogs and cats. Though not yet reported in dogs and cats, the possibility of PCD should be considered in some patients (e.g. older dogs and cats with obvious cerebellar dysfunction and normal or equivocal brain imaging and CSF findings).

C. Infectious/inflammatory

1. Feline (panleukopenia) and canine parvovirus

One of the most well-recognized disorders of cerebellar development is the *in utero* infection of feline embryos with the feline panleukopenia virus (FPV). Kittens infected with FPV either *in utero* or in the perinatal period may develop cerebellar dysfunction secondary to cerebellar hypoplasia. Infections resulting in clinical signs of cerebellar disease cause inflammation of the brain and destruction of cells in the external germinal layer of the cerebellum. This layer is highly active prior to, and in the first few weeks following, birth. This active division leads to the fully functional cerebellum. Disruption of the division of these cells leads to hypoplasia of the granular layer and gross cerebellar hypoplasia. Purkinje cells that are actively growing may also be affected. Kittens typically present with a nonprogressive, symmetric cerebellar ataxia usually noticed at the onset of ambulation. Occasionally, other areas of the CNS will be affected. With time, most cats will compensate for the cerebellar dysfunction and clinical signs may abate. Amplification of parvoviral DNA from the paraffinized brain tissue of two dogs with congenital cerebellar hypoplasia has been performed implicating the *in utero* infection of canine parvovirus as a possible cause of the malformation. The polymerase chain reaction (PCR) technique has also been successfully performed in cats with congenital cerebellar hypoplasia.

2. Canine herpes virus

The predilection of clinical signs related to cerebellar dysfunction secondary to viral infection is likely due to the developmental nature of the tissue affected. The Purkinje neurons in the cerebellum are exquisitely susceptible to all types of injury. This, when considered with the fact that the granular layer is continuing to develop well into the perinatal time period, provides a plausible explanation as to why clinical signs of cerebellar disease would predominate. Puppies exposed to canine herpes virus either *in utero*, during parturition, or within the first 2 wks of life can develop a herpes virus meningoencephalitis that can preferentially affect the cerebellum. Nearly all puppies with an active infection early in life will succumb to the infection. However, a few will live and have residual lesions in the CNS. Although other organs may be affected (lung, kidney, liver), signs of a cerebellar syndrome in a newborn puppy would indicate that a herpes virus infection is a likely differential diagnosis. Surviving puppies may also be affected with retinal dysplasia, as this tissue is also undergoing active differentiation at the time of the infection.

3. Canine distemper virus (CDV)
   Canine distemper virus may affect dogs of any age; however, there is a pattern to the destruction of nervous system tissue that is age-dependent. Those dogs affected with the disease early in life suffer from a polioencephalomyelopathy (gray-matter disease), usually have a history of seizures, and rarely survive. MRI findings associated with the acute form of CDV infection are associated with demyelination and include hyperintense signal changes on T2-W images of the brain. The signal changes are secondary to the accumulation of extracellular water in the space formerly occupied by myelin. Contrast enhancement of the lesions may occur but is not common. There may not be a correlation between the location of the lesion and histopathological confirmation of demyelination. This may be due to the fact that in dogs experiencing seizures similar MRI findings have been observed. However, lesions of the cerebellum are more likely to correlate with histopathological confirmation of demyelination in cases of CDV infection. This MRI characteristic is observed in other demyelinating diseases such as spongy degeneration and globoid cell leukodystrophy; therefore, the MRI changes must be considered in the light of the clinical suspicion for CDV infection. Dogs affected by the disease later in life may have brain-stem, cerebellar, and vestibular signs. They typically have a leukoencephalomyelopathy (white-matter disease) or a combination of gray- and white-matter disease, and in most cases the disease is less severe. The cerebellar peduncles are commonly affected; however, distemper virus can affect all segments of the nervous system. A common sequela of an infection with CDV is a rhythmic myoclonus of a single muscle group that may be mistaken for tremors.
4. Feline infectious peritonitis (FIP)
   The pyogranulomatous (dry) form of feline infectious peritonitis virus can affect the CNS and may result in inflammation of the ependyma, choroid plexus, or meninges that surround the brain stem and junction of the cerebellum and medulla. This disease can be a challenge to diagnose, as definitive antemortem tests to prove a cat has the disease are virtually nonexistent. In one report, it was found that a high CSF IgG titer against feline coronavirus (greater than 1:25) was predictive of FIP as a causative entity. However, in a later report, CSF IgG titers were not found to be predictive of FIP, but rather suspected to be nonspecifically derived from the systemic circulation. Similarly, it is unclear whether PCR testing of CSF for coronavirus in cats is predictive of the existence of CNS-related FIP. It has been reported that over 45% of cats affected with the dry form of the disease will have signs of CNS dysfunction. This results from an inflammatory response to the virus and a lack of a protective cell-mediated immune response. Because the disease occurs as a multifocal pyogranulomatous meningoencephalomyelitis in the CNS, the neuroanatomic localization can be diverse. Various guidelines have been suggested for the clinician to follow in order to make a presumptive diagnosis. They include a history of possible exposure, clinical signs, high CSF coronaviral titers, and concurrent infection with feline leukemia virus. The disease is usually fatal, except in rare cases.
5. Granulomatous meningoencephalomyelitis
   Granulomatous meningoencephalomyelitis (GME) has been reported as primarily affecting the cerebellum; however, the condition typically affects multiple areas of the CNS. Three forms of the disease have been described: the disseminated (multifocal) form, the focal form, and the ocular form. The disseminated form usually has a much more rapid onset and progression than the focal form. This disease is typically characterized by a massive perivascular inflammatory response consisting of histiocytes, plasma cells, and lymphocytes, occasionally mixed with other leukocytes. It primarily affects the white matter, but it can affect the gray matter as well. The condition most commonly affects young to middle-aged small-breed dogs and has a higher incidence in females than males. Lesions in the region of the cerebellomedullary angle are common. Affected animals will present with clinical signs referable to structural disease of the cerebellum (i.e. ataxia, tremors, nystagmus). The extensive accumulations of inflammatory cells are at times so proliferative that they compress surrounding tissue. An antemortem diagnosis of GME is based primarily on demonstrating characteristic contrast-enhancing brain lesions on CT or MRI (Fig. 12.16) and the presence of a mixed, predominantly mononuclear, pleocytosis on CSF examination. The treatment of GME is covered in detail in Chapter 7. Corticosteroid therapy may relieve clinical signs, but this is often for a short period of time (weeks to months). When the histiocytes are admixed with inflammatory cells, the distinction is one of a nonsuppurative meningoencephalomyelitis. If histiocytes are the predominant monomorphic form, then the classification is more akin to neoplasia. It has been suggested that the nonsuppurative form of the disease may be a form of neoplasia as well. Because the predominant cell types appear to originate from the monocyte–macrophage cell lines, radiation therapy has been proposed and has been used successfully in the treatment of focal GME.

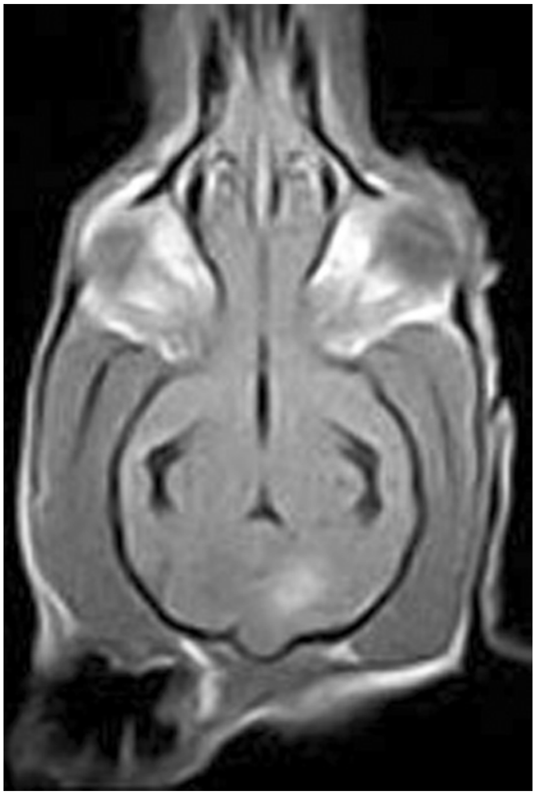

Figure 12.16 Dorsal T1-weighted MRI (with contrast) of dog's brain, demonstrating a contrast-enhancing GME lesion in the cerebellum.

6. Fungal diseases
   All of the commonly encountered mycotic organisms may infect the CNS; however, the most frequently seen infections are *Cryptococcus neoformans*, *Blastomyces dermatitidis*, and *Coccidioides immitis*. They typically result in a diffuse or multifocal meningoencephalitis. The CNS may be infected through systemic dissemination (i.e. hematogenously), local extension (e.g. nasal, frontal sinuses), migrating foreign bodies (e.g. grass awns), or surgical procedure (iatrogenically). CNS infections may involve the junction of the cerebellum and the medulla, resulting in cerebellar, vestibular, and other brain-stem signs. Additionally, because of the typical multifocal presentation of these infections, signs of cerebral and spinal cord involvement may be apparent along with cerebellar signs. Fluconazole is the treatment of choice. Additional information regarding CNS fungal infections can be found in Chapter 7.
7. Rickettsial disease
   The vasculitis caused by either Rocky Mountain spotted fever or ehrlichiosis may cause a meningoencephalitis in dogs. Dogs neurologically infected with a rickettsial disease commonly present with vestibular dysfunction, usually after a history of lethargy, depression, and fever. The hematologic abnormalities secondary to a rickettsial infection or vasculitis may pass without the owners being aware that the animal was infected. Cerebellovestibular signs may be appreciated in combination with clinical signs referable to other areas of involvement in the CNS. Rickettsial diseases are rare in cats. Additional information regarding CNS rickettsial infections can be found in Chapter 7.
8. Protozoal disease
   The nervous system of both dogs and cats may be infected by the coccidian protozoan *Toxoplasma gondii*. *Neospora caninum*, a protozoal organism related to *Toxoplasma*, is known to naturally infect the nervous system of dogs only. These infections typically present as multifocal disease and are supported by systemic illness. They can infect animals of all ages and breeds. Immunocompromised or immunosuppressed animals are more susceptible to infection. The infections cause necrosis, a nonsuppurative encephalomyelitis of both gray and white matter and may cause cerebellar atrophy. Infectious foci can form granulomas, which may result in signs consistent with focal disease. Clinical signs of cerebellovestibular disease would be expected if the lesion caused compression, atrophy, or inflammation of the cerebellum, cerebellar peduncles, or brain stem.

   Additional information regarding CNS protozoal infections can be found in Chapter 7.
9. Algal disease
   Prototheca wickerhamii and *Prototheca zopfii* are species of ubiquitous algae that have been reported to cause CNS disease. The disease is rare, and it is thought that an abnormality of the animal's immune system must contribute to the pathogenesis of the infection. Animals will present with systemic signs of illness and multifocal neurologic disease, the clinical signs of which will be dependent upon the area of the nervous system affected. The pyogranulomatous lesions seen in the brains of dogs with protothecosis may cause signs of cerebellovestibular dysfunction. In one case, an eosinophilic pleocytosis was reported. The organism has a predilection for the eyes, so ocular changes may accompany signs of multifocal neurologic disease.

D. Trauma
   1. Trauma to the brain is discussed in detail in Chapter 6. Trauma involving the cerebellum is uncommon due to the fact that the cerebellum is in a particularly isolated environment. It is almost completely surrounded by bone. Dense bone surrounds three-fifths of the cerebellum as the cranial vault at the caudal, lateral, and dorsal aspects. The rostral aspect of the cerebellum is separated from the cerebrum by the partially osseous tentorium (tentorium cerebelli). Additionally, in dogs there is a large mass of muscle that surrounds the caudal skull.
   2. Trauma to the cerebellum may be divided into primary injuries such as skull fractures, blood vessel damage, and

a tearing/crushing of the cerebellar parenchyma and secondary injuries that are a result of physiological changes, such as increased intracranial pressure (ICP), ongoing hemorrhage, ischemia, and cerebellar edema. In the second class of injuries are the injuries that may benefit from medical or surgical therapy. Primary cerebellar injuries are irreversible. Of major concern is the decrease in cerebellar perfusion secondary to increased ICP. The Purkinje cells of the cerebellum are exquisitely sensitive to ischemic, as well as compressive (edema), injury. There are two types of edema associated with cerebellar injury. Cytotoxic edema results from the failure of membrane transport systems in the cell secondary to a decreased production of ATP. Decreased ATP production is due, in turn, to hypoxia and disruption of the electron transport chain. This cascade of events eventually leads to an accumulation of water and solute in the cells themselves. Vasogenic edema results from the damage to membranes secondary to free-radical production and lipid peroxidation. These damaged membranes then leak protein and other small solutes into the interstitial space. In general, vasogenic edema is more responsive to medical therapy than is cytotoxic edema.

3. Corticosteroid therapy is a focus of great controversy in the treatment of brain trauma. The Brain Trauma Foundation does not recommend the use of glucocorticoids in people. There is conclusive evidence that the use of glucocorticoids does not lower ICP or improve the outcome of humans with severe head injuries. The beneficial effects of corticosteroids in the treatment of brain trauma may be limited to their ability to treat vasogenic edema (edema most commonly associated with brain tumors and other masses). Unfortunately, the major edema associated with brain trauma is cytotoxic. The basics of treatment for brain trauma include adequate fluid resuscitation and support, oxygenation and ventilation if necessary, mannitol, furosemide, hypertonic saline, nutritional support, supportive care (e.g. eye lubrication, padded surface, rotation), adjunctive treatment (moderate hypothermia, free-radical scavengers, etc.), and surgery, if necessary. The pathophysiology of brain trauma is very complex. Additional information concerning brain trauma can be found in Chapter 8.

E. Miscellaneous causes of cerebellar disease

1. Lysosomal storage diseases
Lysosomal storage diseases of the CNS represent a group of disorders that have in common the accumulation of metabolic by-products within the perikaryon, axon, dendrites, or surrounding neuropil. Storage diseases can primarily affect the cerebellum; however, they usually are very diffuse in their localization, affecting multiple areas of the brain and spinal cord. Animals with lysosomal storage diseases affecting the cerebellum will typically present at a young age, due to the fact that these diseases are congenital. However, there are few reports of animals presenting with signs of cerebellar disease later in life. Numerous storage diseases may have the potential to affect the cerebellum. A few of the more commonly documented diseases are discussed here. More information concerning lysosomal storage diseases is provided in Chapter 7.

Lafora bodies are polyglucosan deposits within the CNS. They have been associated with disease of the CNS in various small animals, including a 4.5-yr-old cat that presented for head bobbing and whole-body tremors. The Lafora bodies were most numerous in the granular layer of the cerebellum and in Purkinje neurons. Neuronal ceroid lipofuscinosis has been most commonly reported in the dog. A similar condition affects cats. The disease results from intraneuronal accumulations of ceroid lipofuscin granules, and it can result in gross cerebellar atrophy. It has been related to primary cerebellar disease in dogs. Dogs with this storage disease will usually present at less than 1 yr old; however, they may not show clinical signs until they mature. Niemann–Pick disease type C in cats causes neurologic deterioration and hepatosplenomegaly. This disease is caused by an accumulation of sphingomyelin and other lipids in the CNS and reticuloendothelial tissues (e.g. spleen, liver). Neuroaxonal dystrophy is the primary histologic feature of the disease. Cats affected by this disease will usually show signs of tremor by 8–12 wks. The disease will slowly progress until the cat is unable to stand. Eventually, the menace responses may disappear as well. In people, those children who have the late infantile form (3–5 yrs old) have primarily cerebellar signs. Although these storage diseases are rare, they should be suspected in young animals that present with slowly progressing cerebellar signs.

2. Ischemic/vascular (Video 21)
Because of the cerebellum's sensitivity to ischemic changes secondary to hypoxia, clinical signs of cerebellar disease may be evident before signs related to other areas of the brain following ischemic events. A definitive antemortem diagnosis of cerebellar infarct is usually not possible. With advanced imaging techniques, such as MRI (Fig. 12.17), however, a presumptive diagnosis can usually be made by combining imaging results with history, signalment, and results of ancillary diagnostic tests. Clinical signs of cerebellar disease will typically be ipsilateral to the area damaged in the cerebellum. If the damage to the cerebellum is minor, one would expect the animal to have a good prognosis, with typical improvement in clinical status seen within the initial 72 hrs after the ischemic episode. Causes of thromboembolic disease such as hyperadrenocorticism, hypothyroidism (atherosclerosis), bacterial endocarditis, heartworm disease, hyperlipidemia, hypertension, and neoplasia must be ruled out as potential causes. Sporadic

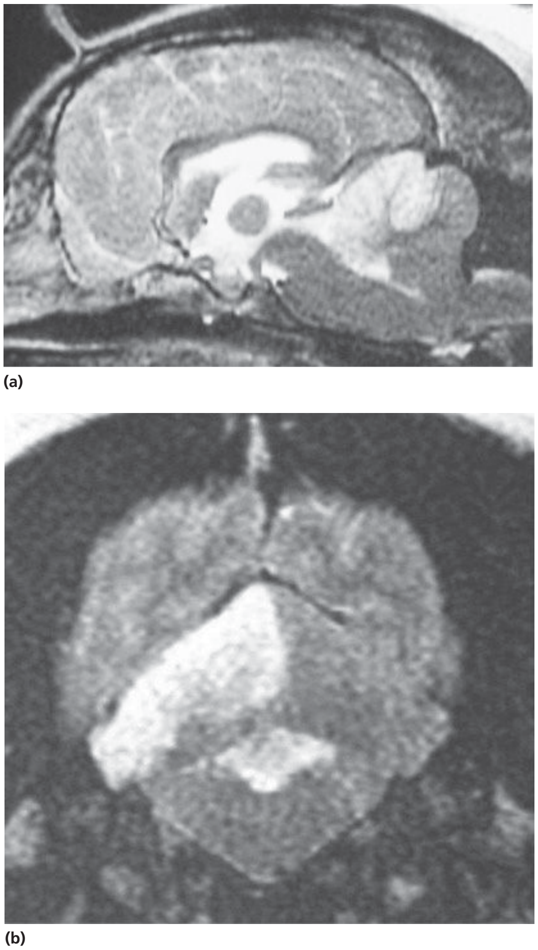

Figure 12.17 T2-weighted sagittal (A) and transverse (B) MR brain images from a dog with a cerebellar infarct.

cases of postanesthetic cerebellar dysfunction have been observed. Clinically normal animals undergoing routine anesthetic procedures have been affected with a cerebellar syndrome. Brachycephalic breeds (e.g. Boston Terriers, Persian cats) may be at a higher risk of developing this anesthetic-related complication. In a retrospective study involving 11 Persian-cross cats affected with cerebellar signs following routine anesthetic procedures, ketamine was used in each case. Although there is no direct implication of ketamine, it is hypothesized that a genetic susceptibility may play a role in the process. Ischemic/vascular encephalopathy is also discussed in some detail in Chapter 7.

3. Intracranial arachnoid cysts (IAC), quadrigeminal arachnoid cysts, ependymal cysts

Intracranial arachnoid cysts, sometimes referred to as quadrigeminal cysts, are described in detail in Chapter 7. The development of these anomalous conditions is poorly understood and they may be considered an incidental finding when occurring concurrently with other disorders of the brain. They are most commonly observed in toy breeds; however, they have been reported sporadically in the veterinary literature affecting a wide variety of breeds of dogs and more uncommonly in cats. While they typically arise from the quadrigeminal cistern, they may exert pressure on the cerebellum resulting in compression and possible foramen herniation. The author has observed a case of a cerebellar IAC in a 2-yr-old Rottweiler with a slowly progressive cerebellar syndrome. In this particular case, the IAC arose from the caudal aspect of the tentorium cerebelli and not the rostral aspect as is commonly reported (quadrigeminal cistern). An ependymal cyst has been reported in an 11-wk-old, Staffordshire Bull Terrier. The dog presented with a cerebellar syndrome present since birth. MRI confirmed a fluid-filled cavity in the region of the left cerebellar hemisphere and vermis. Histopathological determination of an ependymal cyst as opposed to an arachnoid cyst was made through demonstration of glial fibrillary acidic-positive glial cells covered multifocally by epithelial cells. A traumatic origin was suspected due to the presence of hemorrhage and tissue destruction.

Tremor syndromes[5, 9, 11, 26, 38, 44, 53, 55, 63, 65, 7

Pathophysiology and classification

Tremors in dogs and cats can be caused by a variety of conditions affecting the nervous system. The definition of tremor in the human literature is debated based on whether the term "involuntary" should be included. In veterinary medicine, we do not recognize *voluntary tremors*; therefore the definition for our purposes can be modified from a well-accepted human-related definition of tremor (Box 12.1). A tremor is an involuntary, *approximately rhythmic*, oscillatory, or roughly sinusoidal movement of a body part. Tremor can be found in both normal and abnormal animals. It can be distinguished from pure myoclonus, which is a sudden contraction of muscles without necessarily a rhythmic, oscillatory, or sinusoidal nature (such as a tic or twitch). However, certain forms of myoclonic clonus can have a rhythmic characterization and therefore be included under the category of tremor. Certainly, in the broadest sense of the definition of a movement disorder, tremor is a distinct subcomponent. For veterinary purposes, the classification of tremor may be based on the phenomenological or the syndromic schemes (Table 12.2). Much of the understanding of the pathophysiology of tremor in humans has been elucidated in the last 20 yrs. Classification schemes are continually being updated, which is a clear indication that no complete understanding of all the possible etiologies of tremor exists. It is important to

Table 12.2 Classification of tremors in dogs and cats

Phenomenologic	Syndromic
A. Resting tremor B. Action tremor 1. posture tremor a. position dependent b. position independent 2. kinetic tremor a. simple (nontarget directed) b. target directed (intention) 3. task specific or isometric (not present in nonprimate species	A. Physiologic B. Enhanced physiologic C. Essential tremor 1. classic essential tremor 2. intermediate tremor syndrome 3. primary orthostatic tremor 4. position specific tremor D. Cerebellar tremor syndromes E. Holmes' tremor (rest plus intention tremor) F. Drug induced and toxic tremors G. Tremors due to peripheral neuropathy H. Unclassified tremors 1. episodic head tremor syndrome

remember that many of the experiments that have generated the current conclusions regarding the pathophysiology of tremors in people were performed on animals. It is difficult to categorize tremors of dogs and cats in the same groupings as human tremors. Numerous classification schemes have been published in both human and veterinary medical literature. In people, tremors are characterized by their frequency in Hertz (Hz; or cycles per second), the location of the tremor (e.g. fingers, legs, head), and the condition in which the tremor occurs (e.g. at rest, standing, goal-oriented behavior). The origins of tremors are uncertain. The activity of the brain is intensely rhythmic. Oscillators are systems that have the ability to produce rhythmic activity. These are not necessarily discrete anatomic structures. They may likely be neural circuits or connections between subsystems that have an inherent ability to function in this manner. Neurons have the ability to resonate and set up oscillatory firing. The subcortical oscillations of neurons occur through electrical coupling via gap junctions. These neurons resonate at 7–10 Hz, which is the typical range for physiologic tremors.

Box 12.1 Definitions of tremors.

Resting tremor is a tremor of a body that is completely supported against gravity and not voluntarily activated. For example, tremor in a dog's leg as it is lying down.

Action tremor is a tremor that is produced by a voluntary contraction of a muscle.

- *Postural tremor*: tremor is present while voluntarily maintaining a position against gravity.
- *Kinetic tremor*: tremor during voluntary movement. May be target directed (intention) or non-target-directed (simple).
- *Intention tremor*: a tremor that is present during target-oriented voluntary movement, such as visually or olfactory guided movement. The amplitude of the tremor may increase as the target is reached.
- *Task specific or isometric tremor*: these tremors are present during specific activities such as writing or grasping. They are not recognized in dogs and cats.

Holmes' tremor is an irregular, low-frequency tremor that is present both at rest and with intention. It may also occur with posture. It is a characteristic of a specific lesion involving interruption of the dentate, thalamic, and nigrostriatal tracts (typically, hemorrhage or infarct). Also referred to as a *rubral* tremor, *midbrain* tremor and *thalamic* tremor. This form of tremor likely occurs in veterinary patients but may not be recognized.

Physiological tremor: a fine-action tremor that is present in the normal patient due to numerous factors including heartbeat, motor neuron firing, synchronization of muscle spindle feedback, etc.

Enhanced physiological tremor: a pronounced physiological tremor due to muscle fatigue, fear, and excitement.

Essential tremor: typically an age-related, benign form of tremor that may be genetic. The definition would exclude a known etiology such as infarct, drug or toxin exposure, and other neurologic deficits. It would also not be suspect should the onset have been acute.

Intermediate essential tremor: patients with suspected essential tremor with possible early clinical signs of possible neurologic deficits (e.g. mild vestibular signs, mentation changes, periodic weakness). A presumptive diagnosis of another form of tremor cannot be made with confidence at the time of the initial classification of the tremor.

There are four basic modes of tremor genesis in humans. First, mechanical tremor is due to the resonance frequency of the activated muscle, which can be changed based on the load against the muscle. This is the simplest form of tremor. This form of tremor can be reduced by adding a load to the activated muscle (which causes an increased activation of muscles) or increased by adding stiffness or contraction of muscles (e.g. making a fist while trying to support weight). Second, reflexes of the CNS may result in the alternating antagonistic flexion/extension of muscles. For example, when a limb is extended, there are impulses that allow the antagonistic muscle to cause flexion. Conversely, as that muscle is flexing, impulses are generated to allow the antagonistic muscle of that activity to cause extension (this is a component of fluidity of movement) in order to achieve a balance in the movement. The muscles will have synchronized frequency peaks that are equivalent to the frequency of the portion of the limb that generates that movement. Third, in central oscillation, tremors occur either through the rhythmic activity of a group of neurons in a nucleus (the electrotonic coupling of oscillatory activity through gap junctions) or through oscillations created by neural circuits between different nuclei or different populations of neurons. Fourth is tremor that is the result of malfunction of feed-forward loops. This occurs within the CNS and most commonly in the cerebellum. It is commonly recognized as intention tremor. In this case, a deficit of cerebellar function causes a delay of the antagonistic movement, which results in a decreased braking of a ballistic movement and an overshoot movement. Compensation then leads to a correction movement, which causes hypermetria in the opposite direction. Eventually, the abnormality will create an oscillatory movement that is intensified during goal-oriented behavior.

The following will be a classification of tremors in animals based on current human classifications, realizing that certain descriptive aspects and therefore classifications are not possible in animals. By excluding possible categories of tremors based solely on anthropomorphism (e.g. psychogenic tremors) or lack of reported occurrence in animals (e.g. parkinsonian tremors), we may limit the future identification of animal models of tremors. Therefore, although specific examples of tremors in animals that are recognized in humans may not be discussed (because we have not documented them), the categories will be mentioned nonetheless.

Tremors can be divided into two broad categories: *physiologic tremors* and *pathologic tremors*. Pathologic tremors are those that impair motor function. Physiologic tremors are present in normal animals at a low-amplitude movement that is difficult to discern with the naked eye. There are three components to a physiological tremor. The first component, the mechanical component, is due to the passive properties of cardiac activity during systole, referred to as the ballistocardiogram. The second component is the augmentation of the mechanical component by sympathetic reflexes (e.g. epinephrine enhancement of muscle spindle activation). Finally, a central component is hypothesized, wherein synchronization of motor neurons by the brain is responsible for the amplification of the tremor. These tremors can occur at rest or with posture. A group of physiologic tremors that are looked at as "physiological tremor of pathological amplitude" is known as enhanced physiological tremor. These tremors are an exaggeration of the normal physiological tremor and may be caused by metabolic abnormalities (electrolyte disturbances, hypoglycemia, etc.), stress, exercise, certain medications (e.g. metoclopramide, diphenhydramine), and toxins (e.g. lead, organophosphates).

The pathologic tremors, according to human classification schemes, consist of cerebellar tremors, parkinsonian tremors, Holmes' tremor (formerly known as rubral or midbrain tremors), tremors due to peripheral nervous system (PNS) disorders (e.g. neuropathies, myopathies, junctionopathies), dystonic tremors, palatal tremors, orthostatic tremors, and psychogenic tremors. Cerebellar tremors (intention tremors) were discussed previously and may result from any pathology that affects cerebellar function. They have been associated with lesions involving the lateral cerebellar hemispheres, the vermis, and the interposital nucleus. These tremors will be bilaterally symmetrical if due to a toxin or degenerative condition that affects the cerebellum and ipsilateral to specific lesions of the cerebellum such as an infarct or neoplasia. Cerebellar tremors can be presumed when there are other signs of cerebellar dysfunction (e.g. ataxia, nystagmus). Parkinsonian tremors are specifically due to an abnormality in the synthesis of the neurotransmitter dopamine. These tremors are due to alterations in the circuitry of the basal nuclei motor loop. Dopamine plays a very important role in the proper function of this motor loop. In Parkinson's disease there is degeneration of the substantia nigra. The substantia nigra is a group of cells in the midbrain responsible for the synthesis of dopamine. Terminal fields of the substantia nigra are located in the caudate nucleus and globus pallidus, where dopamine exerts some of its major effects. This degeneration of the nigrostriatal pathway is also seen in horses that ingest the toxic weeds yellow star thistle (*Centaurea solstitialis*) and Russian knapweed (*Centaurea repans*). The parkinsonian tremor of humans, which affects fine-motor muscles such as the hands and fingers, may be similarly represented by the slow, rhythmic, oscillatory movement of a horse's muzzle in those animals clinically affected with yellow star thistle poisoning. This particular type of tremor has not been recognized in dogs or cats.

Holmes' tremor is a combination of cerebellar tremor and basal nuclei tremor. It may result from lesions in the cerebellum/midbrain and thalamus. Due to the proximity or involvement of the red nucleus in the midbrain, these are commonly referred to as *midbrain* or *rubral tremors*. These tremors have an erratic, uneven appearance with a relatively low frequency (less than 4.5 Hz). They are differentiated from cerebellar tremors in that they can occur at rest, with intention, and with posture. This form of tremor likely exists in veterinary patients but is unrecognized or categorized as cerebellar tremor (affecting cerebellar outflow tracts). They are often the result of lesions of the cerebellar outflow pathways. In people, there is a delay between lesion onset and activation of the tremor of 4 wks to 2 yrs.

Disorders of the PNS, especially those resulting in demyelination, may cause tremors. These can have an insidious onset and may result from congenital, inherited, metabolic, toxic, and inflammatory etiologies. Dystonic tremors involve muscles affected by abnormal muscle tone; however, it is thought that the origination of the tremor in people is in the basal nuclei. These tremors are typically focal, high-frequency (less than 7 Hz), and of inconsistent amplitude. A rhythmic oscillation of the soft palate in people is a rare condition known as palatal tremor. This condition is known to occur with abnormalities of the inferior (caudal) olivary nucleus. It develops secondary to lesions in the cerebello-olivary projection from the cerebellum to the contralateral olivary nucleus via the superior (rostral) cerebellar peduncle. The lesion causes a disinhibition of the inferior (caudal) olive neurons, which become electronically coupled via gap junctions. It has not been recognized in dogs or cats. Orthostatic tremor is a form of postural tremor reported in people as a sensation of unsteadiness or quivering when standing up. This tremor is a fine tremor (approximately 13–16 Hz) of the legs and is only apparent when standing. It is hypothesized that this tremor disorder originates from the brain stem and/or cerebellum (i.e. a supraspinal tremor generator) in a center responsible for regulating stance or muscle tone. There is an animal model of this disorder in pigs. Orthostatic tremor has been described in young, giant-breed dogs, most notably Great Danes and Mastiffs. This disorder is described in more detail under postural tremors (see "Essential tremors" section below). The condition referred to as *myokymia* is characterized by episodic wavelike undulations of the skin, due to contractions of small subcutaneous muscle fibers. This movement has also been described as "rippling" and "vermicular" (wormlike) and may appear clinically as a form of tremor. Myokymia is probably a manifestation of a more-inclusive disorder called *neuromyotonia*. Neuromyotonia refers to episodic muscle contraction secondary to hyperexcitability of motor nerve axons. A clinical syndrome of neuromyotonia and spinocerebellar ataxia has been described in Jack Russell Terriers and one Dachshund. Myokymia/neuromyotonia is discussed in more detail in Chapter 18.

In people, several criteria must be met before a diagnosis of psychogenic tremor can be made. Essentially, it is a tremor generated as voluntary movement that requires little attention to be maintained. The tremor may be associated with clonus of the affected body part. The amplitude of a hand tremor will usually decrease when a load (weight) is applied to the hand. With psychogenic tremor, the amplitude of the tremor increases when a load is applied. This is interpreted as necessary co-activation of the muscles in order to maintain the reflex activity that generates the tremor. Other clinical signs of psychogenic tremor in people include a history of somatization, which is multiple physical complaints that suggest a physical disorder without any physical impairment to account for them, the sudden onset of the condition or remission of the condition, other unrelated neurologic signs, and a decrease in the tremor amplitude or frequency when the subject is distracted or performing movements of the contralateral hand. Obviously, from this description, it is unlikely that this tremor disorder exists in animals. Many of the tremor classifications described above have not been recognized in animals. It is hoped that with a better understanding of tremor disorders (through those documented in humans) we may better recognize the abnormalities in animals. Based on frequency and circumstance (resting, posture, or intention), a general neuroanatomic localization may be made.

From a practical aspect, the presence of a movement disorder can be subdivided into categories that may lead to a clinical suspicion of a diagnosis—from which diagnostic testing either to elucidate the cause of the movement disorder or more commonly eliminate possible causes (through exclusion) will lead to either potential treatment options or the "peace of mind" that there may be nothing that can be done and the acceptance that the patient will either live with a benign clinical sign or have an adjusted lifestyle to accept the consequences of a progressive movement disorder. We cannot always treat and eliminate the clinical signs of disease, especially when presented with age-related, congenital, or genetic disorders; however, we can help pet owners accept the disorder and try to make the patient's life as comfortable as possible. Descriptions of movement disorders may include terms such as *spasms*, *jerks*, *twitches*, *tremors*, *convulsions*, *seizures*, and *fits*. If the goal is to provide treatment for the clinical signs, the approach should first concentrate on the classification of the movement disorder. Through classification, the clinician can then determine whether a treatment is possible, the movement disorder is benign, or the patient must live with a progressive movement disorder as long as quality of life does not suffer (a very difficult measurement to classify based on a heterogeneous mixture of variables that shape an individual' own idea of *quality of life*).

Tremors and twitches are often the initial presenting clinical sign of a number of disease conditions. Oftentimes, other localizing features of the clinical syndrome must be observed before a neuroanatomical, metabolic, or benign classification can be given to the clinical signs. These movement disorders are typically a piece of a larger clinical puzzle. In certain clinical conditions, a characteristic tremor along with history can provide a relatively confident presumptive diagnosis (such as the constant repetitive myoclonus associated with the CDV).

Tremor disorders in dogs and cats

Hypomyelination/dysmyelination (dysmyelinogenesis)

Congenital tremors due to hypomyelination or dysmyelination have been reported in many breeds of dogs, but rarely in the cat. The condition is known to affect the Chow Chows, Weimaraners, Bernese Mountain dogs, Samoyeds, Springer Spaniels, Dalmatians, Lurchers, mixed breeds, and the Siamese cat. In the majority of congenital tremor syndromes attributable to disorders of myelin formation, the defect is confined to the CNS. Peripheral nerves are unaffected. This discrepancy most likely arises from the difference in the cells responsible for myelination in the CNS and PNS. Oligodendrocytes are responsible for the myelination of many axons within the brain and spinal cord. Once the axons leave the CNS, the Schwann cell takes over the responsibility of myelination; however, a single Schwann cell will only myelinate a single axon. *Dysmyelination*, strictly defined, refers to decreased myelination due to an abnormality of the myelin itself. *Hypomyelination* implies that the myelin is biochemically normal but present in decreased amounts. In almost all cases studied, the clinical signs appear within the first several weeks of age; however, cases of delayed onset have also been described.

In the recessive X-linked hypomyelination disorder of Springer Spaniels ("shaking pups"), a severe generalized tremor is first appreciated in the second week of life in affected male dogs. These dogs are unable to stand or walk, and do not improve over time. Female carriers of the defective gene may display a mild generalized tremor during the second week of life, which resolves by 4–6 wks of age. Dogs with this disorder may develop seizure activity as they mature. The Samoyed breed is affected with a hypomyelination disorder very similar to that of the Springer Spaniel dogs. Other breeds with hypomyelination/dysmyelination disorders tend to have less-severe clinical syndromes, in comparison with Springer Spaniels and Samoyeds. In these breeds, the disorder is suspected to be inherited as an autosomal recessive trait, with incomplete penetrance. Clinical signs of dysfunction often plateau between 6 and 8 mos in these animals and then gradually dissipate. The tremoring resolves in many such cases at approximately 1 yr of age.

In general, patients with hypomyelination/dysmyelination will often have a resting or intentional tremor that worsens with excitement and exercise and resolves with sleep, a "rocking horse" stance, and a bunny-hopping gait when ambulating (in those dogs able to do so). Histologically, the abnormalities appear to have a somewhat consistent involvement of the ventral and lateral columns of the spinal cord white matter. In some cases, there are normal numbers of oligodendrocytes, and in others there are altered ratios of oligodendrocytes and astrocytes. The astrocytosis may be a reaction to the degeneration of oligodendrocytes or the functional cause of the myelin abnormality. Numerous hypotheses have been postulated as to the cause of the disorder. These hypotheses include abnormal stem cell migration, abnormal glial cell differentiation, defects in oligodendrocyte metabolism, and alterations in the genetic code (mutations) responsible for proteins required for normal oligodendrocyte or myelin function. The etiology is likely different for each separate clinical syndrome. Most current research focuses on specific proteins necessary for the normal architectural stability of myelin and terminal differentiation of oligodendrocytes. It is important to remember when presented with an animal that is suspected of a congenital tremor syndrome that numerous etiologies may account for the disorder. These include infectious/inflammatory agents, inherent abnormalities of metabolism, or genetic mutation. Animals affected with congenital hypomyelination or dysmyelination may improve with age and lead acceptable lives.

Central axonopathy of Scottish Terriers

A tremor syndrome has been described in three Scottish Terrier puppies. The etiology of this disorder is unknown. Axonal loss was evident throughout the CNS upon histopathological examination. The affected dogs developed severe generalized tremors and ataxia at 10–12 wks of age. Two of the three dogs were paraparetic. The clinical signs worsened with exercise and excitement and abated with rest or sleep. The disorder is felt to be progressive and is associated with a poor prognosis.

Corticosteroid responsive tremor syndrome (Video 22)

Corticosteroid responsive tremor syndrome (CRTS) is a well-recognized, fairly common disorder. Although white dogs (e.g. Maltese, West Highland White Terrier) appear to be overrepresented, the term "white shaker dog" syndrome is misleading. Approximately one-half of dogs with CRTS do not have white coat coloring. Most dogs affected with this generalized tremor syndrome are young (less than 5 yrs old), and most weigh less than 15 kg. The prevailing clinical sign of dysfunction in CRTS is a fine, whole-body tremor; other reported signs of neurologic dysfunction include decreased menace responses, head tilt, nystagmus, paraparesis, tetraparesis, ataxia, and seizure activity. Dogs with CRTS occasionally have slightly elevated rectal temperatures. The tremors are rarely incapacitating and nearly all affected dogs respond to immunosuppressive dosages of corticosteroids. In one report, 80% of affected dogs responded to immunosuppressive corticosteroid therapy within 3 days. The condition can be separated from other inflammatory causes on the basis of CSF examination. This syndrome is characterized by a minimal to moderate nonsuppurative (i.e. lymphocytic) pleocytosis, in contrast to the polymorphonuclear pleocytosis associated with mycotic and bacterial infections and the mixed-cell pleocytosis typical of GME and protozoal diseases. CSF white blood cell counts are often normal (sometimes with abnormal distribution of cell types) or mildly elevated (typically mononuclear pleocytosis). Histologically, mild perivascular cuffing and lymphocytic infiltrates throughout the CNS (i.e. mild, diffuse meningoencephalomyelitis), especially in the cerebellum, characterize CRTS. It is thought that CRTS may represent an autoimmune disorder.

Prognosis for treatment of this disease with immunosuppressive doses of corticosteroids is excellent. Dosages of prednisone may range from 1 to 2 mg/kg body weight, every 12 hrs. Once clinical signs have resolved, the corticosteroid therapy should be gradually discontinued over a 1- to 3-mo period. Occasionally, dogs may need to be kept on low doses or alternate-day therapy to control the tremors. Some dogs with CRTS benefit from adjunctive oral diazepam therapy (0.2 mg/kg body weight, q 8 hrs).

Tremorgenic toxins and drugs

Numerous toxins are known to either influence cerebellar function resulting in tremors or produce tremors as one of the clinical manifestations of the toxic exposure. Mechanisms of toxin exposure include accidental ingestion, dermal contact, and iatrogenic administration (medications). The mechanisms for the generation of tremors secondary to toxin exposure are not all known. Hexachlorophene, a germicide present in disinfectant solutions, soaps, and shampoos, may produce spongy degeneration of the white matter in the brain, spinal cord, and cerebellum. The ingestion of moldy food containing the mycotoxins penitrem A and roquefortine, produced by *Penicillium* spp., may cause clinical signs of ataxia, tremors, and far-off gaze (staring), possibly due to hallucinations. Organophosphates and pyrethrins/pyrethroids (flea collars, dips), metaldehyde (slug and snail poison), lead, chlorinated hydrocarbons, and bromethalin are common causes of tremors in dogs and cats. Less common are 5-fluorouracil (chemotherapeutic), macadamia nut ingestion, theobromine (chocolate), and strychnine. A single case of Kentucky coffee tree seed ingestion has been implicated in causing cerebellovestibular signs, including intention tremor in a dog. Many of these toxicants will have other concurrent neurologic signs such as seizures and ataxia. Drugs that block dopamine receptors or inhibit the action of dopamine—such as phenothiazines, neuroleptics (haloperidol, droperidol), serotonin agonists (trazodone, fluoxetine), and metoclopramide—may also cause tremors. Treatment may be specific for the underlying cause or generalized decontamination. Prognosis is variable. More information regarding these toxicities can be found in Chapter 23.

Essential tremors

There are a number of enigmatic tremor syndromes described in dogs that are associated with maintaining the tremoring body part(s) against gravity. These disorders can be confusing because they are all of unknown and probably disparate etiologies, and each disorder has multiple terms to describe it. One thing that all of these disorders have in common is their relatively innocuous nature.

Orthostatic tremor (OT), also called *primary orthostatic tremor* and *orthostatic postural myoclonus tremor*, has been described in young (1–2 yrs old at onset) adult giant-breed dogs, including Great Danes, Mastiffs, and one Scottish Deerhound. These dogs exhibited tremors of all four limbs while standing, which appeared as a constant "quivering" or "shivering" of the limbs. On close inspection of limb muscles, fine rippling of the musculature was apparent while the dogs were standing. Less commonly, facial and head musculature has also been reported to exhibit tremor activity. Dogs with OT tend to shift weight from limb to limb and have difficulty lying down from a standing position. The tremors disappear when affected dogs are recumbent, while walking or running, when leaning against objects, or when picked up (to remove all weight support). When a dog with OT is in lateral recumbency, if an examiner pushes against a paw (causing isometric limb muscle contraction), the tremor can be induced. These dogs do not demonstrate fatigue with exercise, and no deficits are apparent on neurologic examination. Blood work (including lactate, pyruvate, creatinine kinase, acetylcholine receptor antibody concentration), brain MR imaging, CSF examination, motor and sensory nerve conduction studies, repetitive nerve stimulation, electroencephalography (EEG), electromyography (EMG) under anesthesia (with a concentric needle electrode), and nerve/muscle biopsies have all been normal in the dogs in which these tests were performed. During auscultation with a stethoscope over an affected muscle during weight bearing, a characteristic low-pitched repetitive noise (tremor) is heard, which sounds like a distant helicopter. Surface EMG recordings taken while these dogs were fully awake and standing demonstrated a characteristic continuous muscle discharge with a frequency of 13–16 Hz, which occurs concomitantly with the visible tremors during the recordings. The clinical characteristics of canine OT fit very well with those of human OT, which was briefly discussed earlier in this chapter. This disorder appears to be very slowly progressive in dogs and tends to respond to oral phenobarbital therapy. Other suggested treatments for people with OT include gabapentin and clonazepam. Clonazepam is actually the preferred drug choice for people, but it is probably ill advised for canine use, due to the rapid development of drug tolerance to this drug in dogs.

Older dogs, especially terrier breeds, occasionally develop a rapid tremor of the pelvic limbs (while standing) of unknown etiology. This is a benign condition overall, but may progress slowly as the dog ages. The tremor may also worsen during excitement and following exercise and tends to disappear as the dog ambulates and during recumbency. Though the pathophysiology of this disorder is unknown, it may involve an age-related dysfunction of the stretch mechanism. Other terms for this condition include essential tremor, senile tremor, and benign postural myoclonus tremor. No treatment is recommended for this tremor syndrome.

Episodic head tremor syndrome

Repetitive, intermittent head bobbing (vertical or horizontal) is a poorly understood movement disorder which is often encountered in dogs, particularly young adult Boxer dogs, English and French Bulldogs, and Doberman Pinschers. This is also a benign condition for which the underlying mechanism remains elusive. Among the possibilities for causes of this disorder is a potentially heritable disorder of the stretch mechanism affecting the neck musculature similar to that described for essential tremor. However, this tremor syndrome differs from essential tremor in that it is paroxysmal (characterized by short, frequent, stereotypic symptoms). As with other postural tremors, the tremors tend to subside if the head is supported (i.e. not supported by neck muscles). However, they may also be present (although often attenuated) when the patient's head is supported (such as on a pillow while lying down). The tremors also tend to stop if the dog is distracted (e.g. calling patient's name, offering a toy or food). Neurologic examination is characteristically normal, as are diagnostic tests (including brain imaging and CSF examination). This is typically a nonprogressive disorder and does not adversely affect quality of life in affected dogs. Other terms for this condition include head-bobber and postural repetitive myoclonus. Within the Doberman Pinscher breed, age of onset is typically less than 1–2 yrs and all cases were traced back to one common sire, suggesting a genetic origin. This disorder is also discussed in Chapters 9 and 10.

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Video Resources

Video resources are available on the companion website: www.wiley.com/go/dewey/neurology

See videos 9, 21 and 22.

CHAPTER 13

Myelopathies: Disorders of the Spinal Cord

Curtis W. Dewey & Ronaldo C. da Costa

Clinical signs of spinal cord dysfunction[73, 78, 78, 146]

The clinical signs associated with spinal cord dysfunction depend upon the location, size, and rate of development of the lesion. A small lesion on one side of the spinal cord without a great deal of associated cord swelling (e.g. a slowly growing tumor) will likely cause signs predominantly on the side of the lesion. However, a large lesion or a lesion associated with substantial cord swelling (e.g. an acute disc herniation in the thoracolumbar region) will likely result in bilateral signs of dysfunction. In most spinal cord disorders, bilateral deficits will be observed, but the deficits are often more pronounced on the side of the lesion. Proprioceptive and nociceptive information traveling toward the brain, as well as voluntary motor impulses traveling from the brain, can be affected by spinal cord-disease. With progressive spinal cord disease, proprioception is usually the first deficit observed (proprioceptive ataxia and/or proprioceptive deficits), followed by deficits in voluntary motor ability (paresis), and finally deficits in the ability to perceive painful stimuli (nociception).

The clinical signs listed below for each of the anatomic subdivisions of the spinal cord represent all of the possible abnormalities that may be encountered with lesions in these respective areas. The clinician may, for example, encounter cases of cervical myelopathy in which severe neck pain is the only clinically detectable abnormality. Alternatively, cases may be encountered with more extensive lesions in the same anatomic location in which the patient is tetraplegic with minimal pain perception to the limbs, and having respiratory difficulty. There is a spectrum of possible clinical presentations between these two extreme examples. A topic that is sometimes confusing to clinicians is that of upper motor neuron (UMN) fecal incontinence. Although it is apparently less common than with cauda equina lesions (see Chapter 14), fecal incontinence may result from cervical or thoracolumbar spinal cord lesions (particularly dorsal lesions, commonly of a cystic nature). This may be due to interruption of ascending information from the rectum to brain-stem and cerebral centers responsible for a normal, coordinated defecation reflex; interruption of descending inhibitory influence from such centers on the local spinal cord sacral defecation reflex; or a combination of both. Since fecal incontinence in these cases does not directly involve the lower motor neurons (LMNs), innervating the anal sphincter musculature or the sensory neurons or nerves innervating the perineum, perineal sensation (in patients with intact pain sensation), as well as anal sphincter tone and perineal reflexes (e.g. anal reflex) are typically normal. The clinical information regarding UMN fecal incontinence in veterinary patients is limited, but it suggests that it may be more responsive to surgical intervention than LMN fecal incontinence. In this text, the cauda equina is defined as the nerve roots derived from the cord segments L7 and caudally. Damage to the spinal cord segments supplying the cauda equina will produce the same clinical signs of dysfunction as disruption of the respective nerve roots, although as nerve roots are more resilient, the signs are less severe. Disorders of the cauda equina are discussed in more detail in Chapter 14. Nursing care, physical therapy, and complications associated with spinal cord disease are discussed in Chapter 20. Neuronopathies, although technically disorders of the spinal cord, appear clinically as neuropathies; these disorders are discussed in Chapter 17. Tetanus is also technically a spinal cord disorder. Because the sustained muscle rigidity characteristic of tetanus more closely resembles a myopathy than a myelopathy, it is discussed in Chapter 18. Finally, the important subject of spinal trauma will not be covered in this chapter; rather, there is a separate chapter (Chapter 15) devoted to the subject of spinal trauma in dogs and cats. Before reviewing the clinical signs associated with lesions in each spinal cord segment, it is important to realize that there is a mismatch between spinal cord and vertebral segments, primarily for the cervical and lumbosacral regions (Fig. 13.1). The signs below refer specifically to spinal cord segments.

A. C1–C5 spinal cord segments
   1. Cervical pain (hyperesthesia).
   2. Proprioceptive deficits ipsilateral to the lesion (thoracic limb and pelvic limb) or all four limbs.

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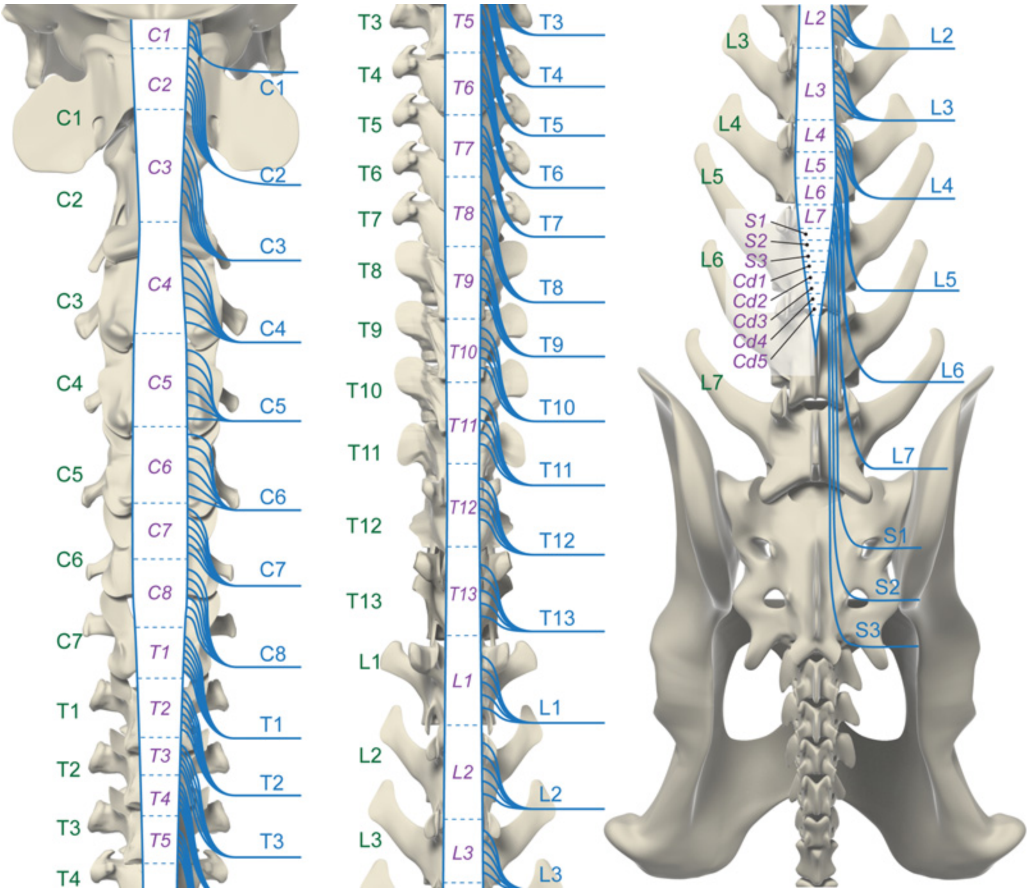


Figure 13.1 Anatomic relationships between spinal cord and vertebral segments. Note the differences in the spinal cord and vertebral level in the cervical and lumbosacral regions. (The Ohio State University. Reproduced with permission.)

3. Voluntary motor deficits ipsilateral to the lesion (thoracic limb and pelvic limb) or all four limbs, varying from paresis to plegia. The paresis or plegia (hemiparesis, hemiplegia, tetraparesis, tetraplegia) is UMN in nature, with normal to hyperactive tone and reflex activity in all limbs.
4. Horner's syndrome ipsilateral to the lesion or bilaterally.
5. Respiratory difficulty (severe lesions) involving both chest excursions and diaphragmatic movements.
6. UMN bladder dysfunction (see Chapter 16).
7. UMN fecal incontinence is possible.
8. Nociceptive (pain perception) deficits are possible in all four limbs.

B. C6–T2 spinal cord segments
   1. Cervical pain (hyperesthesia).
   2. Proprioceptive deficits ipsilateral to the lesion (thoracic limb and pelvic limb) or all four limbs.
   3. Voluntary motor deficits ipsilateral to the lesion (thoracic limb and pelvic limb) or all four limbs, varying from paresis to plegia. The paresis or plegia is classically LMN in nature in the thoracic limbs (involvement of the gray matter of C6–T2 or the efferent axonal processes from that gray matter) and UMN in nature in the pelvic limbs. In some instances (e.g. caudal CSM), caudal cervical lesions may result in obvious signs of UMN paraparesis, with subtle or very mild thoracic limb deficits.
   4. Horner's syndrome ipsilateral to the lesion or bilaterally.
   5. Decreased or absent cutaneous trunci (panniculus) reflex ipsilateral to the lesion or bilaterally. The deficit is due to impairment of the efferent arm of the reflex arc.
   6. Respiratory difficulty with severe lesions. The respiratory pattern often differs from that seen with C1–C5 spinal cord lesions. Since the phrenic nerve arises from spinal cord segments C5–C7, there is usually enough phrenic nerve function to provide diaphragmatic movement, but impulses from the medullary respiratory centers can't effectively traverse the damaged cord segments to stimulate the cell bodies of the intercostal nerves. This is the reason for the "abdominal breathing" pattern seen with severe caudal cervical myelopathies. The thoracic cage moves minimally, if at all, and the exaggerated activity of the diaphragm causes the abdominal contents to move passively.
   7. UMN bladder dysfunction (see Chapter 16).

    8. UMN fecal incontinence is possible.
    9. Nociceptive deficits are possible in all four limbs.

C. T3–L3 spinal cord segments
    1. Thoracolumbar pain (hyperesthesia).
    2. Proprioceptive deficits in the pelvic limb ipsilateral to the lesion or both pelvic limbs.
    3. Voluntary motor deficits in the pelvic limb ipsilateral to the lesion or both pelvic limbs. The paresis or plegia (monoparesis, monoplegia, paraparesis, paraplegia) is UMN in nature, with normal to hyperactive tone and reflex activity in the pelvic limbs.
    4. The thoracic limbs are neurologically normal (normal proprioception, normal voluntary motor activity). Schiff–Sherrington posture may be seen in the thoracic limbs (see Chapter 2) and should not be confused with a cervical spinal cord problem. Schiff–Sherrington posture is an anatomic phenomenon, not a prognostic indicator. Depending on the nature of the injury, spinal shock is also a possibility (see Chapter 3).
    5. Horner’s syndrome is possible with very cranial lesions (T3 spinal cord level), but less likely in comparison with cervical lesions.
    6. Decreased or absent cutaneous trunci (panniculus) reflex, approximately one to four vertebral levels caudal to the spinal cord lesion. The deficit is due to impairment of the afferent arm of the reflex arc.
    7. UMN bladder dysfunction (see Chapter 16).
    8. UMN fecal incontinence is possible.
    9. Nociceptive deficits are possible in both pelvic limbs.

D. L4–L6 spinal cord segments
    1. Lumbar pain (hyperesthesia).
    2. Proprioceptive deficits in the pelvic limb are ipsilateral to the lesion or in both pelvic limbs.
    3. Voluntary motor deficits in the pelvic limb ipsilateral to the lesion or both pelvic limbs. The paresis or plegia (monoparesis, monoplegia, paraparesis, paraplegia) is LMN in nature, with a decreased to absent patellar reflex ipsilateral to the lesion or bilaterally. The withdrawal and gastrocnemius reflexes may be normal or decreased, depending on the extent of damage to the L6 spinal segment (L6 contributes to the sciatic nerve).
    4. A decreased or absent cutaneous trunci (panniculus) reflex may or may not be appreciable one to four vertebral levels caudal to the lesion, because the last three or four lumbar spinal nerves do not give off dorsal cutaneous branches.
    5. UMN bladder dysfunction (see Chapter 16).
    6. UMN fecal incontinence is possible.
    7. Nociceptive deficits are possible in both pelvic limbs.

E. L7–S3 and caudal (coccygeal) spinal cord segments
    1. These spinal cord segments give rise to the spinal nerve roots that comprise the cauda equina. Chapter 14 details the clinical signs associated with diseases of the cauda equina.

Disorders affecting the spinal cord in dogs and cats (Table 13.1)

A. Degenerative
    1. Degenerative disc disease[7, 9, 11, 13, 14, 20–22, 27, 28, 30, 33, 36, 37, 41, 45, 46, 50, 51, 56–58, 62, 63, 67, 71, 73, 75, 79, 87, 89, 97, 104, 123, 124, 127, 128, 147, 148, 153, 157, 165, 167, 169, 170, 177, 178, 180, 181, 183, 184, 186, 187, 191, 192, 199, 203, 204, 206, 210, 211, 216, 217, 225, 226, 228, 229, 236, 237, 240, 243, 245, 248, 249, 260, 261, 265, 268, 270, 271, 274–277, 283, 285, 290–293, 296, 304, 309, 311–313, 319, 322, 326, 327, 329, 334, 341, 343, 346, 347, 359, 360, 368, 370, 373, 377, 380, 381, 388, 398–401, 405, 406, 414, 421, 437, 440, 447, 452, 453, 462, 465, 466, 472, 473, 483, 485, 486, 489, 493–497, 499, 509–511, 521–523, 525, 544, 552, 553]
        a. Degenerative disc disease is the most common spinal problem in dogs, but a relatively infrequent clinical disorder in cats. The anatomy associated with both normal and extruded intervertebral discs are illustrated in Fig. 13.2 and Fig. 13.3. There are two basic types of disc degeneration, referred to as chondroid and fibroid degeneration. These two types of degeneration typically cause two distinct types of disc disease. In chondroid degeneration, the normally gelatinous

Table 13.1 Myelopathies of dogs and cats.

Degenerative	Degenerative disc disease
	Cervical spondylomyelopathy
	Degenerative myelopathy (DM)
	Extradural synovial cysts
	Vertebral articular process (facet) hypertrophy
	Rottweiler leukoencephalomyelopathy
	Leukodystrophies
	Hereditary ataxia
	Labrador Retriever axonopathy
	Lysosomal storage disease
Anomalous/ Developmental	Congenital vertebral malformations
	Stenotic vertebral canal
	Cartilaginous exostoses
	Meningoceles/myelomeningoceles
	Spinal dysraphism
	Syringomyelia (hydromyelia)
	Dermoid sinus
	Spinal arachnoid diverticulum
Neoplastic	Extradural tumors
	Intradural/extramedullary tumors
	Intramedullary tumors
Nutritional	Feline hypervitaminosis A
	Methionine deficiency-related spinal myelinopathy
Inflammatory/ Infectious	Discospondylitis
	Meningitis/meningomyelitis
Ischemic/Vascular	Fibrocartilaginous embolic myelopathy (FCEM)
	Traumatic feline ischemic myelopathy
Traumatic*	Vertebral fracture and luxation
	Traumatic intervertebral disc herniation
Miscellaneous	Tumoral calcinosis
	Dural ossification
	Spondylosis deformans
	Disseminated idiopathic skeletal hyperostosis (DISH)

*See Chapter 15.

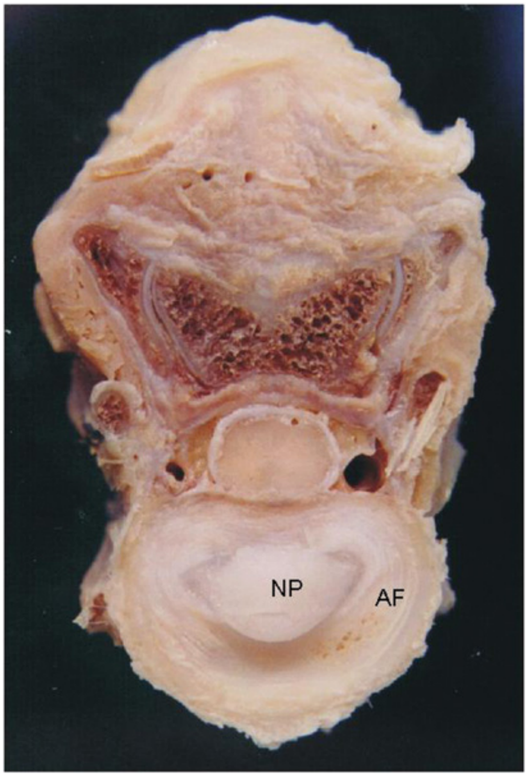


Figure 13.2 Transverse section between the first and second lumbar vertebrae demonstrating the normal anatomy in a dog. Note the location of the annulus fibrosus (AF) and nucleus pulposus (NP) in relation to the spinal cord.

nucleus pulposus (NP) loses water-binding capacity, undergoes degradation of the glycosaminoglycan components, and often becomes calcified (Fig. 13.4). The dorsal annulus often weakens, and the abnormal NP contents extrude through the weakened annulus into the vertebral canal. This type of disc disease is called Hansen type I, or simply type I, disc extrusion (Fig. 13.5). The severity of spinal cord damage caused by type I disc extrusion is believed to be related to the rate of extrusion (force of impact or concussion), duration of compression, and amount of disc material extruded. Fibroid degeneration involves a progressive thickening of the dorsal annulus fibrosus, which protrudes dorsally into the vertebral canal. This type of disc disease is called Hansen type II, or simply type II, disc protrusion (Fig. 13.6). A third type of disc herniation, called type III, or explosive disc herniation, has been identified in recent years. This is a low-volume/high-velocity form of herniation that is typically noncompressive in nature. In extreme cases, the herniated material can penetrate the spinal cord. This "type III" herniation appears to occur most commonly in older chondrodystrophic breeds, but can be seen in any dog.

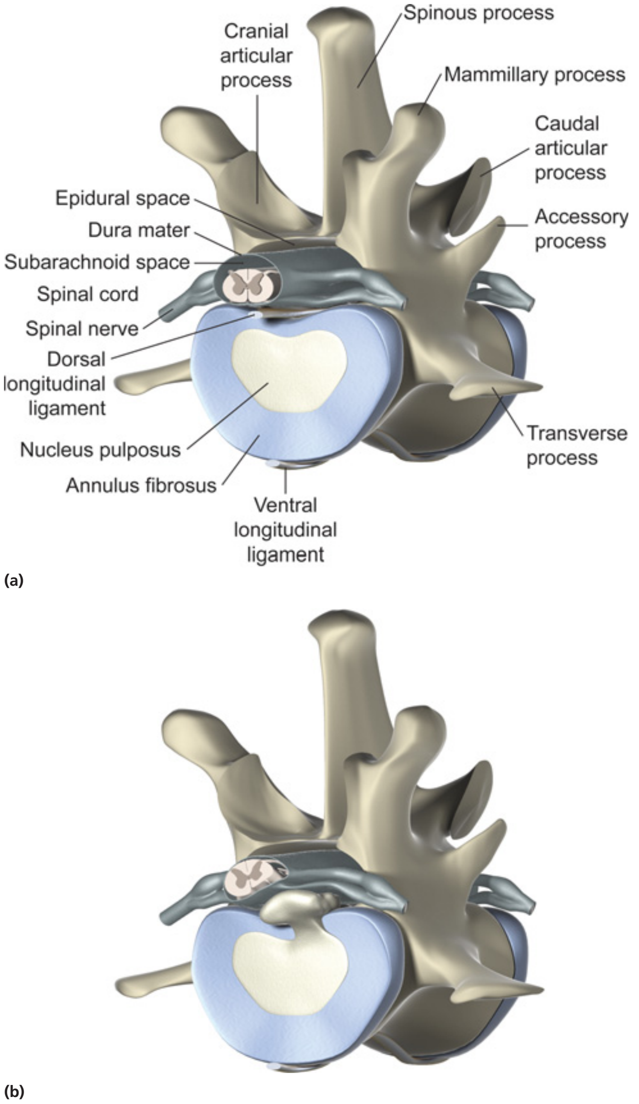

Spinous process
Cranial articular process
Mammillary process
Caudal articular process
Epidural space
Dura mater
Subarachnoid space
Spinal cord
Spinal nerve
Dorsal longitudinal ligament
Nucleus pulposus
Annulus fibrosus
Accessory process
Transverse process
Ventral longitudinal ligament
(a)
(b)

Figure 13.3 Anatomic structures associated with a normal (A) and extruded (B) thoracolumbar disc. (The Ohio State University. Reproduced with permission.)

b. Clinical features of both types of disc disease are listed below (Videos 11, 12, 23, 24):
   1. Hansen type I extrusions typically occur in small-breed dogs, particularly the chondrodystrophic breeds (Dachshund, Beagle, Basset Hound, Shih Tzu, Pekingese, Lhasa Apso, etc.). The Dachshund is by far the most commonly affected breed. Within the Dachshund breed, certain physical characteristics (e.g. short T1–S1 and TC–PT [tuber calcaneus to mid-patellar tendon] distances) have been correlated with an increased likelihood of disc extrusion. Another study found that Dachshunds that had longer backs and were skeletally smaller and overweight had a higher risk of intervertebral disc extrusion. Hansen type II disc protrusions

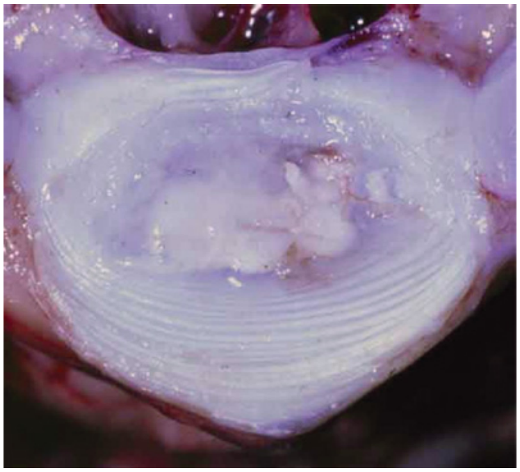


Figure 13.4 Transverse section through a degenerate IVD from a chondrodystrophic dog. Note that the gelatinous nucleus pulposus has been replaced by mineralized and chondroid material. (Brisson, 2010.[56] Reproduced with permission from Elsevier.)

typically occur in nonchondrodystrophic, larger-breed dogs. Either type of disc disease can occur in any breed of dog, however, and both types have been reported in cats. In one report of thoracolumbar disc disease in large (more than 15 kg) nonchondrodystrophic dogs, 92% of the cases were found to have type I disc extrusions. Large-dog breeds that seem to be most commonly encountered with type I disc extrusions include mixed-breeds, German Shepherd dogs, Labrador Retrievers, Doberman Pinschers, and Rottweilers.

2. Hansen type I extrusions typically occur in dogs older than 2 yrs of age. In chondrodystrophic dogs, such as the Dachshund, it peaks at between 3 and 6 yrs of age. A recent study showed that French Bulldogs have extrusions at an earlier age, peaking at 2–4 yrs of age, with 6% of dogs having disc extrusion at 1 yr of age. Naturally occurring extrusions do not occur in dogs younger than 1 yr of age on any breed. In one study, the mean age of cats with thoracolumbar type I disc extrusions was 9.8 yrs; no breed or sex predilection was found in that study. Hansen type II protrusions typically occur in dogs 5 yrs of age and older.
3. Hansen type I disc extrusion usually causes rapidly developing clinical signs (minutes/days), whereas Hansen type II disc protrusions typically cause chronically developing clinical signs (weeks to months, sometimes years).
4. Both types of disc disease may affect cervical, caudal thoracic, and lumbar discs. In small-breed dogs, type I cervical disc disease usually affects cranial cervical discs (C2–C3 most commonly), and typically causes severe neck pain, usually with inapparent or mild neurologic deficits. In large nonchondrodystrophic dogs, the most common site for type I cervical disc extrusions is at the C6–C7 intervertebral disc space; these dogs also tend to present with acute onset of severe neck pain. The patient often adopts a guarded neck posture (nose down) with a kyphotic posture (arched back) that should not be confused with thoracolumbar pain (Fig. 13.7). When turning, these dogs tend to move the head and the neck as one unit, rather than bending at the neck. Fasciculations of the neck musculature can often be appreciated, especially upon palpation of the neck. Occasionally, these dogs will scream in apparent pain and fall over. This may be mistaken for seizure activity by the

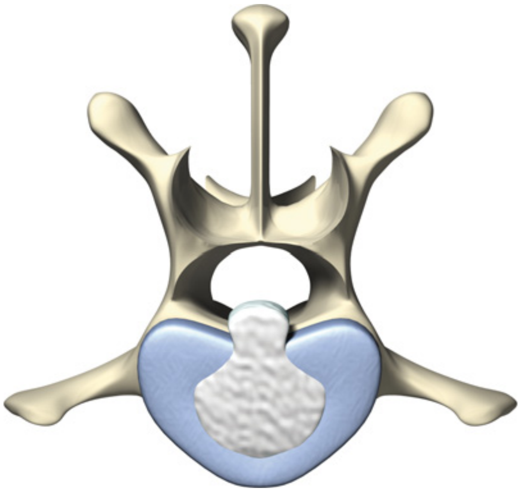


Figure 13.5 Representation of intervertebral disc extrusion. (The Ohio State University. Reproduced with permission.)

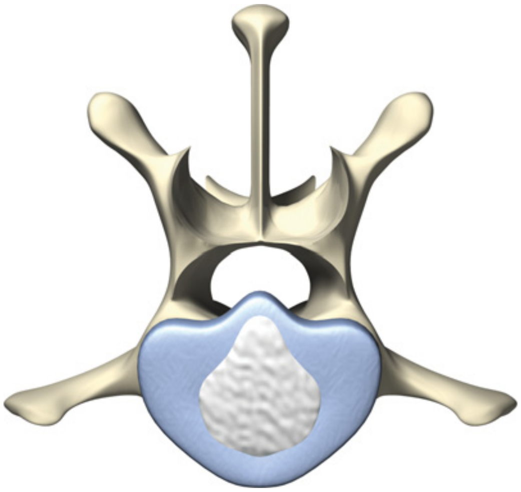


Figure 13.6 Representation of intervertebral disc protrusion. (The Ohio State University. Reproduced with permission.)

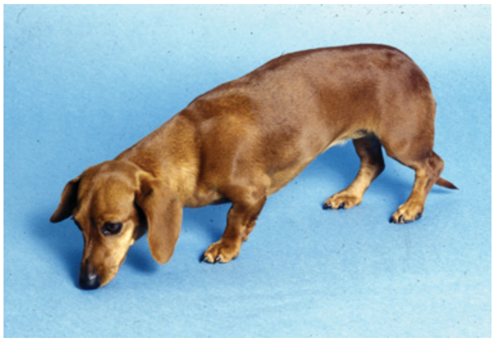


Figure 13.7 Typical posture of a dog with a type I cervical disc extrusion. (J. Coates, University of Missouri, Columbia, MO, 2014. Reproduced with permission of J. Coates.)

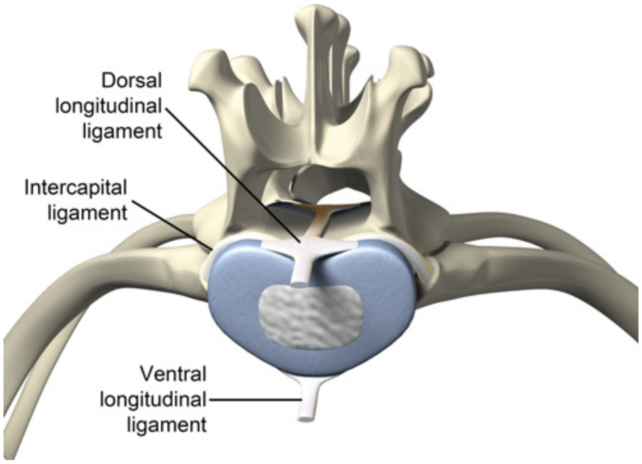


Figure 13.8 Illustration of the main ligaments in the thoracic region. The intercapital ligament offers additional support and minimizes the risk of disc extrusion in the thoracic region. (The Ohio State University. Reproduced with permission.)

owner. Lameness of one thoracic limb, referred to as "root signature," is exhibited sometimes, and is thought to be caused by irritation of cervical nerve roots by laterally extruded disc material. Pelvic limb root signature is less commonly encountered. In many cases of root signature, the abnormal limb will be held in a flexed position and caudal extension of that limb elicits a painful response (presumably due to stretching of irritated nerve roots).

Type II cervical disc disease may result in clinically appreciable neck pain, but rarely to the degree encountered in type I cervical disc disease. Type II cervical disc disease usually causes slowly progressive paresis. This can occur as an isolated process, or as a component of cervical spondylomyelopathy (CSM) (discussed later in this chapter).

5. Disc disease in the thoracolumbar region is more frequently encountered than cervical disc disease. Disc problems cranial to the T10–T11 disc space are uncommon, probably due to the stabilizing influence of the intercapital ligament (Fig. 13.8). This ligament passes over the dorsal annulus from rib head to rib head in all but the first and last two pairs of ribs. An exception to this would be German Shepherds, with two recent studies showing that they are predisposed to cranial thoracic disc herniations (Fig. 13.9). Type I disc extrusions usually occur between vertebral levels T11 and L3. The T12–T13 and T13–L1 discs are the most common sites for type I disc extrusions to occur in small-breed dogs. In larger dogs, the L1–L2 and L2–L3 disc spaces are the most common sites for type I extrusions. The L4–L5 intervertebral disc space appears to be the most common site for thoracolumbar disc extrusion in cats.

While patients with signs of back pain with minimal to no neurologic deficits are occasionally

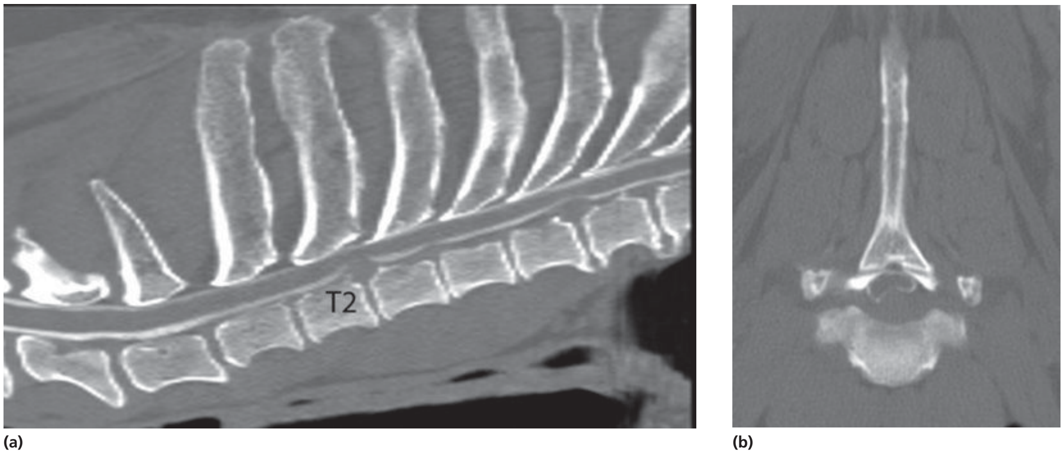


Figure 13.9 (A) Sagittal CT myelography of a dog demonstrating thoracic disc herniations at T2–T3 and T5–T6. (B) Transverse section between T2–T3 demonstrating spinal cord compression.

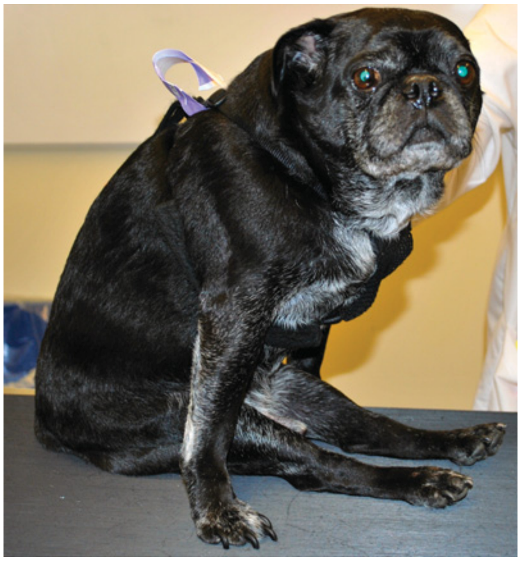


Figure 13.10 Typical posture of a dog with a severe type I thoracolumbar disc extrusion.

encountered, type I thoracolumbar disc extrusions more typically result in acute paraparesis or paraplegia (Fig. 13.10). This may be due to the limited epidural space in the thoracolumbar vertebral canal, as compared to the cervical region. These patients often exhibit back pain in the general area of the disc extrusion. Type II thoracolumbar disc protrusions typically cause progressive signs of paraparesis, often with some degree of back pain. Protrusion of the L7–S1 disc is often a component of degenerative lumbosacral stenosis and is discussed separately in Chapter 14.

c. Diagnosis of disc disease is based upon signalment, history, clinical signs, and results of diagnostic tests such as cerebrospinal fluid (CSF) analysis, and imaging of the spine. Traditionally, spinal imaging for pets with suspected disc disease consisted of plain radiographs followed by myelography, both performed under general anesthesia. Survey radiographs may reveal changes suggestive of intervertebral disc disease (Fig. 13.11). Myelography is useful to confirm the location of disc extrusion or protrusion (Fig. 13.12).

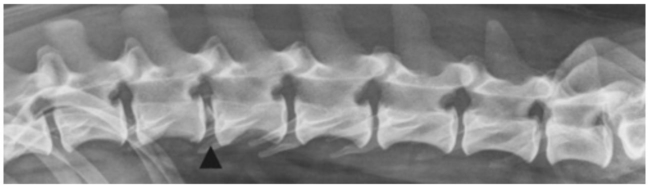
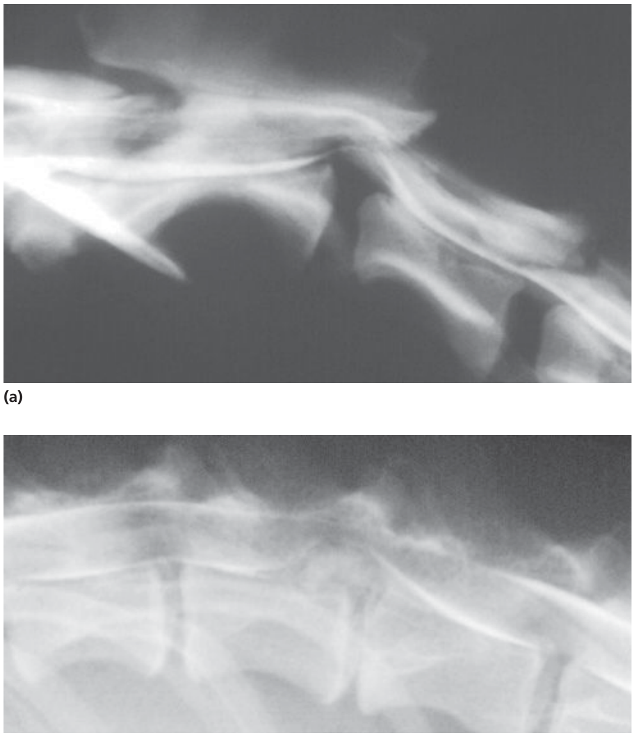


Figure 13.11 Survey radiograph of the thoracolumbar vertebral column demonstrating intervertebral disc calcification at L2–L3 (arrowhead).

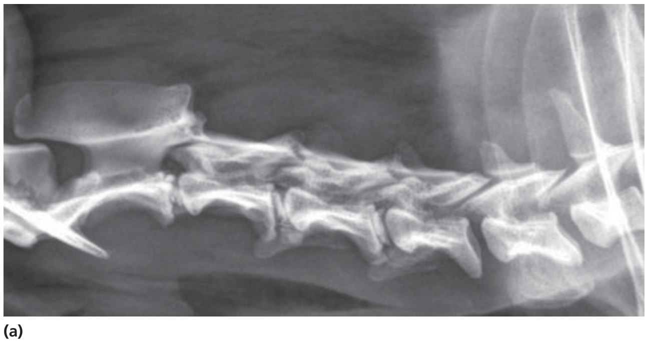


(a)

(b)

Figure 13.12 Lateral myelographic views of an extruded cervical disc (A) and an extruded thoracolumbar disc (B).

Currently computed tomography (CT) and magnetic resonance imaging (MRI) are superior imaging modalities in the diagnosis of intervertebral disc disease. CT has the advantage of being a very fast imaging modality that can diagnose disc disease without myelography in many chondrodystrophic dogs (Fig. 13.13 and Fig. 13.14). In cases where no lesion is found on plain CT, CT myelography is necessary to diagnose the compressive lesion (Fig. 13.15). MRI is rapidly becoming a standard imaging modality for dogs and cats with suspected intervertebral disc disease. In addition to providing superior anatomic detail in disc disease patients compared with myelography and CT, MR imaging is the best modality for diagnosing other spinal disorders that may have similar clinical presentations as intervertebral disc disease and is associated with fewer side effects than myelography. Normally, the NP has high signal intensity on T2-weighted (T2-W) images (the annulus is hypointense). The NP of a degenerative disc is hypointense and the distinction between the nucleus and annulus fibrosus may be lost. Two recent studies comparing MR imaging with myelography or CT showed its superiority. The diagnostic sensitivity of MR imaging was approximately 10% superior to noncontrast CT or myelography in both studies (Fig. 13.16). The decision of what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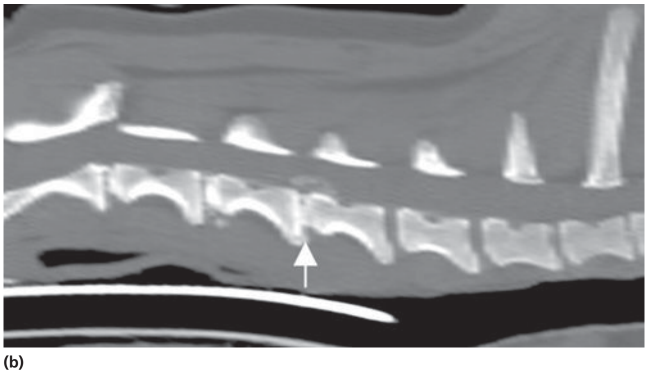
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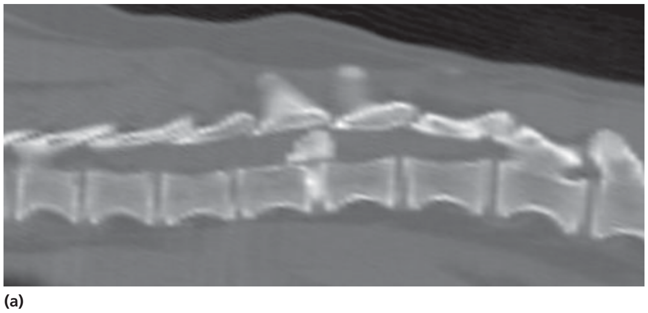
Figure 13.13 Cervical disc disease. (A) Survey radiograph showing calcified disc material between C2–C3, C3–C4, and C4–C5. (B) Noncontrast (plain) CT confirmed disc extrusion at C4–C5 (arrow).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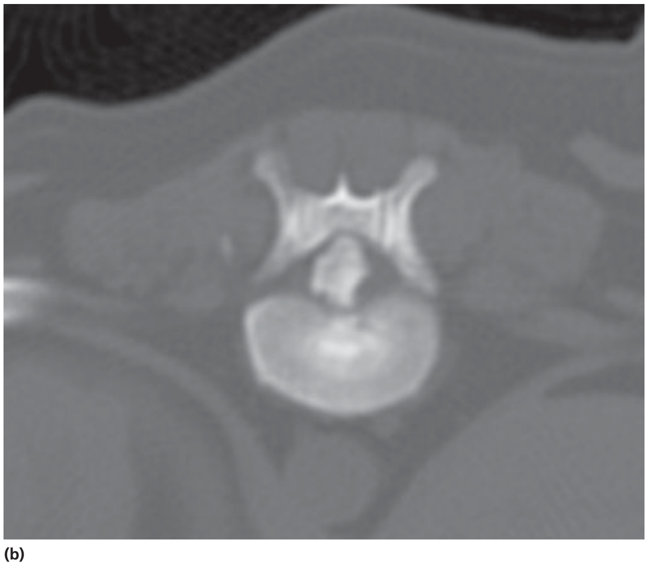
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Figure 13.14 Thoracolumbar disc disease. (A) Sagittal noncontrast CT shows a large amount of mineralized nucleus pulposus within the vertebral canal. (B) Transverse section shows the material occupying most of the vertebral canal causing significant spinal cord compression.

diagnostic tests (if any) to perform for an individual case usually depends on the expected treatment protocol for that patient. For example, a young Dachshund with an acute onset of neck pain and no neurologic deficits is likely to have a type I cervical disc extrusion, and will likely respond to cage confinement with or without anti-inflammatory drugs. In this case, survey radiographs of the cervical vertebral column are the only imaging modality needed. It would be illogical to anesthetize this patient and perform spinal imaging to confirm the most likely diagnosis if surgical therapy is not the treatment protocol of choice at that time.

The typical myelographic (or CT/MR) finding in disc extrusion/protrusion is focal extradural spinal cord compression centered over a disc space. Sometimes, a disc extrusion will lacerate a venous sinus, leading to large extradural accumulations of hemorrhage (in addition to disc material), which can cause extensive cord compression and/or swelling. Occasionally, a type I disc extrusion will be lateral enough that myelographic results are normal. In such lateralized extrusions, hyperesthesia with or without unilateral limb lameness (ipsilateral to the extrusion) is a likelier clinical sign of dysfunction than overt proprioceptive or voluntary motor deficits. CT or MRI may be the only imaging modality capable of diagnosing these conditions (Fig. 13.17). Another important consideration in such a clinical scenario is the presence of syringomyelia, which is usually not evident on myelography (requires MR imaging). In some cases of high-velocity concussive disc-related injury, there can be severe motor deficits (due to a small amount of rapidly extruding disc material) with minimal evidence of extradural compression on imaging studies; in such cases there is typically evidence of spinal cord swelling. This may be difficult to distinguish from a vascular event (see FCEM discussion) if an imaging modality other than MR is used. There are several reports of intramedullary disc extrusions. In this scenario, nuclear material extrudes with enough force to penetrate the meninges and enter the spinal cord. A characteristic MRI feature in such a case is a linear tract extending from the affected disc space into the spinal cord (Fig. 13.18).

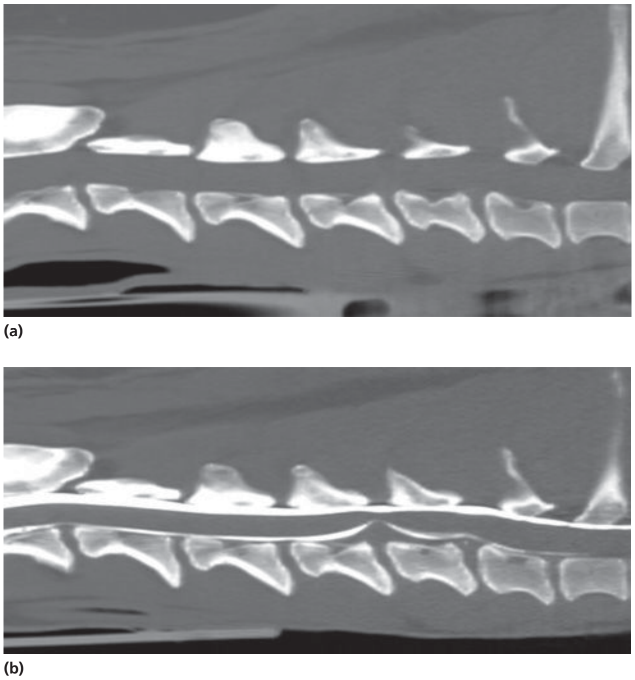


Figure 13.15 (A) Noncontrast CT of a dog with cervical disc disease showing no abnormalities. (B) CT myelography clearly delineates the compressive disc lesion at C5–C6.

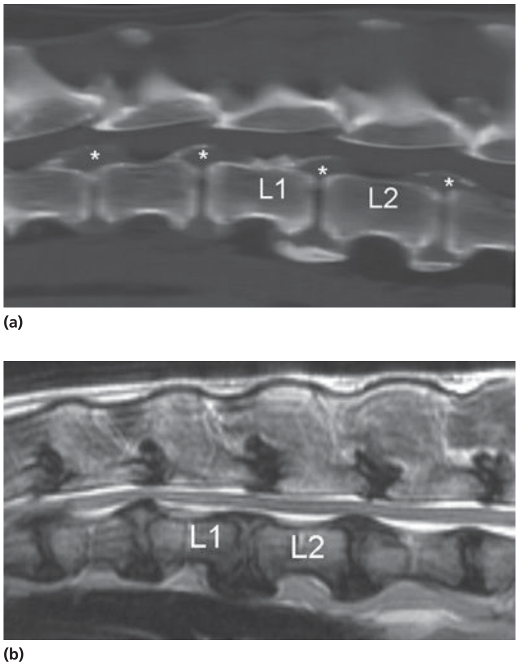


Figure 13.16 (A) Noncontrast sagittal CT of a dog with chronic mineralized disc protrusions in the thoracolumbar region. (B) Sagittal MR image (T2-weighted) of the same region.

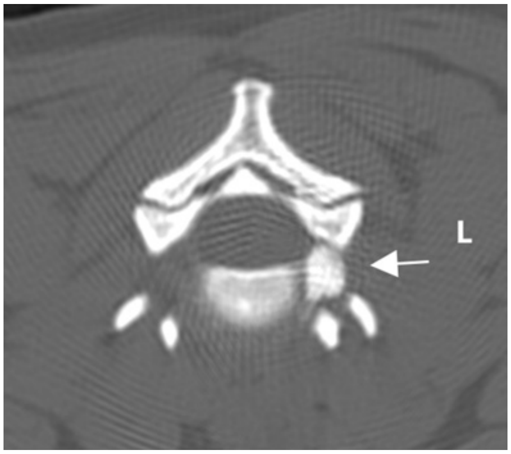


Figure 13.17 Transverse CT image demonstrating lateralized disc material (arrow) causing unilateral nerve root compression.

d. Treatment of acute and chronic disc disease is a subject of considerable debate, but there are a number of established guidelines. The guidelines center around whether to include surgical intervention as part of the patient's therapy. There are positives and negatives

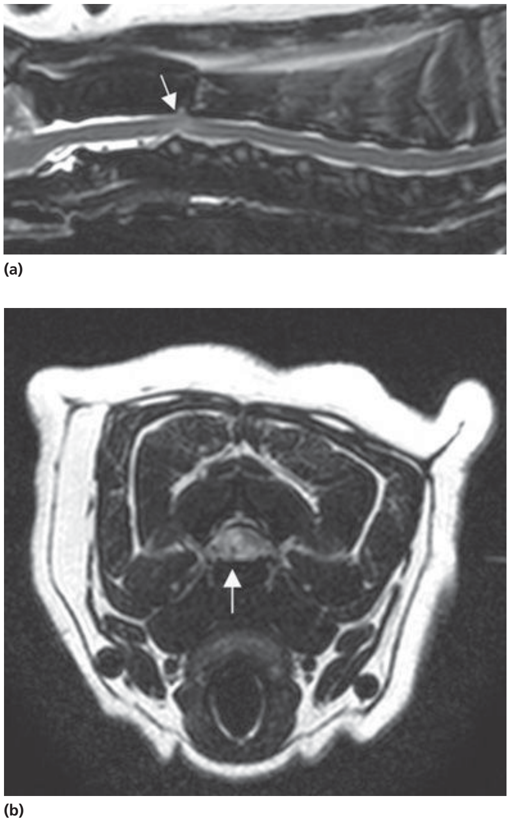


Figure 13.18 Sagittal (A) and transverse (B) MR image (T2-weighted) of a type III disc extrusion. Note the spinal cord hyperintensity in the sagittal images (arrow), and the hypointense disc material (arrow) within the spinal cord in the transverse image.

associated with the surgical and nonsurgical management of disc disease patients, and the clients need to be informed of the benefits and risks associated with either approach.

Patients with suspected type I cervical or thoracolumbar disc extrusions are often successfully treated nonsurgically initially if they exhibit mild to no neurologic deficits (i.e. mainly neck or back pain) and have not had repeated episodes of pain. Medical management traditionally consists of strict cage confinement for 3–4 wks, with or without anti-inflammatory medication and analgesics. The cage or crate should be of such size that the patient can change positions, but cannot walk around or jump. Activity should be restricted to short walks to urinate/defecate, at which times the owner can assess the progress of the patient. If the patient fails to improve or worsens at any time during the confinement period, surgical options should be pursued. If necessary, it is acceptable to administer an anti-inflammatory dose of prednisone in a decreasing regimen, such as the following:

1. 0.5 mg/kg, PO, every 12 hrs for 5–7 days.
2. 0.5 mg/kg, PO, every 12 hrs, every other day, (i.e. skip a day) for the following 5–7 days.
3. 0.5 mg/kg, PO, every 48 hrs, for the final 5–7 days.

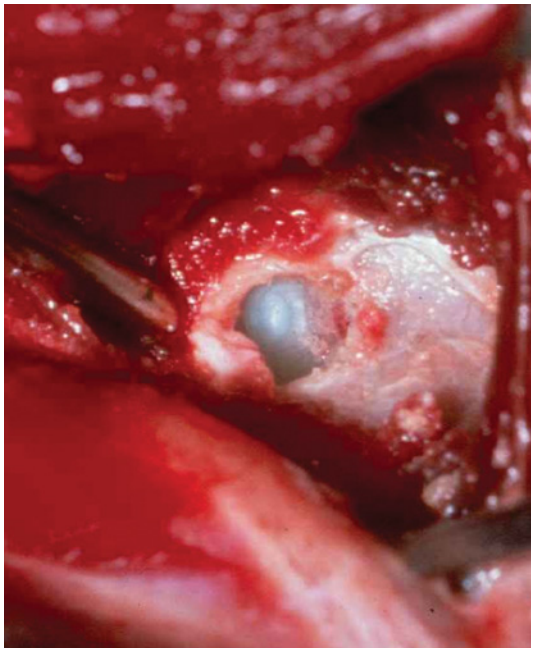
It is unacceptable to administer anti-inflammatory drugs to a patient exhibiting signs of an extruded disc, without concurrently confining that patient. The anti-inflammatory drugs alleviate the patient's pain, and most dogs will subsequently become more active. Increased activity is thought to cause more pressure to be placed on the abnormal disc by the adjacent vertebrae; subsequently, more disc material is extruded into the vertebral canal, and clinical signs acutely worsen. It is also unacceptable to concurrently administer steroidal and nonsteroidal anti-inflammatory drugs (NSAIDs) to disc disease patients, as this combination increases the chances of severe gastrointestinal complications. It is important to realize that subclinical gastroduodenal ulceration is likely to be present in dogs with type I disc extrusions, even without the administration of potentially ulcerogenic drugs (e.g. NSAIDs, glucocorticoids), so the use of such drugs should be minimized if at all possible. Spinal pain is typically managed with gabapentin (10–20 mg/kg q 8 hrs) or tramadol (2–4 mg/kg q 8 hrs). Some dogs with cervical intervertebral disc disease have severe muscle spasms, and while the effectiveness of muscle relaxants can be questioned, diazepam (0.5–1.0 mg/kg q 8 hrs) or methocarbamol can be used in these cases.

The traditional recommendations for the medical management of dogs with type I disc extrusions have recently been called into question, especially the recommendations dealing with cage confinement and glucocorticoid administration. In two retrospective reports evaluating the medical management of dogs with presumptive type I disc extrusions (one report on cervical disc extrusions, one on thoracolumbar disc extrusions), no association was found between duration of cage confinement and success of medical therapy. In addition, there was no beneficial effect of glucocorticoid administration on success in the cervical disc extrusion group, and there was a negative effect of glucocorticoid administration on success in the thoracolumbar extrusion group of dogs. However, the use of NSAIDs was positively associated with a successful outcome in the dogs with cervical disc extrusions. These findings suggest both that an extended cage confinement recommendation is often not adhered to by dog owners and that it may be an excessive recommendation in the first place. In the retrospective studies discussed, the average confinement period was approximately 2 wks, which may be a more realistic recommendation. Various pain-relieving drug options are discussed in detail in Chapter 21. In one report, the use of electroacupuncture as an adjunct to traditional medical therapy in dogs with suspected disc thoracolumbar disc extrusions was more successful in alleviating clinical signs than was traditional medical therapy alone.

Many dogs will respond favorably to medical management. In the authors' clinical experience, 50 to 70% of ambulatory patients with presumptive type I disc extrusions (cervical or thoracolumbar) will have an initial positive response to medical therapy, though many of these dogs tend to have a recurrence of clinical signs. In the retrospective reports discussed in the previous paragraph, sustained success was achieved with medical management in approximately half of the patients (48.9% for cervical extrusions, 54.7% for thoracolumbar extrusions), whereas initial success with subsequent disease relapse was experienced by about 30% of the dogs (33% for cervical, 30.9% for thoracolumbar). Medical failure was considered a failure from the onset of its institution in 18.1 and 14.4% of cervical and thoracolumbar cases, respectively. The mean follow-up time from onset of disease until collection of data was approximately 3 yrs in these two retrospective investigations. In another retrospective study concerning medical treatment of ambulatory dogs with suspected thoracolumbar disc extrusions (back pain with mild neurologic deficits), all 78 dogs had an initial positive response to medical treatment, but 50% of them (39 dogs) subsequently experienced a recurrence of clinical signs (median follow-up time of 25 mos). In this study, recurrence was more common in dogs receiving glucocorticoids than those that received NSAIDs.

However, fewer recurrences occurred in dogs initially treated with "high-dose" methylprednisolone sodium succinate (MPSS; discussed later in this section) than dogs treated with other glucocorticoid protocols, and there was no difference in the recurrence rates between MPSS and NSAID dogs. Other reports of medically treated dogs with presumptive thoracolumbar disc extrusions presenting primarily for back pain cite recurrence rates of approximately 30–40% as well. Enforced rest is thought to minimize further disc extrusion into the vertebral canal, while allowing tears in the annulus fibrosus to heal (preventing further disc extrusion). The inflammatory reaction caused by the extruded disc material is thought to subside during this enforced resting period. Interestingly, a recent study showed spontaneous regression of disc extrusion in a dog confirmed with a follow-up MRI study. This phenomenon, which appears common in humans, is now shown to also occur in dogs. The extruded disc material is probably resorbed secondary to the inflammatory reaction and macrophage activation. If confinement therapy is successful, the patient should be gradually allowed to return to a normal level of activity over a period of 4–6 wks. The owners need to be informed that the patient may acutely worsen during confinement and, especially with thoracolumbar disc disease, may become a surgical emergency.

Type II disc disease that is not associated with CSM or degenerative lumbosacral stenosis is typically managed medically with restricted activity and anti-inflammatory drugs. The injection of proteolytic enzymes (e.g. chymopapain) into type II discs to dissolve the NP and cause a flattening of the protruded annulus has been evaluated and may hold some promise as a treatment for this disease. When surgical intervention is indicated for a disc disease patient, spinal imaging and CSF analysis is typically performed on the anesthetized patient immediately prior to surgery. In this text, surgical intervention for disc disease specifically refers to those procedures that allow for the decompression of the spinal cord and the removal of disc material from the vertebral canal (e.g. ventral slot, hemilaminectomy, dorsal laminectomy, pediculectomy, corpectomy). There are multiple variations of decompressive procedures in the literature, which can be found in the reference section and will not be discussed in detail here. Disc fenestration is still considered by many to be an optional, ancillary surgical procedure, although there is enough evidence to suggest it should no longer be considered an optional procedure. Fenestration involves removing a segment of annulus fibrosus and NP (Fig. 13.19). The effectiveness of fenestration is governed by the amount of NP removed. A study comparing blade and drill-assisted fenestration revealed that drill-assisted fenestration removed on average 65% of the NP, whereas blade fenestration removed 41%. Fenestration was first proposed in 1970 to minimize the chances of recurrence. In fact, a recent study that performed follow-up MRI immediately and 6 wks postoperatively confirmed recurrent disc herniation in six out of 10 patients that did not undergo fenestration of the affected disc space at the time of surgical decompression. Three of these six patients displayed clinical signs (pain and or paresis) compatible with the recurrent herniation noted on MRI. Early recurrences reportedly occur within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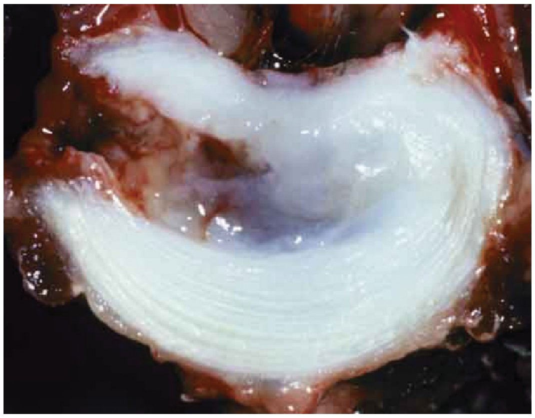
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Figure 13.19 (A) Disc space after surgical fenestration through a dorsolateral approach to the vertebral column. (B) Transverse section through a disc space after fenestration was performed. (Brisson, 2010.[56] Reproduced with permission from Elsevier.)

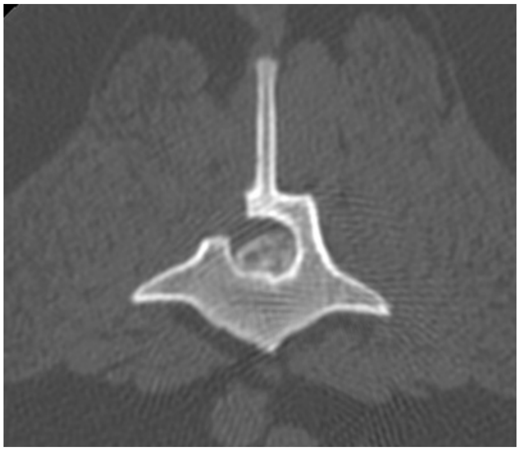


Figure 13.20 Transverse CT image of the lumbar spine showing recurrence of disc extrusion. The dog had a decompressive hemilaminectomy for treatment of disc extrusion 4 wks prior to presentation without fenestration of the affected disc space.

4–6 wks (or sooner) after surgery and are generally related to nuclear extrusion at the site of initial intervertebral disc extrusion (Fig. 13.20).

The fenestration is performed in the ventral aspect of the disc in the cervical region, and the lateral aspect of the disc in the thoracolumbar region. Disc fenestration is considered a prophylactic measure. Previous evidence of retrospective studies reported recurrence rates of 19.2% without prophylactic fenestration and 4.4% in a population of dogs that frequently underwent prophylactic fenestration. Stronger evidence comes from a prospective, randomized study to suggest that fenestration is effective in reducing the recurrence of intervertebral disc extrusion. A recent prospective study randomized 207 small-breed dogs undergoing surgical decompression for thoracolumbar intervertebral disc extrusion to either receive single-site fenestration at the site of decompression ($n = 103$) or multiple-site prophylactic fenestration of all disc spaces between T11–L4 ($n = 104$) with a median follow-up for recurrence of 3.4 yrs. The surgically confirmed recurrence rate in this study was 12.7% (7.45% multiple-site and 17.89% single-site) with dogs undergoing single-site fenestration being significantly more likely to develop recurrence than dogs undergoing multiple-site fenestration. Fenestration is generally a safe procedure, but may have adverse consequences on rare occasion (e.g. cause disc to rupture into the vertebral canal during the procedure), hemorrhage, nerve-root trauma, scoliosis, abdominal wall weakness, and discospondylitis. There is also some concern that fenestration may predispose neighboring, nonfenestrated discs to rupture, leading to a recurrence of clinical disease.

Surgical intervention is the preferred treatment modality for the following scenarios:

1. Suspected type I cervical or thoracolumbar disc disease patients with minimal to no neurologic deficits, but repeated episodes of pain, or pain that is not responding to appropriate medical therapy.
2. Suspected type I cervical disc disease patients with moderate to severe neurologic deficits (tetraparesis, tetraplegia). An acutely tetraplegic patient should be handled as a surgical emergency.
3. Suspected type I thoracolumbar disc disease patients that are nonambulatory. This includes patients that are nonambulatory paraparetic (voluntary motor ability to hind limbs present, but can't walk unassisted) and those that are paraplegic (no voluntary motor ability to pelvic limbs). These patients are to be considered surgical emergencies, as many will continue to deteriorate to the point of losing pain perception to the pelvic limbs, if surgical intervention is not pursued quickly. The success rate of medically managing nonambulatory dogs with type I thoracolumbar disc extrusions is based on older literature, but appears to center around 50%. For dogs with absent deep pain perception (DPP, or nociception), a 5–10% recovery rate has been suggested with medical management. Obviously, medical management is not ideal for these patients, but should still be considered (as an alternative to euthanasia) if surgical intervention is not an option (e.g. financial issues, precluding concurrent health conditions).
4. Suspected type I cervical or thoracolumbar disc disease patients exhibiting obvious deterioration in neurologic status, whether or not the patient is still ambulatory. The surgical procedure of choice for cervical disc extrusions is usually a ventral slot procedure (Fig. 13.21, Fig. 13.22), and for thoracolumbar disc extrusions, either hemilaminectomy (Fig. 13.23), pediculectomy (Fig. 13.24), or (less preferable) dorsal laminectomy (Fig. 13.25). Ideally, one should choose the most minimally invasive procedure. Occasionally, a dorsal laminectomy is indicated for cervical disc extrusions (Fig. 13.26), in which there is dorsal or lateral accumulation of disc material and/or extensive spinal cord swelling. Fenestration of discs as a prophylactic maneuver is commonly performed in both the cervical and thoracolumbar regions, usually concurrently with a ventral slot or hemilaminectomy, respectively.

Surgery is sometimes required in cases of type II disc disease, usually using hemilaminectomy, pediculectomy, or corpectomy (Fig. 13.27). Specific surgical options available for CSM and disc-related cauda equina syndrome are discussed elsewhere in this

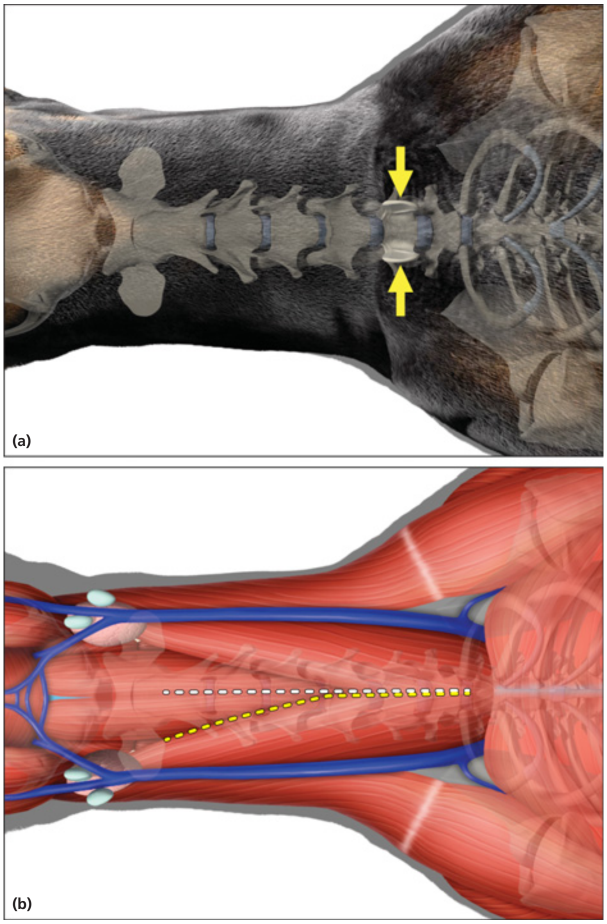


Figure 13.21 Approach for a ventral slot. (A) Observe the large ventrally positioned transverse processes of the sixth cervical vertebra (arrows). Identification of C6 is important to allow identification of the correct disc space. (B) Median approach is shown by the dotted white lines over the sternohyoideus and sternocephalicus muscles. Paramedian approach is illustrated by the dotted yellow lines. (The Ohio State University. Reproduced with permission.)

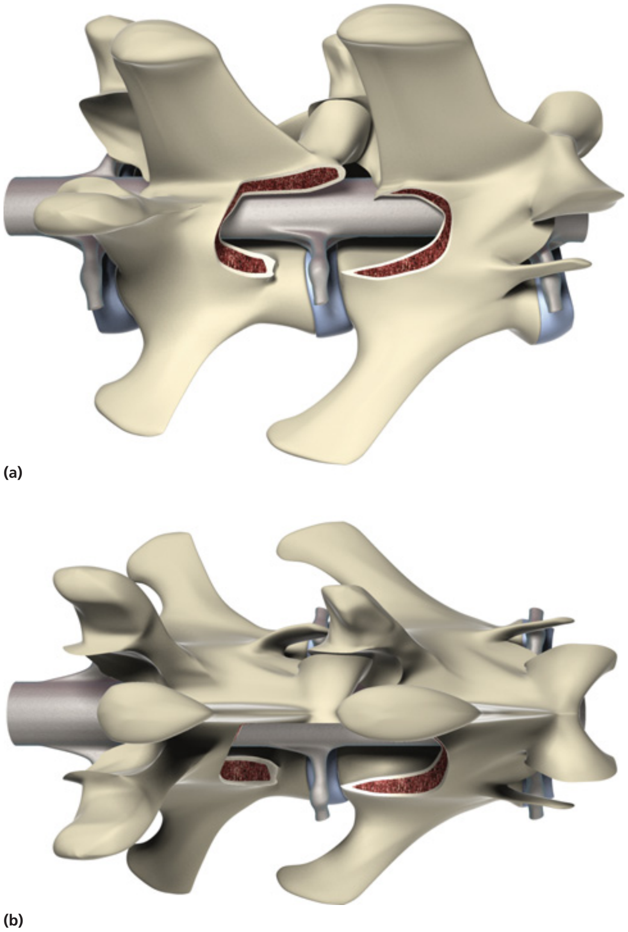


Figure 13.23 Illustrations of a hemilaminectomy. (A) Dorsolateral view. (B) Dorsal view. Note complete removal of the articular process, pedicles, and ipsilateral lamina. (The Ohio State University. Reproduced with permission.)

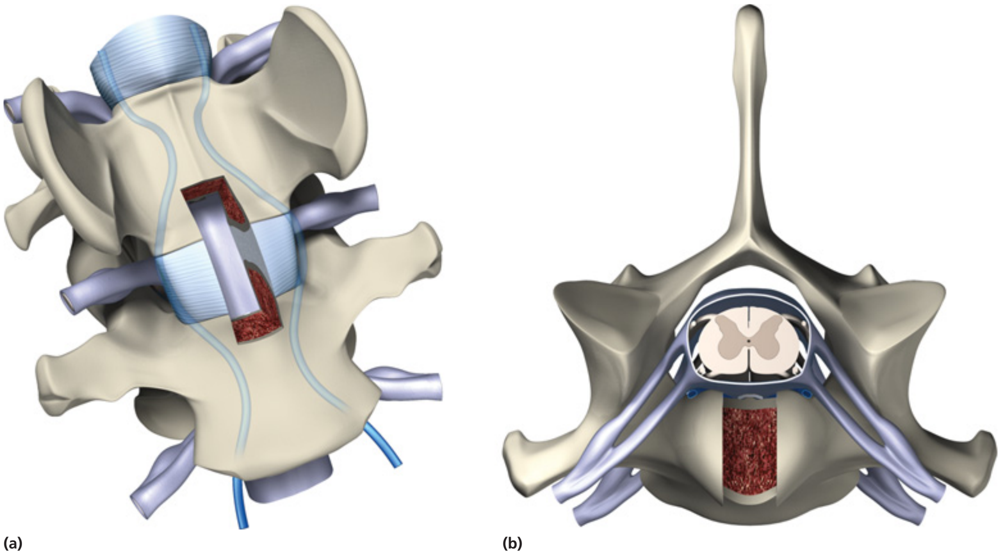


Figure 13.22 Illustrations of a ventral slot. (A) Ventral view. (B) Transverse view of a ventral slot at C6–C7. The slot width and length should ideally be kept at about one-third of the vertebral bodies to avoid injuring the vertebral venous plexus (illustrated in blue, immediately ventral to the nerve roots). (The Ohio State University. Reproduced with permission.)

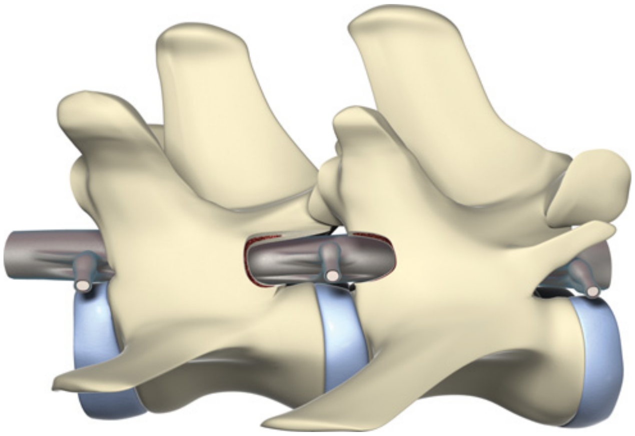


Figure 13.24 Illustration of pediculectomy or mini-hemilaminectomy. This approach preserves the articular processes and removes only the cranial and caudal pedicles along with the accessory process. (The Ohio State University. Reproduced with permission.)

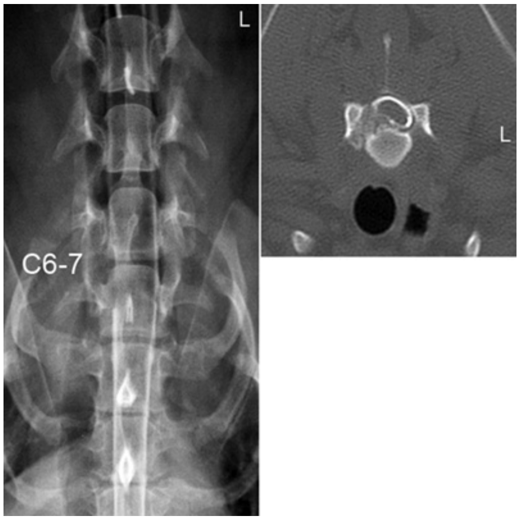


Figure 13.26 Transverse CT myelogram image showing lateralized disc extrusion at C6–C7 in a dog.

text. Despite the lack of evidence of efficacy, glucocorticoid therapy is often recommended for type I disc extrusion patients with rapid development of moderate to severe neurologic dysfunction (e.g. paralyzed Dachshund). Although glucocorticoid administration is often associated with minimal clinical consequences, complications ranging in severity from vomiting/diarrhea to fatal colonic perforation have been reported. In order to minimize gastrointestinal side effects, it is always recommended to use a proton pump inhibitor (e.g. omeprazole), in conjunction with steroids. In one study of dogs with surgically confirmed thoracolumbar disc extrusions, the consequences of preoperative dexamethasone

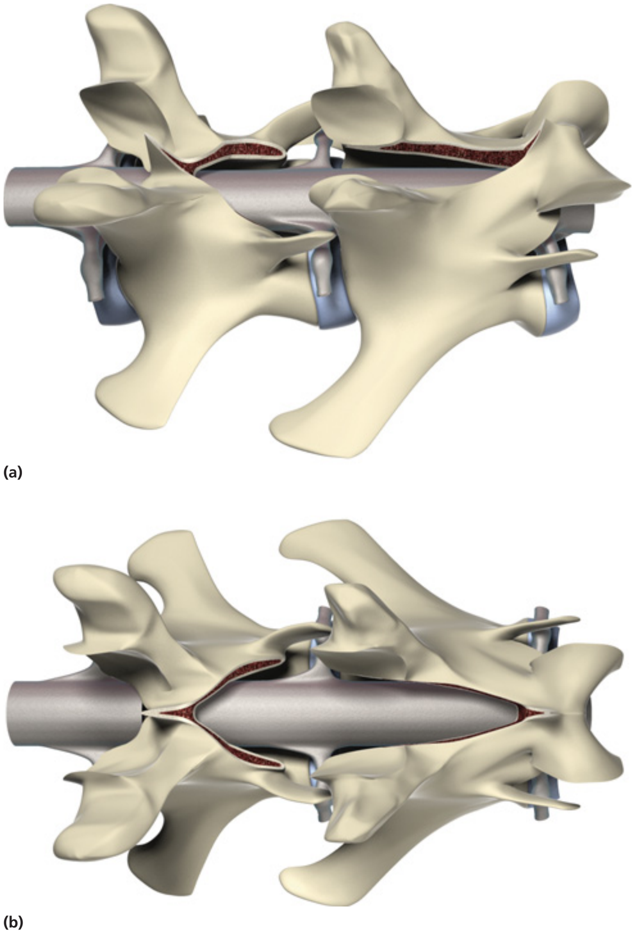


Figure 13.25 Illustrations of a dorsal laminectomy. (A) Dorsolateral view. (B) Dorsal view. The caudal articular processes are removed but the cranial processes are kept intact. The cranial and caudal extension varies according to the lesion. (The Ohio State University. Reproduced with permission.)

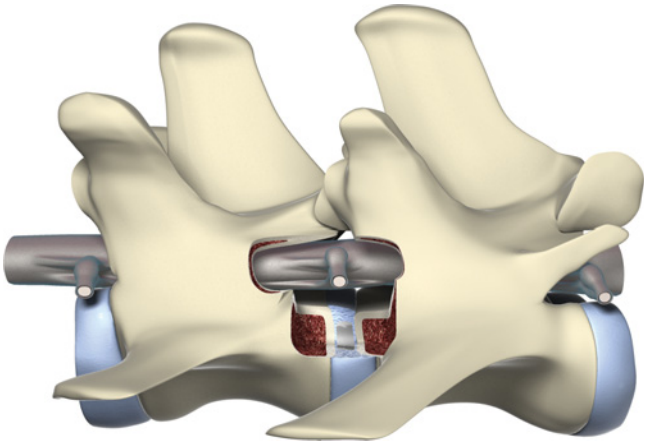


Figure 13.27 Illustration of a corpectomy in the lumbar spine. This approach is usually combined with a hemilaminectomy or mini-hemilaminectomy to gain access to the vertebral canal. (The Ohio State University. Reproduced with permission.)

administration (within 48 hrs of hospital admission) were compared with those associated with the administration of other glucocorticoids (within the same timeframe) and no administration of glucocorticoids. There were no differences in neurologic outcomes between groups. However, dexamethasone-treated dogs were 3.4 times more likely to have post-operative complications than the other two groups. More specifically, dogs treated with dexamethasone were 11.4 times more likely to develop a urinary tract infection (UTI) and 3.5 times more likely to develop diarrhea. It is important to emphasize that the mean dose of dexamethasone used in the study was high (2.2 mg/kg ± 4.2). Dexamethasone has an anti-inflammatory potency seven times higher than prednisone. A dose of 2.2 mg/kg of dexamethasone is equivalent to 15.4 mg/kg of prednisone. If one were to use such high doses of prednisone, side effects would also be expected, so it is not related to the specific corticosteroid but to the incorrect doses used. If one chooses to use corticosteroids, the recommended initial dose would be 1 mg/kg of prednisone and 0.15 mg/kg of dexamethasone. It is absolutely unnecessary to use dexamethasone doses higher than 0.25 mg/kg (equivalent to 1.7 mg/kg of prednisone). The only glucocorticoid treatment that was considered of some potential benefit in spinal trauma was the “high-dose” MPSS protocol. This protocol is discussed in Chapter 15. The therapeutic efficacy of high-dose MPSS in human and veterinary spinal trauma has been questioned, and recent evidence in veterinary medicine suggests that is an ineffective therapy. Another potential treatment, polyethylene glycol (PEG) was also shown to not be beneficial. This therapy is discussed in more detail in Chapter 15.

The prognosis for functional recovery in type I cervical and thoracolumbar disc disease patients is generally good to excellent. Functional recovery for surgically treated patients with type I thoracolumbar disc extrusions and intact pain perception (nociception) to the pelvic limbs is expected in roughly 80–95% of cases (reports range from 72 to 100%). The largest study in the subject with 831 cases reported a 97.7% recovery in ambulation after surgery in dogs that had intact nociception. In one study of surgically managed type I cervical disc extrusions in small- and large-breed dogs, the overall success rate was 99%. The average time to ambulatory status following surgery in patients with thoracolumbar disc extrusion is approximately 2 wks (10–14 days), although in many cases it occurs much more rapidly (3–5 days). Return to ambulation following surgery for nonambulatory tetraparetic or tetraplegic small- and large-breed dogs with type I disc extrusions has been reported to average approximately 1 wk (4.5–7 days). There is no difference in outcome between dogs with UMN and LMN pelvic limb dysfunction with thoracolumbar disc extrusions. Neither the degree of spinal cord compression nor whether disc extrusions are focal or dispersed on MR imaging is associated with prognosis in surgically treated dogs with type I thoracolumbar disc extrusions. The prognosis appears to be similarly favorable for cats with intervertebral disc extrusions treated surgically.

Most neurologists and surgeons would agree that surgical intervention should be pursued in a timely manner once a dog with a thoracolumbar disc extrusion has become nonambulatory in the pelvic limbs. However, the literature regarding the timeliness of surgical intervention and its effect on time to return to ambulation in such cases is conflicting. In one study of dogs with type I thoracolumbar disc extrusion and intact DPP, an inverse relationship was found between the time from nonambulatory status to surgical intervention and the time from surgical intervention to regaining ambulatory function. These results do not necessarily diminish the need for expediency in operating patients without voluntary motor function. However, they may suggest that patients with a more rapid loss of motor function sustain more severe spinal cord injury than those dogs with a more progressive loss of motor function. The former animals likely sustain more severe concussive (force of impact) spinal cord injury at the time of disc extrusion, which may be more damaging than progressive compression. In this same study, dogs with voluntary motor function regained ambulatory ability significantly sooner postoperatively than those without motor function (7.9 days vs. 16.4 days). Ninety-six percent of the dogs were walking within 3 mos. In another similar study of paraplegic dogs with intact DPP, the rate of development of paraplegia had a negative association with outcome, but not with the length of recovery time in those dogs regaining ambulatory function. In this same study, the duration of clinical signs prior to surgery (i.e. time from becoming paraplegic to surgical intervention) did not significantly affect outcome but was associated with longer recovery times; dogs paraplegic for longer periods prior to surgery took longer to regain ambulatory status compared to those with shorter periods to surgical intervention. In nonambulatory dogs with thoracolumbar disc extrusions and intact DPP, the amount of time elapsing from loss of motor function to surgical intervention has not been associated with eventual outcome. In one report of thoracolumbar disc extrusions in large-breed dogs, approximately 40% of dogs that were ambulatory had residual neurologic deficits at last follow-up. The average time for nonambulatory large-breed dogs to regain ambulatory function postsurgically in this study was 7.6 wks.

The loss of clinically detectable DPP in the pelvic limbs occurs with some frequency in type I thoracolumbar disc disease, and is associated with a guarded to poor prognosis. In this subset of patients, the amount of time elapsed from the loss of DPP to surgical decompression has been inversely associated with prognosis. Unfortunately, an accurate estimate of when DPP was lost is not always attainable in clinical practice. Most reports suggest a functional recovery rate in the vicinity of 50% (between 25 and 78%) for paraplegic dogs that have lost DPP to the pelvic limbs. A peracute (less than 1 hr) loss of voluntary motor function has been associated with a statistically significantly worse prognosis for functional recovery, compared with acute (1–24 hrs) or gradual (more than 24 hrs) loss of voluntary motor function in these dogs. Similar to the situation in dogs with intact DPP, acute concussive spinal cord injury in dogs without DPP seems to be more related to the eventual outcome than duration of spinal cord compression. There is a tendency for a better functional results when dogs with absent DPP are operated on within 12 hrs of losing DPP. The contention that the absence of DPP for more than 48 hrs precludes a chance of functional recovery after surgery is probably inaccurate. The development of focal or diffuse myelomalacia (liquefaction of the spinal cord parenchyma) is a concern with dogs that have lost pain perception, and can be visualized at surgery (via a durotomy). Occasionally, myelomalacia will be evident on myelography (e.g. contrast medium infiltrating spinal cord parenchyma) or on MRI (e.g. hyperintensity six times longer than body of L2). Myelomalacia appears to affect 10% of dogs with absent nociception. Unfortunately, even with surgical confirmation of myelomalacia in dogs with no DPP, there remains some level of subjectivity. Dogs with focal myelomalacia may still recover function, though the likelihood of this is unknown. In one study of thoracolumbar disc extrusion patients with no DPP to the pelvic limbs, the performance of a durotomy had no effect on outcome. One of the authors (CD) routinely performs durotomies on dogs with no DPP in order to inspect the spinal cord for prognostic purposes. Dogs with no DPP prior to surgery that eventually recover ambulatory function tend to do so over longer periods than dogs that had DPP prior to surgery. It is important to emphasize that most reports describing the outcome of dogs with absent nociception refer to lesions in the T3–L3 region. Dogs with L4–S3 lesions displaying LMN signs (i.e. gray-matter injury) and absent nociception (i.e. white-matter injury) carry a poorer prognosis than those with T3–L3 lesions. These dogs can still recover but will take longer and will require more intensive physical therapy than those with T3–L3 lesions.

Cervical type I disc extrusions severe enough to cause respiratory compromised respiratory function occur uncommonly; such cases are often associated with a poor prognosis. However, with appropriate respiratory support (i.e. ventilator therapy) following surgery, the majority of these cases are likely to recover ambulatory function within 2–3 mos.

In general, it appears from the available literature that a recurrence of clinical signs of type I disc extrusion is substantially higher for medically treated versus surgically treated cases. Reported recurrence rates for surgically managed dogs with type I disc extrusions vary in the literature, as do the definitions of recurrence. Recurrence of clinical signs of disc extrusion for surgically treated type I disc disease patients is reported to be roughly between 10 and 25%, but the vast majority of these recurrences do not require repeat surgical intervention (i.e. transient neck or back pain that responds to medical management). In one report, the reoperative rate for dogs with thoracolumbar type I disc extrusions was found to be 6.4%. Most (83%) recurrent disc extrusions occurred more than 1 mo from the time of the initial surgery, and the majority of these (88%) were from a separate disc site. All recurrent disc extrusions occurring less than 1 mo after the initial surgery were from the initial disc extrusion site. Dogs were found to be just as likely to achieve functional recovery following repeat surgery as they were after the initial surgery. Dachshunds were thought to be at highest risk for reoperative disc extrusions, compared with other breeds (almost 10% in this study). In another study evaluating surgically managed dogs with type I thoracolumbar intervertebral disc extrusions, the recurrence of clinical signs of disc extrusion was 19.2%. Among these cases were 24 reoperative recurrences (10.5%), and 11 dogs euthanized because of recurrence (4.8%). Fifty percent of all dogs with recurrence in this study were Dachshunds. Also in this study, risk of recurrence increased by 1.4 times for each opacified disc evident on thoracolumbar radiographs; dogs with five or six opacified discs evident at the first surgery had a 50% recurrence rate. In one study of small and large dogs with surgically managed type I cervical disc extrusions, the recurrence of cervical spinal hyperesthesia was documented in 10% of patients (8% in small-dog group, 13% in the large-dog group). However, only 4% of dogs required a second surgery (2.1% in the small-dog group, 8.7% in the large-dog group). In one study of large-breed dogs with thoracolumbar disc extrusions, the reoperative recurrence rate was 12%.

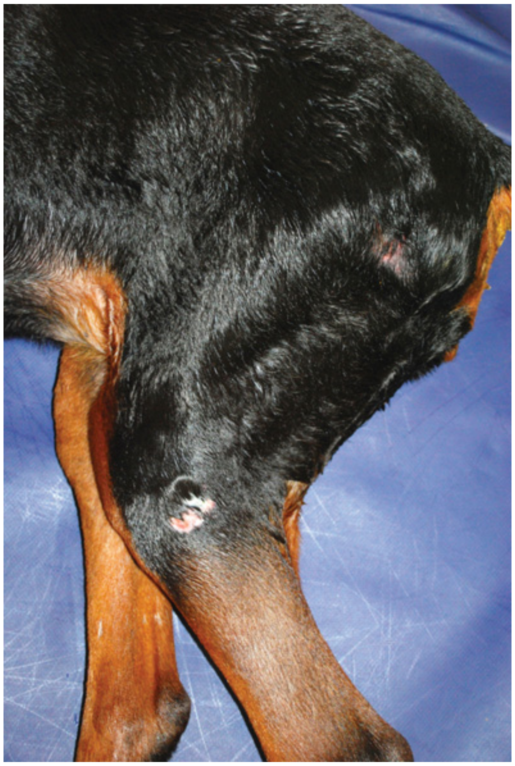


Figure 13.28 Decubital ulcers in the stifle and hip areas in a paraplegic dog. Note also urine soiling in the abdominal area.

Paraplegic or tetraplegic dogs require intensive nursing care (see Chapter 20) to prevent complications such as decubital ulcers (Fig. 13.28). Postoperative urinary tract infections (UTIs) are common in dogs with thoracolumbar disc extrusions, with estimates of 22 to 27% from two separate studies. In many cases, UTIs are often subclinical and may occur prior to surgery and up to several months following surgery. These findings emphasize the need to routinely monitor such patients for UTI and to treat them accordingly. Commonly incriminated organisms include *Escherichia coli*, *Enterococci species*, and *Staphylococcus intermedius*. In one study, several predictive factors were identified. Female dogs were three times more likely to develop UTI than males, and dogs not administered perioperative antibiotics were three times more likely to develop a UTI. Other factors that were significantly associated with an increased chance of UTI included nonambulatory status (especially with advancing age), inability to urinate voluntarily, and length of time the body temperature was below 35°C (95°F) while under anesthesia. In yet another study that evaluated postoperative disc disease patients (cervical and thoracolumbar discs) with indwelling urinary catheters, 42% had UTIs and the odds of developing a UTI increased by 20% for each year of patient age, and 27% for each day of catheterization. Antibiotic administration during the catheterization period increased the odds of developing a UTI by 454%. The isolated organisms were similar to those found in the other two studies. In all of these reports, the majority of UTIs were not characterized by multiple drug-resistant organisms. The anatomic and nursing care principles associated with bladder management are covered in Chapters 16 and 20, respectively.

Patients with type II disc disease are often controlled adequately for long periods with medical therapy. The prognosis for surgical treatment of type II disc disease is generally guarded, as compared with type I disease, especially for lesions in the thoracolumbar spinal cord. Substantial, sometimes permanent, neurologic deterioration after surgery is more likely in these patients. The reason(s) for this phenomenon is (are) unknown, but may be due to such factors as reperfusion injury and lack of spinal cord functional reserve capacity (due to chronic compression and atrophy). Aggressive blood pressure monitoring preventing transoperative hypotension may help to minimize postoperative deterioration. Despite the prevalence of type II disc disease in dogs, the literature regarding surgical success for these patients is relatively sparse. What is available, however, suggests a much lower success rate compared with type I disc extrusions. In the authors' clinical experience, even with minimal manipulation of the spinal cord at surgery, dogs with chronic type II disc protrusions are often (at least 30%) permanently worse postoperatively. A surgical procedure termed lateral corpectomy has been reported to have a high success rate in 15 dogs with chronic type II disc protrusions. This procedure involves creating a lateral slot in two adjacent vertebral bodies and the intervening (protruding) disc, the dorsal limit of the slot being the floor of the vertebral canal. With this procedure, the protruding disc material can be removed from the ventral aspect of the spinal cord, minimizing spinal cord manipulation. A recent study described corpectomy in 72 dogs, although only 16 dogs were nonchondrodystrophic. Postoperative worsening was common in ambulatory dogs, and only 30% of dogs with type II IVDD were improved at 4 wks. Long-term outcome (> 6 mos) revealed improvement in approximately 65% of dogs with type II IVDD.

2. Cervical spondylomyelopathy (CSM; "wobbler syndrome")[3–6, 35, 53, 59–61, 63, 64, 74, 76, 98, 106–115, 117, 118, 121, 122, 129–131, 135, 136, 138–141, 150, 160, 163, 174, 182, 193, 209, 212, 215, 227, 231, 232, 238, 246, 251, 285, 288, 299, 300, 303, 318, 337–339, 353, 354, 356, 357, 384, 394, 396, 403, 410, 412, 420, 428, 430, 431, 437, 446, 458, 470, 473, 476, 478–480, 490, 506, 521, 526, 527, 534–536, 540, 541, 558, 564, 567, 570]
   a. Cervical spondylomyelopathy or "wobbler syndrome" is a common disease of the cervical vertebral column

of large- and giant-breed dogs. It is characterized by dynamic and static compressions of the cervical spinal cord, nerve roots, or both, leading to variable degrees of neurologic deficits and neck pain. A variety of names (at least 15) have been used to describe the disease: cervical vertebral instability, cervical malformation/malarticulation syndrome, and disc-associated wobbler syndrome are some of the terms most commonly used. Even though the disease can affect essentially all canine breeds, two breeds represent approximately 60–70% of all affected dogs: the Doberman Pinscher and the Great Dane. They also represent the two distinct forms of the disease, the disc-associated CSM, which is typically seen in middle-aged large breed dogs (primarily Dobermans), and the osseous form of CSM, commonly seen in young adult giant-breed dogs, such as Great Danes. Current evidence suggests that CSM in Dobermans has a hereditary basis.

1. The pathophysiology of CSM involves both static and dynamic factors. The key static factor is vertebral canal stenosis. It may be an absolute vertebral canal stenosis (which then causes direct spinal cord compression and neurologic signs) or a relative vertebral stenosis, which by itself does not lead to myelopathic signs but predisposes the patient to develop myelopathy. Despite some degree of overlap, the pathophysiology of the spinal cord compressions can be divided into osseous- or disc-associated compression.
2. Disc-associated compression is typically seen in middle-aged large-breed dogs (mostly Dobermans). It is caused by a combination of intervertebral protrusion with or without ligament hypertrophy (either the dorsal longitudinal ligament or ligamentum flavum) (Fig. 13.29). Three factors act in combination to explain the pathophysiology of disc-associated CSM: (a) relative vertebral canal stenosis, (b) more pronounced torsion in the caudal cervical spine leading to intervertebral disc degeneration, and (c) protrusion of larger-volume discs in the caudal cervical spine. Affected dogs are apparently born with a congenital vertebral canal stenosis. The vertebral canal stenosis per se does

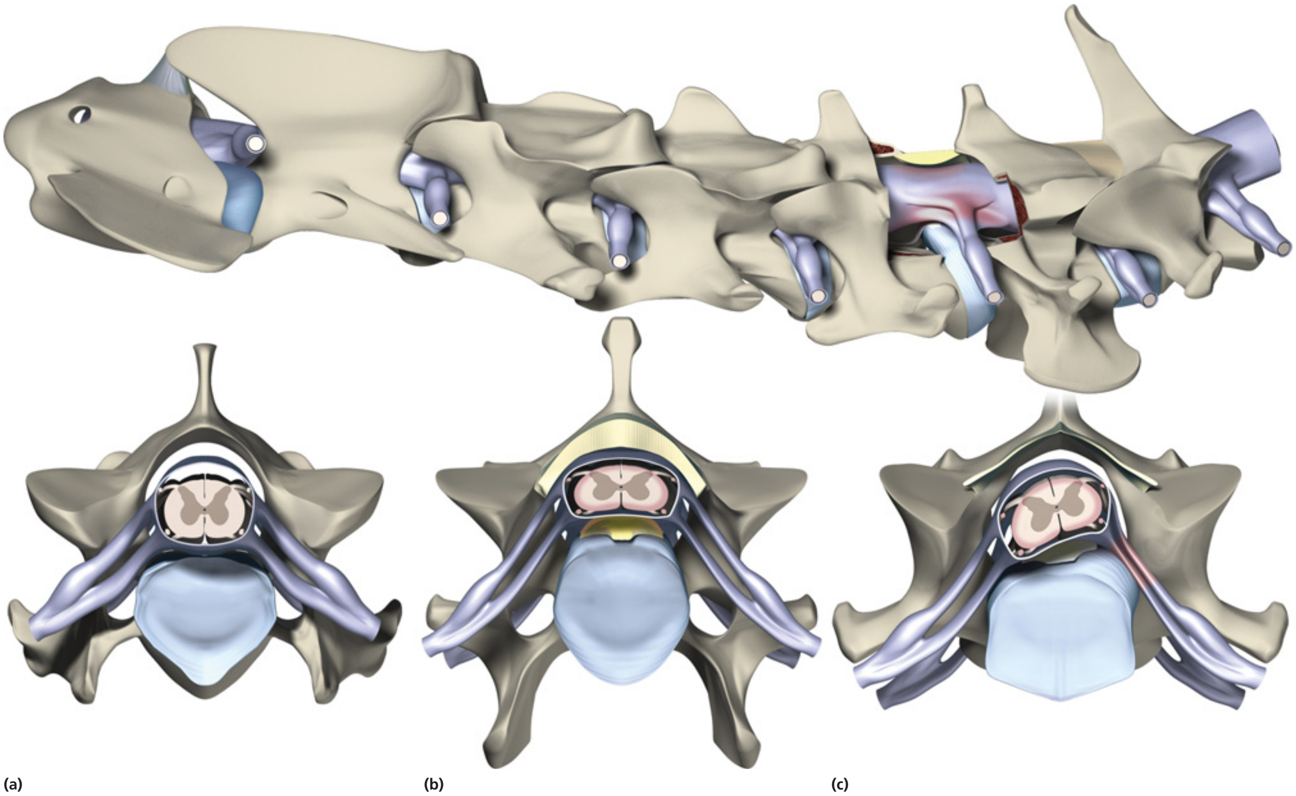


Figure 13.29 Disc-associated CSM. Top image shows ventral spinal cord compression and nerve root compression at C5–C6 caused by intervertebral disc protrusion. Dorsally, hypertrophy of the ligamentum flavum causes mild spinal cord compression. Bottom images. (A) Transverse section at the level of the C4–C5 disc region showing normal spinal cord and vertebral canal. (B) Ventral compression at C5–C6 region caused by intervertebral disc protrusion and hypertrophy of the dorsal longitudinal ligament (yellow) and ligamentum flavum (causing mild dorsal compression). (C) Asymmetric intervertebral disc protrusion at C6–C7 causing spinal cord and nerve root compressions. (Da Costa RC. Cervical spondylomyelopathy (Wobbler syndrome) in dogs. *Vet Clin North Am Small Anim Pract*. 2010;40:881–913. Reproduced with permission from Elsevier.)

not lead to clinical signs but predisposes them to the development of clinical signs. The vast majority of the disc-associated spinal cord compressions are located in the caudal cervical spine, affecting the discs C5–C6 and C6–C7.

3. The pathophysiology of osseous- or bony-associated CSM is different. Osseous-associated CSM is seen predominantly in young adult giant-breed dogs. Even though a hereditary basis is unproven, a familial predisposition has been identified. Giant breeds usually have severe absolute vertebral canal stenosis secondary to proliferation of the vertebral arch (dorsally), articular processes (dorsolaterally), or articular processes and pedicles (laterally) (Fig. 13.30). The cause of the compression appears to be a combination of vertebral malformation and osteoarthritic/osteoarthrotic changes at the level of the articular processes. Even though most giant-breed dogs have osseous compression, occasionally these compressions are complicated by disc protrusion, especially in older dogs. Ligamentous compression (ligamentum flavum) may be associated in the pathophysiology of the disease in giant- and large-breed dogs, but pure ligamentous compression as the single source of compression appears uncommon.
4. Critical to the development of clinical signs in CSM-affected large-breed dogs is the concept of dynamic lesions. Dynamic spinal cord compressions are present in both the disc and osseous form of CSM. A dynamic lesion would be one that worsens or improves with different positions of the cervical spine. Continuous flexion and extension of the cervical spine can lead to spinal cord elongation, causing axial strain and stress within the spinal cord, which have been proposed as a key mechanism of spinal cord injury in cervical spondylotic myelopathy in humans. This concept is very different from instability, which has been defined as the loss of ability of the cervical spine under physiologic loads to maintain its normal pattern of displacement so that there is no damage to the spinal cord or nerve roots. Instability has not yet been proven in dogs with CSM.

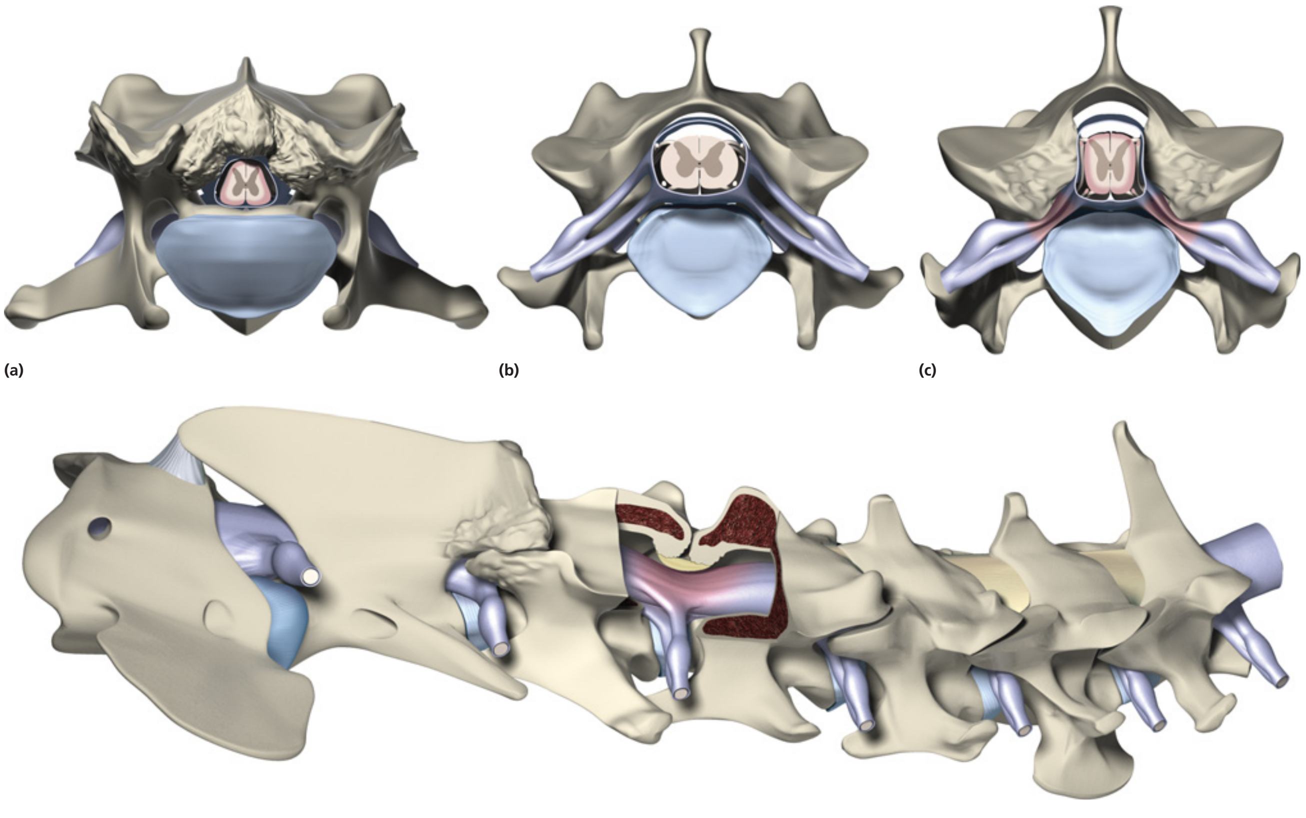


Figure 13.30 Osseous-associated CSM. (A) Severe dorsolateral spinal cord compression at C2–C3 caused by osseous malformation and osteoarthritic changes. (B) Normal C3–C4 disc region. (C) Bilateral compression at C4–C5 caused by osteoarthritic changes and medial proliferation of the facets causing absolute vertebral canal stenosis and foraminal stenosis leading to spinal cord and nerve root compressions, respectively. Bottom image shows dorsal spinal cord compression at C3–C4 caused by lamina malformation and hypertrophy of the ligamentum flavum. Osteoarthritic changes are also shown at C2–C3. (Da Costa RC. Cervical spondylomyelopathy (Wobbler syndrome) in dogs. *Vet Clin North Am Small Anim Pract*. 2010;40:881–913. Reproduced with permission from Elsevier.)

5. The most common location of compressive lesions in both large- and giant-breed dogs is at C5–C6 and C6–C7. The lesion is located at either site in 90% of large-breed dogs. In giant-breed dogs, the C4–C5 site is also commonly affected. Approximately 50% of large-breed dogs have a single site of spinal cord compression, and 50% have two or more sites of similar severity. In giant-breed dogs, approximately 20% of dogs have a single site of compression, whereas 80% have multiple compressive lesions. A CT myelography study identified lesions affecting the T1–T2 and T2 regions in 14% of giant-breed dogs and the C7–T1 region in 22% of all dogs. These lesions were not the primary site of compression but were part of the multiple compressions seen in giant-breed dogs. As such, it is important to include the cranial thoracic region in imaging studies of dogs suspected of having CSM.

b. Clinical features of CSM (Video 25)
   1. History and clinical signs—the majority of Dobermans and other large-breed dogs with CSM (Weimaraners, Dalmatians) are older than 3 yrs of age at presentation (mean age approximately 7 yrs). Great Danes and giant breeds (Mastiffs, Rottweilers, Bernese, Swiss Mountain dogs) with CSM are seen usually at a younger age. The mean age of giant-breed dogs with CSM is 3.8 yrs, and the disease may be seen in dogs just a few months old. A chronic progressive history (several weeks to months) is typical. Acute presentations are usually associated with neck pain (Fig. 13.31). Neck pain or cervical hyperesthesia is a common historical finding, but typically is not the main reason for presentation. Forceful manipulations of the cervical spine are unnecessary to document the presence of neck pain and can lead to severe neurologic decompensation. Evaluation of the posture and deep palpation of the transverse processes can identify pain in the majority of cases. In cases with dynamic pain, evaluation of the voluntary range of motion (side-to-side, ventrally and dorsally) using a food treat is recommended to document it.
   2. Neurologic evaluation—gait evaluation is the most important component of the examination in dogs suspected of having CSM, because it reliably identifies proprioceptive ataxia, even in the absence of conscious proprioceptive deficits. Proprioceptive ataxia is seen in most dogs with CSM. Dogs with lesions in the cranial or mid-cervical spine tend to present with ataxia affecting all four limbs more uniformly. Typically, however, affected dogs have obvious pelvic limb ataxia with milder abnormalities in the thoracic limbs. In some cases, the thoracic limb ataxia or weakness may be very mild in comparison with the pelvic limbs, making the thoracic limb abnormalities go unnoticed. The thoracic limb gait can appear choppy, short-strided, or spastic with a pseudohypermetric (“floating”) appearance. Occasionally, thoracic limb lameness can be seen, suggesting nerve-root entrapment. The pelvic limb gait is often wide-based (abducted) and markedly uncoordinated. The stride length of the pelvic limbs is prolonged, causing the swaying movements of the hind end, typical of the disease. Scuffing of the pelvic or thoracic limb toes/nails can also be seen. Postural reaction deficits (proprioceptive positioning deficits) are seen in most dogs with CSM, but may not be evident in those with a chronic history despite the presence of proprioceptive ataxia. In many cases the neurolocalization is of a C6–C8 myelopathy because the osseous and disc lesions are concentrated in the C5–C6 and C6–C7 regions. In these cases, the gait is affected in all four limbs but more severely in the pelvic limbs. Evaluation of the spinal reflexes in the thoracic limbs will show a decreased flexor (withdrawal) reflex, indicating involvement of the musculocutaneous nerve from C6 to C8 spinal cord segments, with normal to increased extensor tone suggesting a UMN lesion and release of the radial nerve from spinal cord segments C7, C8, T1, mostly C8–T1. The pelvic limb reflexes will be normal to increased.

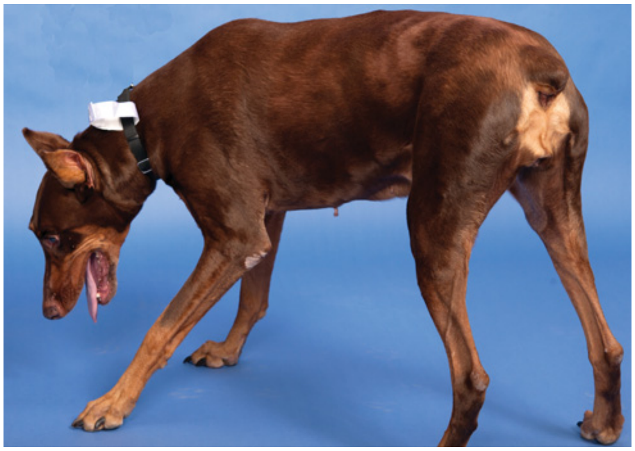


Figure 13.31 Posture of a Doberman Pinscher with cervical pain secondary to cervical spondylomyelopathy.

c. Diagnosis

Survey radiographs can only be used as a screening test to rule out other differential diagnoses. Radiographic findings seen in disc-associated CSM are primarily changes in the shape of the vertebral body (assuming a triangular shape in severe cases), narrowing of the intervertebral disc space, and vertebral canal stenosis. Osteoarthritic, sclerotic changes of the articular facets are the radiographic hallmarks in giant-breed dogs with osseous compressions, and can be seen on lateral and ventrodorsal projections (Fig. 13.32). Myelography is no longer the method of choice to diagnose CSM. It can be used if CT and MRI are not available but these other tests, primarily MRI, offer significant advantages over plain myelography. If myelography is to be performed, lateral and ventrodorsal views should be obtained. CT is a rapid test that allows visualization of transverse sections of the cervical spine. It has to be combined with myelography to identify the exact location of the compressive lesion(s) (Fig. 13.33). It provides superior visualization of the direction and severity of the spinal cord compression compared with myelography, and identification of spinal cord atrophy. Plain CT can be performed with sedation only, which may be useful for cases where general anesthesia is contraindicated. MRI is the gold standard test for evaluation of dogs suspected of having CSM. The main advantage of MRI is that it detects signal changes in the spinal cord and thus allows assessment of the spinal cord parenchyma.

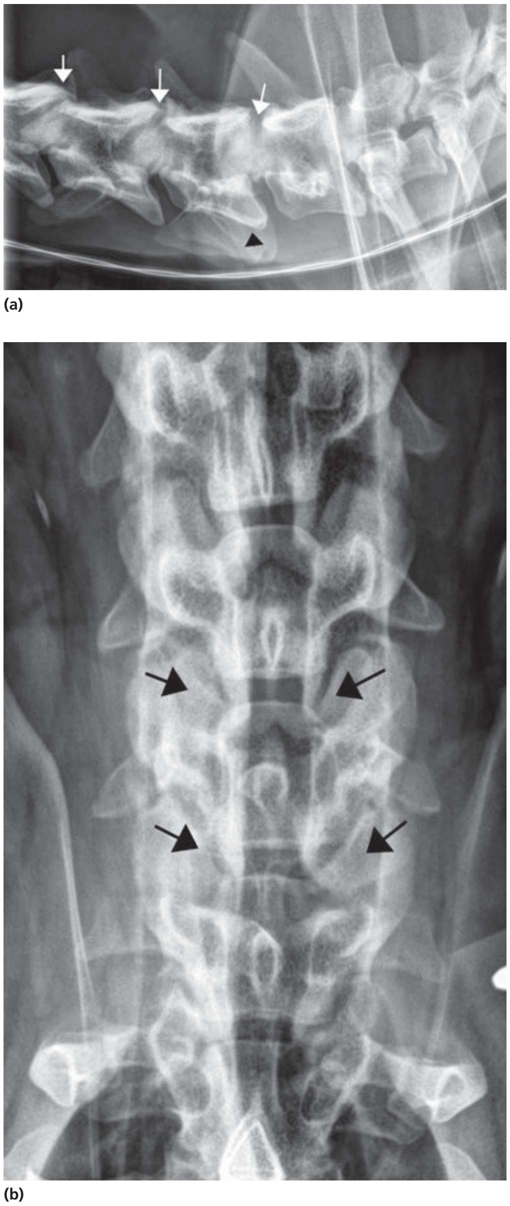


Figure 13.32 Radiographs of a 1-yr-old dog with osseous-associated CSM. (A) Lateral radiograph. Observe severe osteoarthritic changes in the articular processes of C4–C5, C5–C6, and C6–C7 regions (white arrows). The black arrowhead indicates C6 vertebra. (B) Ventrodorsal radiograph shows medial proliferation of the enlarged/arthritic processes (arrows). (da Costa RC. Cervical spondylomyelopathy (Wobbler syndrome) in dogs. *Vet Clin North Am Small Anim Pract*. 2010;40:881–913. Reproduced with permission from Elsevier.)

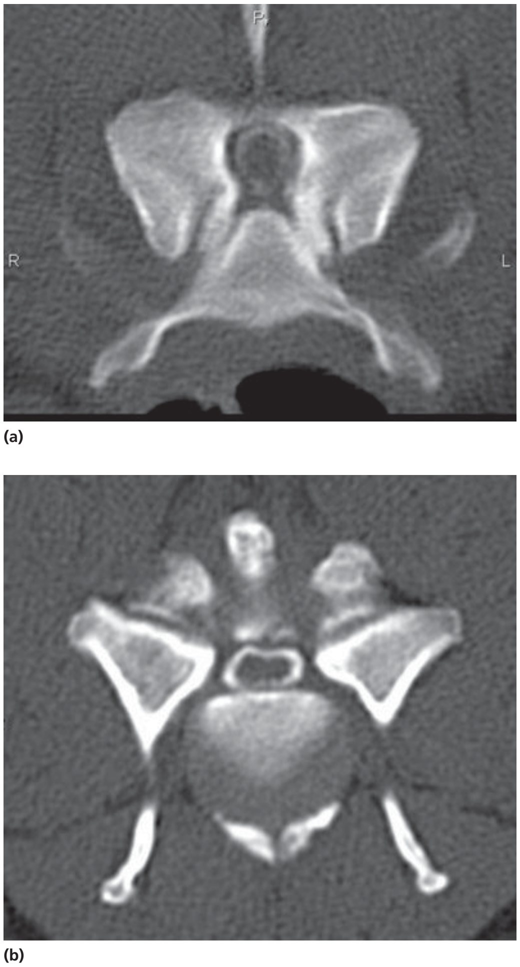


Figure 13.33 CT images of two Great Danes with CSM caused by osseous compressions. (A) Bilateral spinal cord and nerve root compressions at C6–C7. (B) Dorsal spinal cord compression at C4–C5. (da Costa RC. Cervical spondylomyelopathy (Wobbler syndrome) in dogs. *Vet Clin North Am Small Anim Pract*. 2010;40:881–913. Reproduced with permission from Elsevier.)

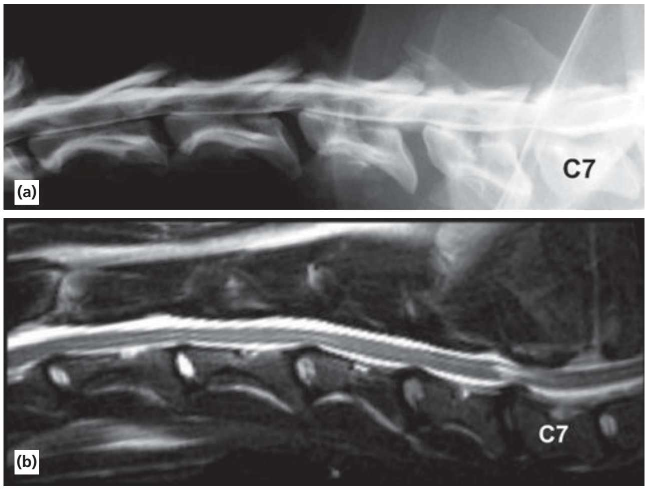


Figure 13.34 Cervical myelogram and T2-weighted (W) MR images of a 7-yr-old, Doberman with disc-associated CSM. (A) Cervical myelogram shows a ventral extradural compression at C6–C7. (B) Sagittal T2-weighted MR image shows ventral and dorsal spinal cord compression with marked spinal cord hyperintensity at C6–C7. Complete intervertebral disc degeneration is also seen at C6–C7.

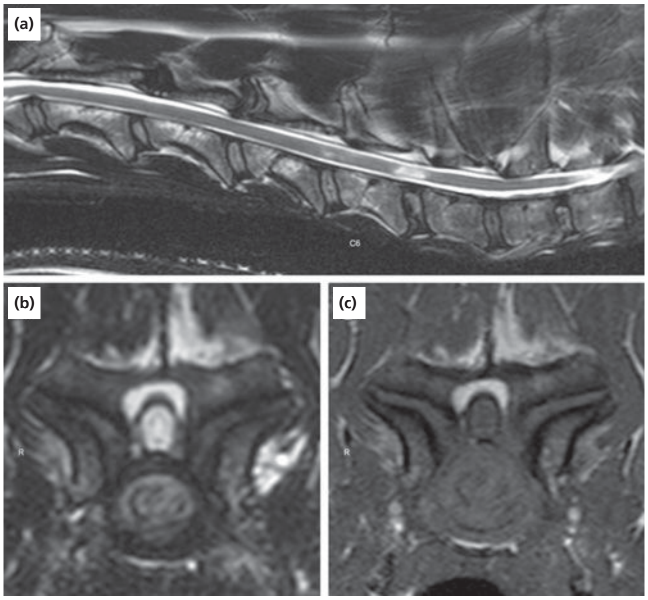


Figure 13.35 MR images of a Great Dane with osseous-associated CSM. (A) Midsagittal T2-weighted image. (B) transverse T2-weighted image at C6–C7, and (C) corresponding transverse T1-weighted image. The midsagittal image reveals two areas of spinal cord signal changes at C5–C6 (ill defined) and C6–C7 (well defined). Transverse images through C6–C7 reveal marked spinal cord T2-hyperintensity and T1-hypointensity, secondary to severe compression due to bilateral lateral articular process joint proliferation. (Martin-Vaquero and da Costa, 2014.[337] Reproduced with permission from American Veterinary Medical Association.)

These parenchymal signal changes are seen in approximately 50% of dogs with CSM and allow for the precise identification of the site most severely affected. A recent study compared myelography and MRI in the diagnosis of CSM and concluded that MRI was more accurate in predicting the site, severity, and nature of spinal cord compression (Fig. 13.34). The presence of spinal cord signal changes, namely hyperintensity on T2-W images is associated with severity of clinical signs, severity of spinal cord compression, and chronicity of signs. Hyperintensity on T2-W images does not appear to correlate with prognosis in dogs, but preliminary evidence suggests that the combination of hyperintensity on T2-W images and hypointensity on T1-weighted (T1-W) images may be associated with a worse prognosis (Fig. 13.35). Current evidence in humans suggests that multilevel hyperintensity on T2-W images and hypointensity on T1-W images are associated with a poorer prognosis. In some cases, the degree of spinal compression is minimal relative to the severity of clinical signs. Dynamic spinal cord compressions are assumed to be present in such cases. Testing for dynamic compression can be done using traction MRI. It is recommended to use a cervical harness and approximately 20% of the dog's weight for traction. Kinematic MR imaging with flexion and extension is currently being investigated for dogs with CSM.

d. Treatment

1. Conservative (medical) treatment—medical management is a viable option for many dogs with CSM, primarily those giant-breed dogs with multiple compressive lesions affecting the lateral (ventrolateral or dorsolateral) aspect of the spinal cord. The authors also like to start all dogs on medical management initially to evaluate the improvement obtained with it and to give owners the opportunity to decide on surgery. The response to medical management (corticosteroids and exercise restriction) can be used to indirectly evaluate how reversible the spinal cord lesions are. The most important component of medical management is exercise restriction to minimize high-impact activities that would exacerbate the dynamic component of spinal cord compression. Dogs can be leash walked, but free, unsupervised activity is strongly discouraged. A body harness should be worn instead of a neck collar. Corticosteroids appear to benefit dogs with CSM, and anti-inflammatory dosages of prednisone are often used (0.5 to 1.0 mg/kg q 12–24 hrs) progressively tapering the dosage over the course of 2–3 wks. In some patients, dexamethasone appears to elicit a better response, and so it can be used for more severely affected patients or as a rescue therapy for dogs with sudden deterioration. Only low doses of

dexamethasone should be used, usually 0.1 mg/kg and never more than 0.25 mg/kg q 24 hrs. The severe complications reported with dexamethasone use were seen mainly when much higher dosages were used (2 mg/kg/day). Corticosteroids, particularly dexamethasone, improve neurologic function in chronic spinal cord compression predominantly by decreasing vasogenic edema. Other proposed mechanisms include protection from glutamate toxicity and the reduction of neuronal and oligodendroglial apoptosis. Despite the potential benefits associated with corticosteroid therapy, the use of corticosteroids, particularly for long periods, can be associated with important adverse effects. Due to the possibility of gastrointestinal complications, omeprazole (0.7 mg/kg q 24 hrs) or famotidine (0.5 mg/kg q 12–24 hrs) often are used in conjunction with corticosteroid therapy. NSAIDs can be used in place of corticosteroids if neck pain appears to be a main component of the syndrome or if the adverse effects of the corticosteroids cannot be tolerated. One reason for the success with medical management is the slow progression of spinal changes associated with the disease. Surviving demyelinated axons also may remyelinate with treatment. Remyelination has been shown in the spinal cords of horses and humans with cervical myelopathy treated medically.

2. Surgical treatment is generally assumed as the treatment of election for CSM. As most affected dogs have spinal cord compression, decompressing the spinal cord would, in theory, lead to definitive treatment. The decision to recommend surgical treatment should, however, be based on several factors such as severity of neurologic signs, pain, type and severity of compressive lesion(s), response (or lack of response) to medical management, the short- and long-term expectations of the owner, and the presence of other concurrent neurologic or orthopedic problems, or extraneurologic diseases, such as dilated cardiomyopathy, that would affect the long-term outcome.

   The decision on the specific surgical technique can be complicated. Twenty-six surgical techniques have been proposed to treat CSM. They can be broadly divided into direct decompression (e.g. ventral slot), indirect decompression (e.g. pins and polymethyl methacrylate [PMMA]), and motion-preserving techniques. It is important to consider that a significant proportion of dogs worsen approximately 2–3 yrs after surgery. Therefore, whenever possible, the surgical technique should allow long-term postoperative imaging using MRI. All metallic implants, except those made of titanium, will cause significant artifacts, precluding the use of MRI. In general, as the source and direction of compression can be broadly divided into disc-associated or osseous-associated, general treatment recommendations can be made as follows:

3. *Disc-associated CSM*—disc-associated CSM is the most common form of CSM and the one with the largest number of surgical techniques proposed to treat it. Many, if not most, of the surgical techniques have been based on the concept of static or dynamic lesions, following stress or traction myelography, which is highly subjective. Nevertheless, the outcome for most surgical techniques is quite similar and generally positive. Ventral static compressions are usually treated with the traditional ventral slot or the inverted cone slot (Fig. 13.22). Dynamic compressions can be treated with distraction/stabilization techniques and the PMMA plug, or pins/screws combined with PMMA, are commonly used (Fig. 13.36). Multiple compressive sites can be treated with distraction/stabilization techniques, the most common one being distraction with a PMMA plug (Fig. 13.37). Dorsal laminectomy is an alternative for multiple ventral compressions. A newer alternative, which has the theoretical advantage of keeping the intervertebral mobility while allowing direct spinal cord decompression, is disc arthroplasty. This technique can also be used for multiple compressive lesions and it might be the ideal technique for dogs with three or more ventral compressive lesions (Fig. 13.38).
4. *Osseous compressions*—typically, these compressions are thought to be primarily static and, as such, direct decompression of the affected sites is recommended. This is typically achieved by dorsal laminectomy (Fig. 13.39), but can also be achieved by cervical hemilaminectomy. Another way to treat osseous lesions is by distraction/stabilization of the affected segments ventrally. Stabilization and fusion of the affected segments does not directly decompress the affected sites but eliminates the dynamic component of the spinal cord compression. The technique used in these cases is the PMMA plug.

e. Prognosis—the outcome of surgical treatment for disc-associated CSM is usually successful, with approximately 80% (70–90%) of dogs improving after surgery. No surgical technique stands out as being clearly superior, even for dogs with disc-associated CSM. In contrast to older studies, new reports on medical management indicate an improvement rate of approximately 50% (45–54%). Considering the

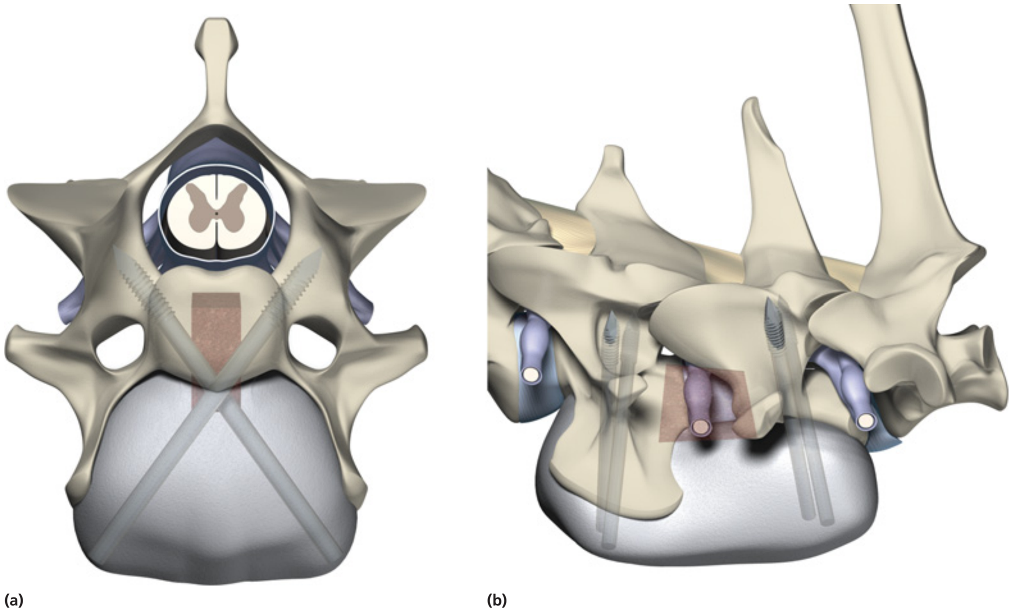


Figure 13.36 Representation of the technique of pins and polymethyl methacrylate combined with a partial slot. (A) Transverse view. Note the location of pin insertion avoiding the transverse foramina and vertebral canal. (B) Lateral view, showing the position of the pins. (The Ohio State University. Reproduced with permission.)

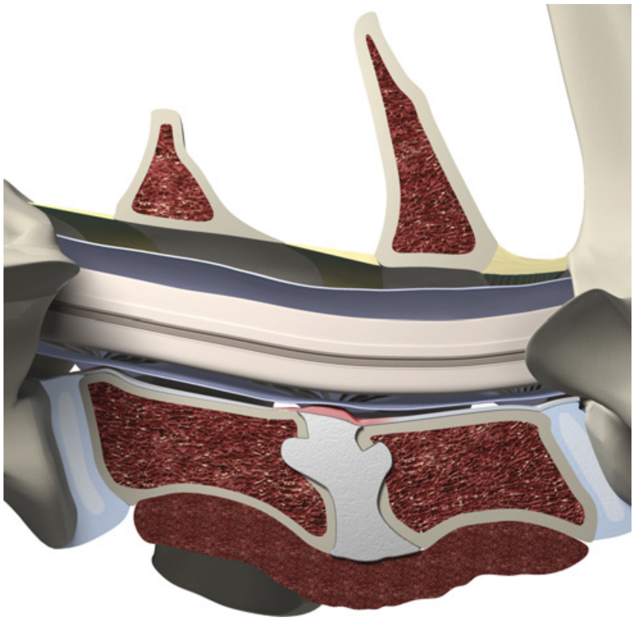


Figure 13.37 Polymethyl methacrylate plug distraction technique. (A) Representation of the plug is in place (gray). Two anchor holes in the cranial and caudal endplates prevent plug displacement. The dorsal annulus is left intact. Multiple small holes should be drilled in the ventral aspect of the vertebral bodies to promote incorporation of the cancellous bone graft (dark red) and fusion. (The Ohio State University. Reproduced with permission.)

success rate of surgical and medical treatments for CSM, surgery more consistently leads to clinical improvement, and should always be considered in the treatment of dogs with CSM. Surgery, however, does not alter the long-term survival of dogs with CSM. The survival time of 76 dogs (mostly large-breed dogs) with CSM (33 dogs treated surgically and 43 dogs treated medically) was found to be exactly the same (median survival time [MST] 36 mos), regardless of whether the dog was treated medically or surgically. Recent data on giant-breed dogs with osseous compressions indicate similar results, with MST of 41 and 33 mos, for dogs treated surgically and medically, respectively. This finding indicates that CSM continues to progress independent of the method of treatment, and that the clinical deterioration seen months

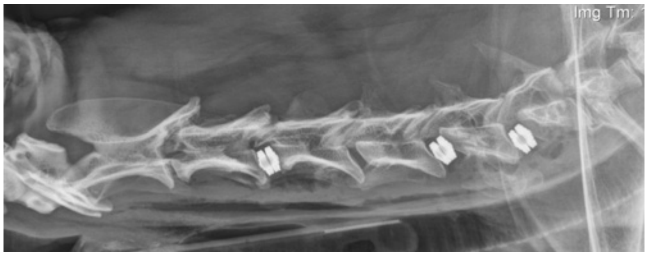


Figure 13.38 Postoperative radiograph of dog that underwent a three-level cervical disc arthroplasty for treatment of a multilevel disc-associated CSM. Prior to disc implantation all sites were decompressed with a dorsal annulectomy. The vertebral tipping noted at C6 was present preoperatively.

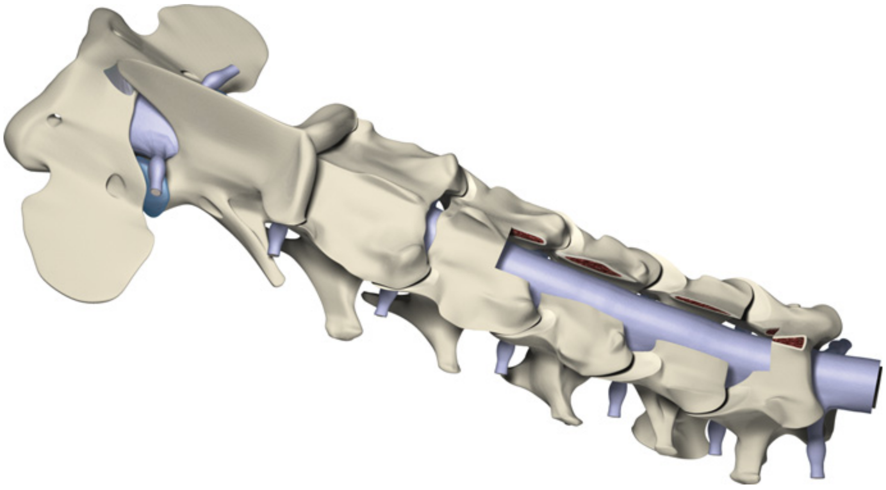


Figure 13.39 Representation of a dorsal laminectomy from C4 to C7. (The Ohio State University. Reproduced with permission.)

to years after treatment may not be due solely to failure of surgery or development of adjacent segment disease, which appears to occur in 20% of dogs (Fig. 13.40), but also may occur secondary to other mechanisms, such as apoptosis, that was recently shown to be present in the spinal cord of dogs with CSM.

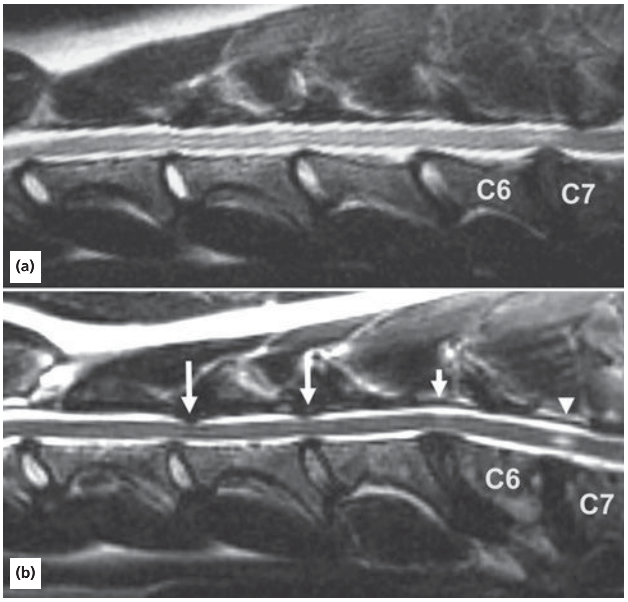


Figure 13.40 MR images of the cervical spine of a 7-yr-old Doberman Pinscher with CSM treated with ventral slot decompression at C6–C7. (A) Midsagittal T2-weighted image shows spinal cord compression and cord hyperintensity at C6–C7 before surgery. (B) Midsagittal T2-weighted image obtained 14 mos after the first MRI. Spinal cord compression is no longer visible at C6–C7, but cord hyperintensity is more evident (arrowhead). There are new areas of spinal cord compression at C5–C6 (ventrally) and at C3–C4 and C4–C5 dorsally (long arrows). Mild cord hyperintensity can be seen associated with the compression at C5–C6 (short arrow). (Da Costa and Parent 2007.[114] Reproduced with permission from American Veterinary Association.)

3. Degenerative myelopathy (DM)[15,17,26,39,49,88,90,91,166,218,255,256,259,285,306,307,315,331,363,366,371,397,402,424,438,500,532] (Video 26)
   a. This is a degenerative disease of unknown etiology primarily affecting the thoracolumbar spinal cord of medium- to large-breed dogs over 5 yrs of age. It has also been called degenerative radiculomyelopathy because of nerve-root involvement. Among the large-breed dogs, the German Shepherd and Boxers are the most commonly affected breeds. Several breeds were reported to have histologically confirmed DM, namely German Shepherd, Siberian Husky, Miniature and Standard Poodle, Boxer, Pembroke and Cardigan Welsh Corgis, Chesapeake Bay Retriever, Rhodesian Ridgeback, Bernese Mountain Dog, Kerry Blue Terrier, Golden Retriever, Wire-haired Fox Terrier, American Eskimo dog, Soft-coated Wheaten Terrier, and Pug. Pathologically, DM is a primary central axonopathy restricted to the spinal cord. Axon and myelin degeneration of the spinal cord occur in all funiculi but primarily in the dorsal aspect of the lateral funiculi and dorsal funiculi, in the absence of observable neuronal cell body degeneration or loss (Fig. 13.41). Hence the lesion description is best denoted as a segmental degeneration of the axon and associated myelin rather than Wallerian degeneration. The degeneration starts in the thoracic spinal cord region. Associations between low serum levels of certain vitamins (Vitamins B_{12} and E) have been made in some German Shepherd dogs with DM, but these associations have been questioned by subsequent studies. There has also been some speculation that this disorder may have an autoimmune basis; however, there is more recent evidence that an autoimmune etiology is unlikely. Another theory suggests a predisposition for spinal cord damage due to oxidative or metabolic disturbances in the thoracolumbar region, due to a

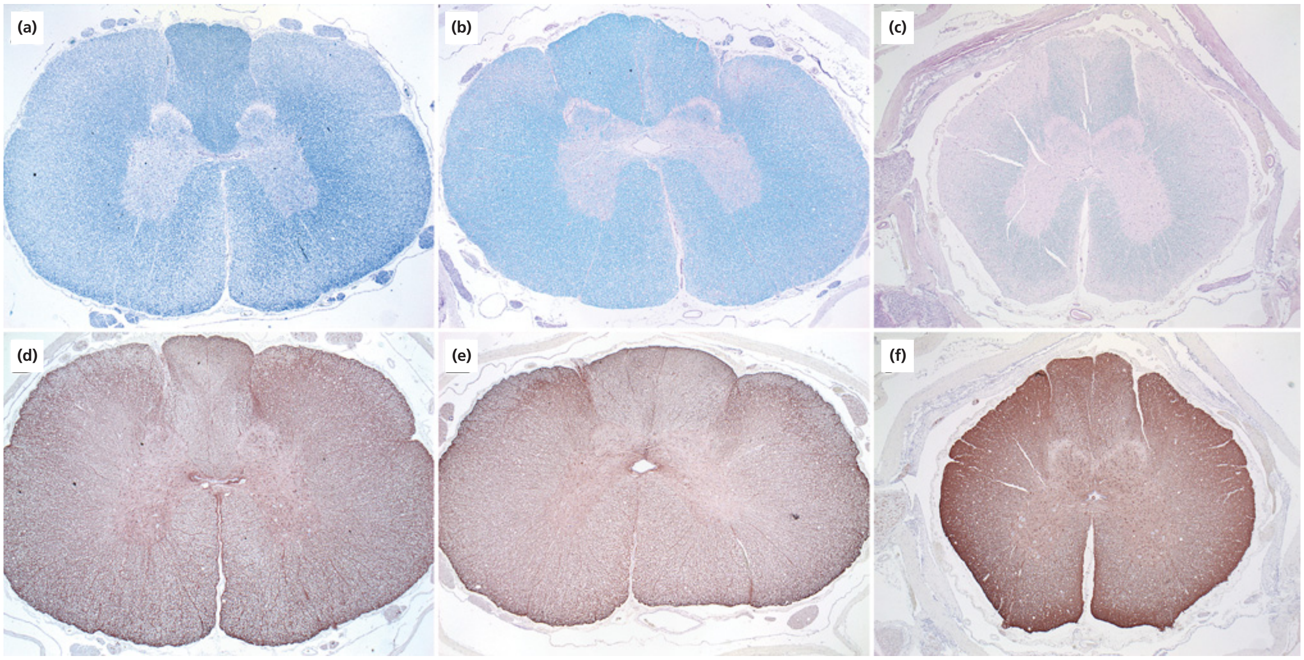


Figure 13.41 Histopathology of the thoracic spinal cord. Comparison of Luxol fast blue with a periodic acid-Schiff counterstain (LFB/PAS) staining (A, B, C) and immunohistochemistry detecting glial fibrillary acidic protein (D, E, F) from a normal unaffected 14.5-yr-old Pembroke Welsh Corgi (PWC) (A, D), a 10-yr-old PWC with clinical signs of DM for 6 mos and mild paraparesis and pelvic limb ataxia (B, E), and a 14-yr-old PWC with clinical signs of DM for 48 mos and flaccid tetraplegia (C, F). Myelin loss in the white matter is depicted by loss of blue color with LFB (B, C). Note the severity of pallor in the white matter and increased areas of astrogliosis in the PWC with longer disease duration. (Coates JR, Wininger FA. Canine degenerative myelopathy. *Vet Clin North Am Small Anim Pract.* 2010;40:929–950. Reproduced with permission from Elsevier.)

relative lack of vascular supply (in comparison with other regions of the central nervous system [CNS]). One study identified histopathologic evidence of neuronal degeneration and loss in various brain regions of dogs with DM, suggesting secondary axonal degeneration as a possibility (e.g. Wallerian degeneration). Recently, a mutation in the superoxide dismutase 1 (*SOD1*) gene has been shown in some affected dogs. The discovery of this mutation, which is also found in amyotrophic lateral sclerosis (Lou Gehrig's disease) of people, has made DM to be considered as a model for the human disease. However, there are significant clinical and pathologic differences between the canine and human disease. The genetic aspect of DM is still unclear, mostly because of the late onset of the disease. Familial reports of DM have been reported in the Siberian Husky, Pembroke Welsh Corgi, Chesapeake Bay Retriever, Rhodesian Ridgeback, and Boxer.

b. The clinical picture typically consists of a slowly progressive, nonpainful T3–L3 myelopathy in a middle-aged to older large-breed dog, usually of the German Shepherd breed. Age of onset of neurologic signs is usually 5 yrs or older with a mean age of 9 yrs in large-dog breeds with DM. Most dogs are at least 8 yrs of age at onset of clinical signs. The mean age of affected Pembroke Welsh Corgis was 11.2 yrs in one study. There appears to be a female predominance (1.6:1) for the disease in Corgis but not in other breeds. Loss of pelvic limb proprioceptive ability (ataxia, toe-dragging) is noticed initially, followed by a gradual loss of voluntary motor function. Spinal reflexes in the pelvic limbs are typically normal to hyperreflexive. Decreased to absent patellar reflexes are found in approximately 10–15% of patients, however, and may reflect selective damage to dorsal lumbar nerve roots in these dogs. The extensor tone of these dogs is always increased in the earlier phase of the disease, which suggests that the patellar areflexia is a sensory, rather than LMN, disturbance. Pelvic limb tremors may be present during weight support. Late in the disease process, urinary and/or fecal incontinence may develop. Dogs often develop disuse atrophy of the pelvic limb musculature over time. The disease usually progresses over a 6- to 12-mo period (longer in small dogs like Corgis), at which time most owners elect for euthanasia, due to the nonambulatory status of the affected patient (Fig. 13.42). The disease can progress to involve the thoracic limbs and eventually the brain stem in dogs kept alive after this degree of deterioration.

c. A tentative diagnosis is based upon signalment, clinical features, and exclusion of other spinal cord disorders with imaging. Patients with DM typically have

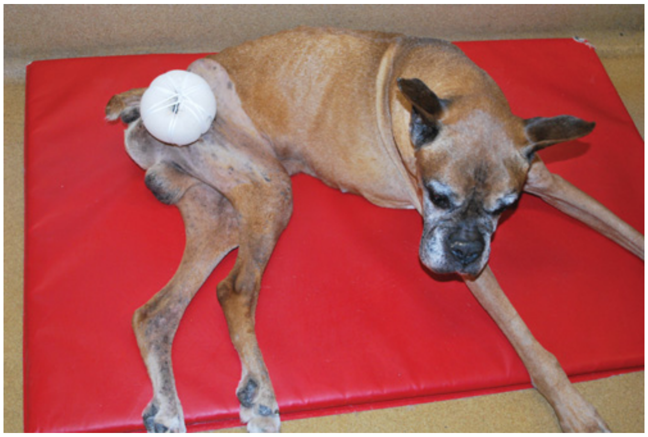
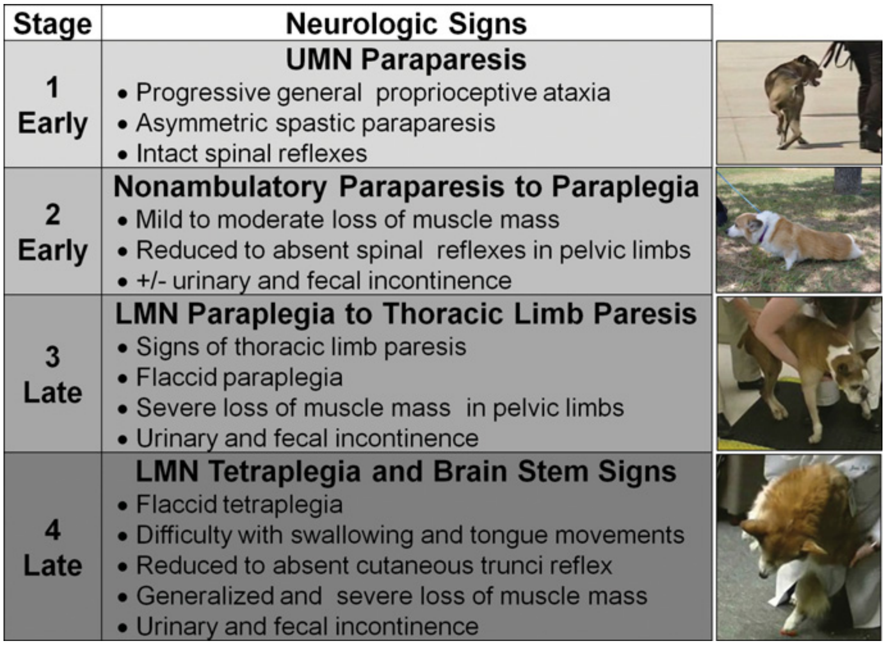


Figure 13.42 Boxer with suspected late-stage degenerative myelopathy. The dog was nonambulatory tetraparetic with severe muscle atrophy in pelvic limbs. Figure shows a protective "doughnut" shape bandage over the hip area.

normal CSF results, or increased protein levels with a normal cell count. In one study, lumbar-derived CSF concentrations of myelin basic protein (MBP) in German Shepherd dogs (measured via a commercially available ELISA test for humans) with DM were significantly higher than concentrations in control dogs. Spinal imaging (myelogram, MRI, CT) is typically normal, but some dogs may have concurrent mild type II disc lesions that are probably clinically insignificant. In one study of CT myelography performed in dogs with DM, a number of abnormalities were identified when compared with normal dogs, including vertebral canal stenosis, deformed spinal cord, small spinal cord, focal attenuation of the subarachnoid space, and paraspinal muscle atrophy. Some clients are reluctant to pursue advanced imaging when DM is one of the differentials, because of the poor prognosis associated with it. In these cases a corticosteroid trial might be useful. Corticosteroids will typically lead to improvement in dogs with compressive myelopathies, but will not benefit dogs with DM. A DNA test based on the *SOD1* mutation is commercially available. The dogs homozygous for the mutation are at risk of developing DM and will contribute one chromosome with the mutant allele to all of their offspring. The heterozygotes are DM carriers that are unlikely to develop clinical DM but could pass on a chromosome with the mutant allele to half of their offspring. The normal homozygotes are unlikely to develop DM and will provide all of their offspring with a protective normal allele. Thus, the *SOD1* DNA test is of potential use to dog breeders wishing to reduce the incidence of DM in the breed or line. Coates and Winninger proposed a scheme with clinical progression and diagnosis shown on Fig. 13.43.[91] A definitive diagnosis of DM is based upon characteristic histopathologic lesions in the spinal cord at necropsy.

d. Vitamin supplementation, glucocorticoid administration, and treatment with the protease inhibitor aminocaproic acid have all been advocated as potential therapies, in addition to myriad other putative treatments for the disease. However, none of these treatments has been shown to alter the progression of the disease. Aminocaproic acid is commonly used, despite its lack of confirmed efficacy, at a dose regimen of 15 mg/kg PO, q 8 hrs. The long-term prognosis is poor,



Stage	Neurologic Signs
1 Early	**UMN Paraparesis** • Progressive general proprioceptive ataxia • Asymmetric spastic paraparesis • Intact spinal reflexes
2 Early	**Nonambulatory Paraparesis to Paraplegia** • Mild to moderate loss of muscle mass • Reduced to absent spinal reflexes in pelvic limbs • +/- urinary and fecal incontinence
3 Late	**LMN Paraplegia to Thoracic Limb Paresis** • Signs of thoracic limb paresis • Flaccid paraplegia • Severe loss of muscle mass in pelvic limbs • Urinary and fecal incontinence
4 Late	**LMN Tetraplegia and Brain Stem Signs** • Flaccid tetraplegia • Difficulty with swallowing and tongue movements • Reduced to absent cutaneous trunci reflex • Generalized and severe loss of muscle mass • Urinary and fecal incontinence

Figure 13.43 Classification scheme of clinical signs for *SOD1* associated canine degenerative myelopathy (DM). Dogs with DM follow a pattern of clinical signs which initially begins with upper motor neuron (UMN) pelvic limb paresis and GP ataxia to progress to lower motor neuron (LMN) weakness and then involve the thoracic limbs. Smaller breeds with DM may have a slower disease progression when compared to larger breeds. (J. Coates, University of Missouri, Columbia, MO, 2014. Reproduced with permission of J. Coates.)

and most dogs are euthanized due to severe pelvic limb dysfunction within 6–12 mos. In the study of Pembroke Welsh Corgis, the average time from diagnosis to death was 1.25 yrs. Although exercise has been traditionally recommended in cases of DM, there has been a lack of objective evidence to substantiate this recommendation. In one retrospective study of dogs with suspected DM, however, intensive daily controlled physical therapy—including walking, passive range of motion of the pelvic limbs, massage of pelvic limb and paraspinal muscles, and hydrotherapy—was shown to significantly improve mean survival time (255 days), compared with dogs receiving moderate physiotherapy (130 days) or no physiotherapy (55 days).

4. Extradural synovial cysts[149, 176, 295, 417, 451, 546]
   a. A number of dogs have been reported in which single or multiple protrusions of cystic tissue from the intervertebral articular facet joints resulted in clinical signs of myelopathy or cauda equina dysfunction. There are a number of other terms used to describe this disorder, including intraspinal synovial cyst, extradural spinal juxtafacet cysts, and ganglion cysts. Technically, a ganglion cyst is separate from a synovial cyst as it is a fibrous or collagenous cyst associated with the articular processes (facets) that does not have a synovial lining and contains myxoid or mucinous material. It is generally believed that ganglion cysts and synovial cysts represent variations of the same clinical disease process. In addition, the term degenerative intraspinal cyst has also been proposed as an encompassing term to include cysts that arise from ligamentous structures (e.g. yellow ligament) and the intervertebral discs that do not fit the histologic description of synovial or ganglion cysts. All of these extradural cysts are believed to have similar clinical presentations, as well as identical treatment options and prognoses. Multiple cervical cysts tend to occur in young, giant-breed dogs (e.g. Mastiff, Great Dane), whereas single thoracolumbar or lumbosacral cysts are more likely to occur in older large-breed dogs (e.g. German Shepherd dog, German Shorthaired Pointer). These protrusions are typically dorsolateral, primarily causing an axial deviation of the spinal cord or cauda equina. The etiology of this disorder is unknown, but is most likely associated with degenerative change in the articular facet joint, with subsequent protrusion of collagenous periarticular joint tissue with or without synovium through a weakened joint capsule. Transitional lumbar vertebrae have been associated with these cysts in the lumbosacral region.
   b. In addition to the breeds mentioned above, extradural synovial cysts have been reported in the following breeds: Boxer dog, Border Collie, Irish Setter, Siberian Husky cross, and Boerboel (South African dog resembling a Mastiff). An extradural cyst arising from the annulus fibrosus was also described in a Rottweiler. Clinical signs of myelopathy correlate to the location of the cystic lesions. The progression of clinical signs has been reported to vary from several days to a year, with most cases progressing over several months.
   c. Tentative diagnosis depends upon imaging findings, with MRI (Fig. 13.44) being preferable to

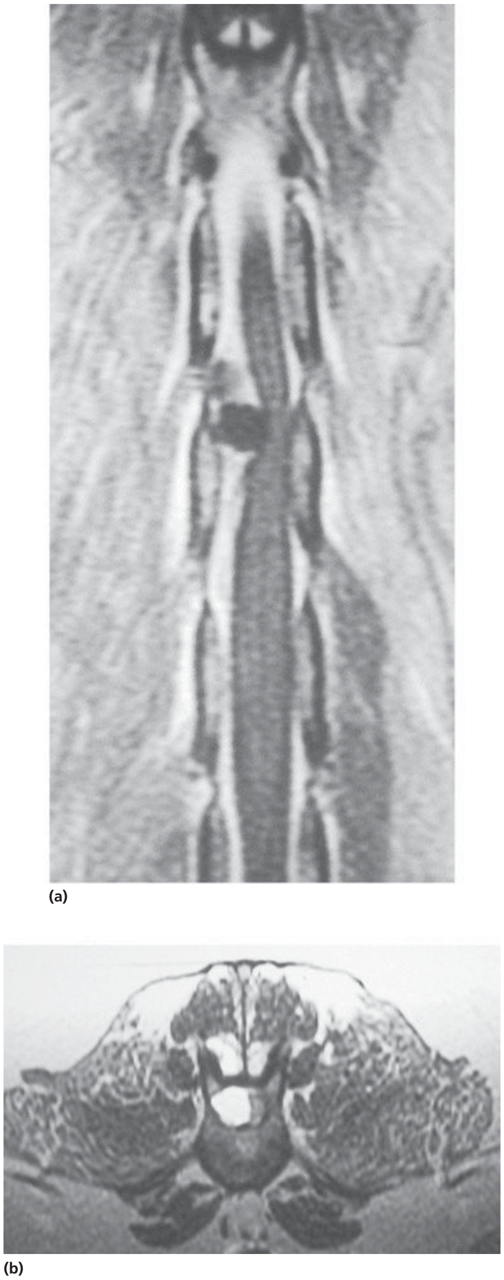


Figure 13.44 Dorsal T1-weighted (A) and transverse (B) MRIs of a dog's lumbar vertebral region, showing an extradural synovial cyst. (Dr. Jason Berg, 2014. Reproduced with permission from Dr. Jason Berg.)

myelography or CT. Degenerative changes in the facet joints are typically evident on plain radiography, and myelography typically reveals axial deviation of the spinal cord by the cystic structures, best visualized on ventrodorsal views. Myelography will verify an extradural mass, but will not identify the mass as cystic, making it difficult to discern from other extradural compressive diseases. A consistent CSF finding for this disorder is elevated protein levels with normal cell count, but a mild pleocytosis can occur. Definitive diagnosis requires a histopathologic examination of the cysts.

d. Surgical treatment of this disorder involves laminectomy (dorsal laminectomy or hemilaminectomy) and removal of the compressive synovial cyst(s). The prognosis for recovery with surgical management appears to be excellent.

5. Vertebral articular process (facet) hypertrophy[24, 264, 348, 413]

a. Hypertrophy of the vertebral articular processes (facets) in both the cervical and thoracolumbar region has been identified in dogs as a degenerative process that can lead to pain and/or signs of myelopathy as an independent entity. Although facet joint hypertrophy is often documented both as a component and as a potential consequence of other degenerative spinal disorders (e.g. type II disc protrusion, CSM), it has been documented to cause spinal cord disease in the absence of these other disease processes. It is generally thought that malarticulation between the cranial and caudal articular processes leads to joint instability and progressive hypertrophy. Theories proposed to account for such a malarticulation include trauma, prior (i.e. resolved) infection, and congenital malformation. The most likely explanation for this phenomenon is congenital malformation. Specifically, caudal vertebral articular process dysplasia or aplasia has been documented in dogs that have developed articular process (facet) hypertrophy in the thoracolumbar region. The chronic instability caused by congenitally abnormal articular processes is thought to lead to progressive hypertrophy of the facet region (in addition to adjacent soft tissue structures like the yellow ligament and synovium) over time.

b. Breed-associated vertebral articular process (facet) hypertrophy has been described in Shiloh Shepherd dogs (five dogs) and Scottish Deerhounds (nine dogs). The Shiloh Shepherd dogs were young, ranging in age from 3.5 mos to 16 mos, and had one or more compressive articular process hypertrophy lesions in the region from T11–L2 vertebrae. All of these dogs presented with clinical signs of a progressive T3–L3 myelopathy (paraparesis, pelvic limb ataxia). The dogs were closely related, and three of them were littermates. The Scottish Deerhounds were young adults, between 3 and 6 yrs of age, and all presented with severe neck pain without neurologic deficits. Unilateral or bilateral articular process hypertrophy at the C2/C3 space was documented in all dogs. In addition to these cases, similar articular process (facet) hypertrophy in the thoracolumbar region has been described in a 6-yr-old Great Dane, two German Shepherd dogs (10 mos and 2 yrs of age), a 4-yr-old mixed-breed dog, and a 10-mo-old Cavalier King Charles Spaniel (CKCS). In one of the German Shepherd dogs, the abnormal facet joint was an incidental finding. In the remainder of the cases, a progressive T3–L3 myelopathy was described.

c. Tentative diagnosis of this condition is based on spinal imaging. Although these lesions are typically evident on radiographs and myelography, CT (Fig. 13.45) and MR imaging provide more detail regarding the extent of spinal cord compression. In the Scottish Deerhound disorder, no evidence of spinal cord compression was evident on myelography, suggesting that the pain was emanating from the abnormal facet joints. Definitive diagnosis is via histopathologic evaluation of the abnormal articular process (facet) tissue, documenting degenerative joint disease.

d. In the Scottish Deerhound disorder, intra-articular injection (of affected joints) of corticosteroid (10 mg triamcinolone acetonide per joint) and lidocaine (20 mg per joint) was effective in relieving neck pain in 8/9 dogs. Seven dogs remained free of clinical signs for more than 4 mos with this treatment. For the other dogs with evidence of spinal cord compression, surgical decompression and removal of the abnormal facet tissue appears to be the most reasonable approach. Although based upon a limited number of cases, the surgical success rate for this disease process appears to be high.

6. Hypoplasia or aplasia of the caudal articular processes[173, 413, 548]

a. This is a disease reported recently in Pugs, although the disease was also reported in a Pomeranian and other breeds. Affected dogs appear to be born with aplastic or hypoplastic articular processes over the thoracolumbar region (centered between T9 and L2). The abnormally formed articular processes were proposed to cause microinstability resulting in a fibrous constrictive myelopathy involving the dura mater. Interestingly, this congenital anomaly is also found in clinically normal Pugs; therefore, the actual significance of this malformation remains to be clearly established in a broader patient population of normal and affected Pugs.

b. Affected Pugs had an age of 7.7 yrs at the time of diagnosis (range 2–11 yrs). Dogs presented with a chronic

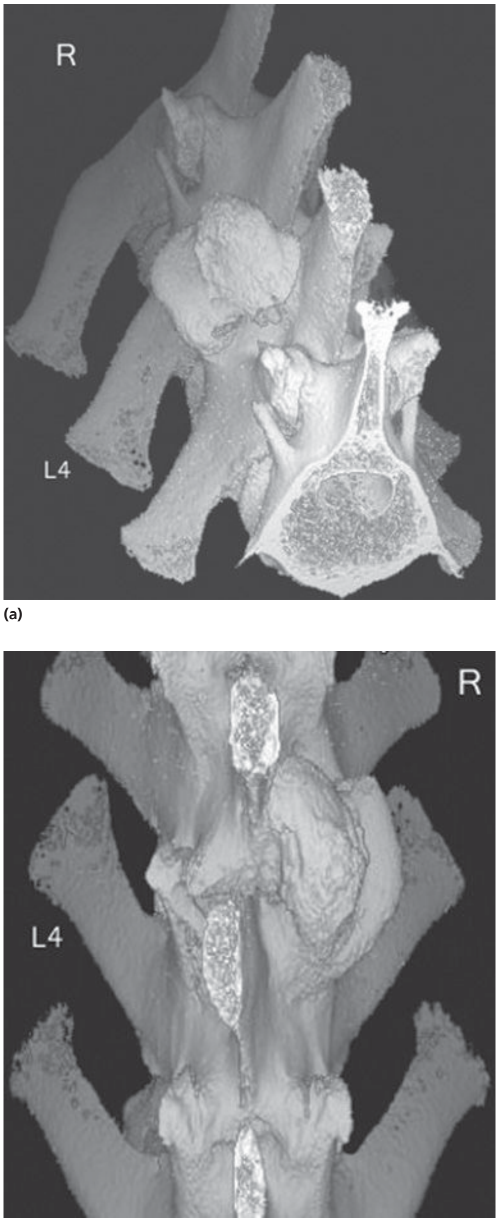


Figure 13.45 Three-dimensional CT reconstructions of the midlumbar vertebrae of a dog with vertebral articular process (facet) hypertrophy at L3/L4, viewed from right craniodorsally (A) and dorsally (B). (Dewey *et al.* 2007.)[146]

progressive history of proprioceptive ataxia and paraparesis. None of the dogs had spinal pain on palpation, which seems a consistent feature of this disease. One-third of the dogs had a history of fecal and/or urinary incontinence.

c. Diagnosis can be established based on the lack of articular processes on radiographs (Fig. 13.46). Considering that the anomaly can be found in clinically normal dogs, either MRI or CT myelogram needs to be used to confirm the diagnosis. The microinstability can also lead to the formation of arachnoid diverticula. Three-dimensional CT is useful to visualize the malformation.

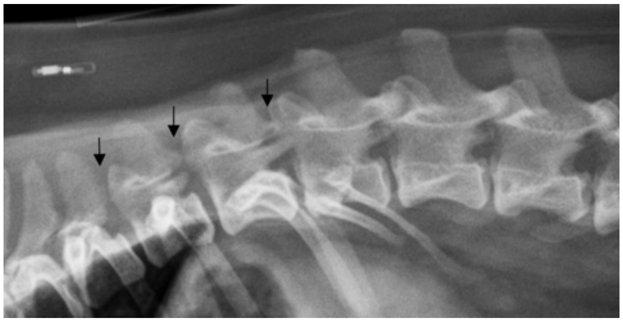


Figure 13.46 Lateral radiograph of a Pug dog with hypoplasia of the caudal articular processes (arrows). Compare with affected sites with regions T13–L1 and L1–L2.

d. Dogs can be treated medically or surgically. The prognosis of affected dogs with the constrictive fibrotic myelopathy is guarded. All dogs treated with surgical decompression showed no clinical improvement.

7. Rottweiler leukoencephalomyelopathy[83, 125, 197, 235, 285, 488, 500, 563]

   a. This is a progressive, nonpainful demyelinating disease of unknown etiology reported in young adult (1.5–4 yrs of age) Rottweilers and a Rottweiler crossbred dog. This disease is classified as a leukodystrophy, a CNS white-matter disorder characterized by abnormal myelin synthesis and/or maintenance. The mode of inheritance is suspected to be autosomal recessive.
   b. Clinical signs are suggestive of a slowly progressive cervical myelopathy. Hypermetria is often more pronounced in the thoracic limbs, while conscious proprioceptive deficits are often more obvious in the pelvic limbs. The tetraparesis slowly worsens over 6 to 12 mos.
   c. A tentative diagnosis is based upon signalment, history, and clinical signs. Recently, the MRI findings were reported for this disease and, as such, MRI can be used to confirm the diagnosis, as well as rule out other causes of cervical myelopathies (Fig. 13.47). Results of other tests such as CSF analysis, radiography/myelography, and electrodiagnostic studies are normal with this disease. Histopathologically, symmetrical demyelinating lesions are seen in the spinal cord (especially cervical), brain stem, optic nerves and tracts, and the cerebellum. Despite the cerebellar lesions, these dogs typically do not exhibit classic features of cerebellar dysfunction. In another disease of Rottweilers, neuroaxonal dystrophy, clinical signs of cerebellar dysfunction are common; neuroaxonal dystrophy is discussed in Chapter 12.
   d. There is no effective treatment available for this disease and the prognosis for recovery is poor.

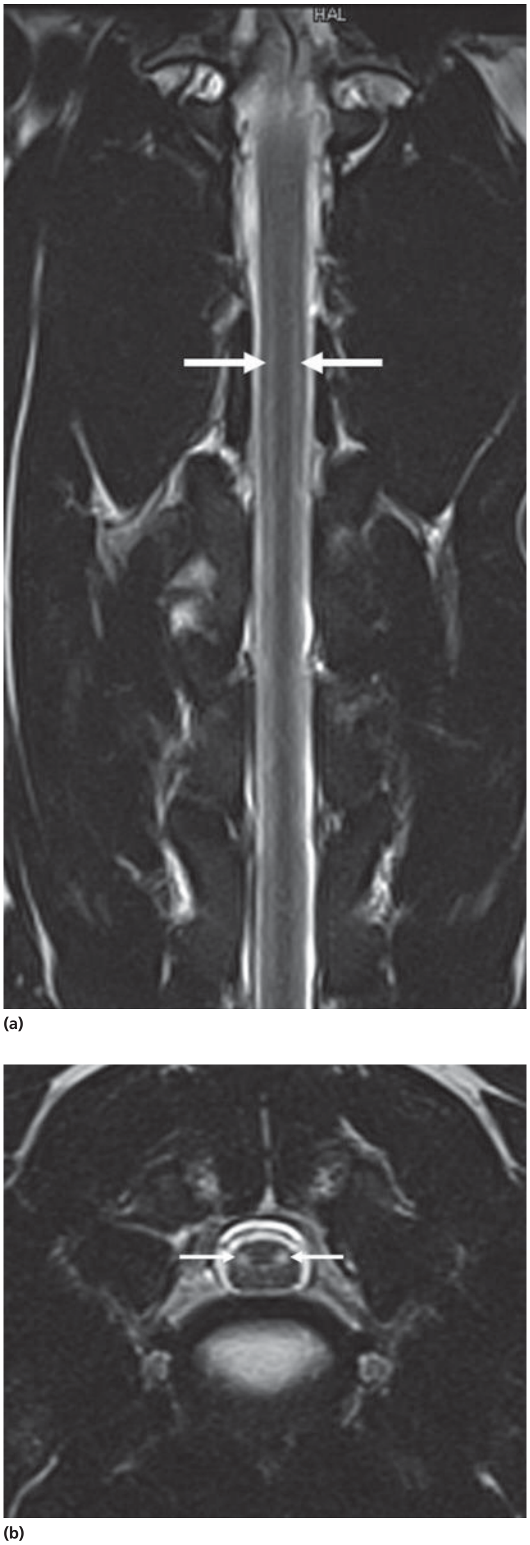


Figure 13.47 MR images of a dog with Rottweiler leukoencephalomyelopathy. (A) Dorsal T2-weighted MR image showing the bilateral areas of linear hyperintensities (arrows). (B) Transverse T2-weighted image, showing the focal hyperintensities in the dorsolateral funiculi. (Hirschvogel *et al.*, 2013.[235] Reproduced with permission from BioMed Central.)

8. Afghan hound hereditary myelopathy[16,92,105,285,328,500,532]
    - a. A rapidly progressive leukodystrophy has been described in young (3- to 13-mo-old) Afghan Hounds with an autosomal recessive mode of inheritance.
    - b. Clinical signs are initially consistent with either a C6–T2 or a T3–L3 myelopathy. These patients typically present with a symmetrical paraparesis and may display a “bunny-hopping” gait. Within 1–3 wks, these dogs become paraplegic and some may become tetraparetic or tetraplegic. Respiratory dysfunction can subsequently occur and lead to death, if euthanasia is not performed prior to this development.
    - c. Other than elevated CSF protein levels in some dogs with this disease, results of diagnostic tests are normal. A tentative diagnosis is based upon signalment and clinical findings. Histopathologically, there is bilaterally symmetrical vacuolation of spinal cord white matter with extensive myelin loss from caudal cervical to lower lumbar segments. There may be lesions in the brain-stem area, but there is no clinical evidence of brain-stem disease.
    - d. There is no treatment for this disease and the prognosis is poor. A similar disorder has been reported in Kooikerhondje dogs.
9. Other leukodystrophies[340,432,500,532]
    - a. Leukodystrophies resulting in clinical signs of spinal cord dysfunction have been reported in young Dalmatians and Miniature Poodles. A rare disorder called fibrinoid leukodystrophy has been sporadically reported in a number of young dogs. Dogs with this latter disease typically show signs of brain and spinal cord dysfunction. Histologically, astrocytic inclusion bodies, called Rosenthal fibers, are seen in dogs with fibrinoid leukodystrophy. Recently, a leukoencephalomyelopathy was reported in Border Terrier dogs. Even though the spinal cord was affected (Fig. 13.48), the predominant clinical signs were generalized tremors.
    - b. In general, no treatments are available for these progressive diseases, and prognosis is poor. Some diseases previously classified as leukodystrophy/spongy degeneration have subsequently proved to be mitochondrial disorders or organic acidurias, some of which may respond to therapy. These disorders are discussed in more detail in Chapter 7.
10. Hereditary ataxia of Jack Russell and Smooth-coated Fox Terriers[40,221,500,549]
    - a. This is a rare, presumably inherited, disorder in which spinal cord axons and myelin in the cervical and thoracolumbar areas undergo progressive degeneration. This is thought to be predominantly an axonopathy and has been reported in Parson Russell Terriers, Jack Russell Terriers, and Fox Terriers. A similar

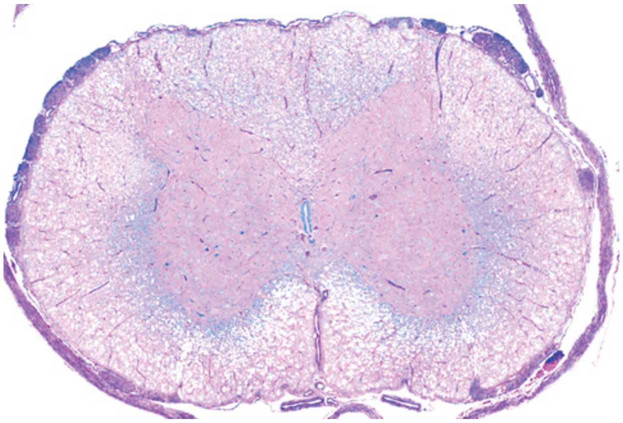


Figure 13.48 Spinal cord from a Border Terrier with leukoencephalomyelopathy. Note severe demyelination and spongiform degeneration in all funiculi, worse in the ventral funiculi (Luxol fast blue 2x).

pathologic condition has been described in Ibizan Hounds. Lesions in central auditory pathways have also been described, most notably in the lateral lemniscus and trapezoid body.

b. Clinical signs begin with pelvic limb ataxia at 2–9 mos of age, and eventually all four limbs are affected. The dysmetric gait and occasional intention tremor are more suggestive of cerebellar dysfunction than a myelopathy. It is suspected that the lesion responsible for the characteristic spastic gait is in the spinocerebellar tracts of the cervical spinal cord. There is no clinical evidence of hearing impairment. Clinical signs often worsen with activity and excitement, and muscle fasciculation may be observed. In one study of 35 affected Jack Russell Terriers, other clinical abnormalities included generalized seizures (13 dogs), respiratory distress (seven dogs, after minimal exercise), exercise intolerance (11 dogs), and behavior changes (seven dogs, aggression or anxiety). Focal or generalized seizures were also described in Ibizan Hounds with a similar disorder.

c. A tentative diagnosis is based upon characteristic signalment and clinical features, in addition to normal imaging and CSF results. Abnormal brainstem auditory evoked response test results have been described in some Jack Russell Terriers with this disorder. Definitive diagnosis is based upon characteristic histopathologic features of the brain and spinal cord post mortem.

d. There is no treatment for this disorder and the prognosis is guarded to poor. The disease is slowly progressive and may stabilize. Affected animals may have a good quality of life, despite the gait abnormalities. In the study of 35 Jack Russell Terriers, clinical signs worsened in 34 dogs, necessitating euthanasia at an average of 16 mos following presentation.

11. Labrador Retriever axonopathy[132, 500]
   a. This is a recently described degenerative disease of young (3- to 4-wk-old) Labrador Retrievers, presumably of autosomal recessive inheritance. Progressive axonal degeneration occurs throughout the spinal cord, as well as in the brain stem and cerebellum. Abnormal development of the corpus callosum is a consistent feature.
   b. Clinical signs begin with pelvic limb ataxia and paresis that rapidly progresses to a dysmetric tetraparesis. Some dogs display intention tremors. Most dogs cannot rise without assistance by 3–5 mos of age. Signs are suggestive of cerebellar and spinal cord disease.
   c. Most dogs progress to a nonambulatory status by 5 mos of age. There is no effective treatment and the prognosis is poor.
12. Golden Retriever axonopathy and neuronopathy[119]
   a. This is a novel disease of Golden Retrievers. It affects both the white and the gray matter of the spinal cord. The distribution of the lesion was unique affecting the lateral and ventral funiculi of the spinal cord but sparing the dorsal funiculus (Fig. 13.49). Severe neuronopathy (cell body involvement) was also seen.
   b. Affected dogs presented with a progressive history of weakness between 3 and 8 mos of age. In spite of the spinal cord lesion in the lateral funiculus, proprioceptive ataxia was not seen. Instead, the dogs showed marked tetraparesis with a kyphotic posture (Fig. 13.50). It appears that the involvement of the motor neurons in the ventral gray matter prevails over the white-matter signs.
   c. Prognosis is poor as the disease continues to progress.
13. Leonberger leukoencephalomyelopathy[393]

This condition was seen recently in two Leonberger dogs. Affected dogs were young adult dogs (2 yrs old) and the

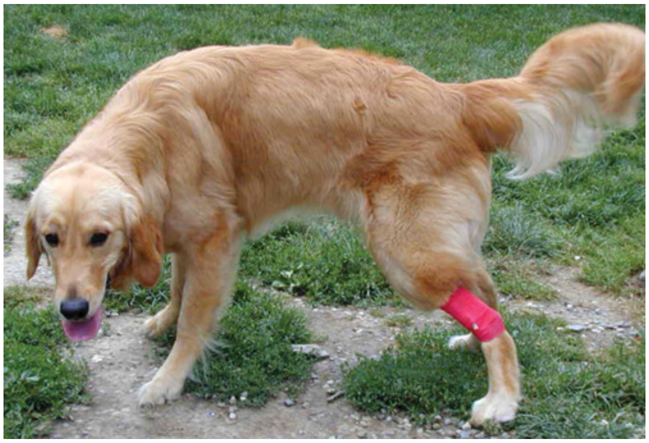


Figure 13.49 Eight-month-old Golden Retriever dog affected with multisystem axonopathy and neuronopathy. Observe the kyphotic posture indicating axial weakness.

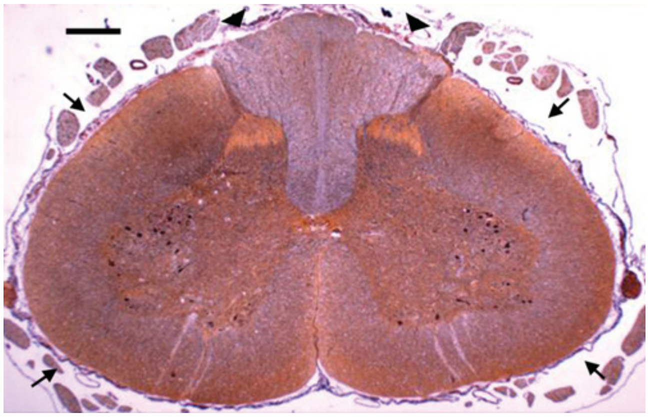


Figure 13.50 Spinal cord from a dog with multisystem axonopathy and neuronopathy. Observe the symmetry of the lesion in the lateral and ventral funiculi (arrows) and the sparing of the dorsal funiculi (arrowheads). The reactive astrocytes that are replacing the degenerate axons stain brown in the peripheral portions of the lateral and ventral funiculi (arrows). Bielschowsky stain. Scale bar = 0.5 mm. (From da Costa *et al.*, 2009.[119])

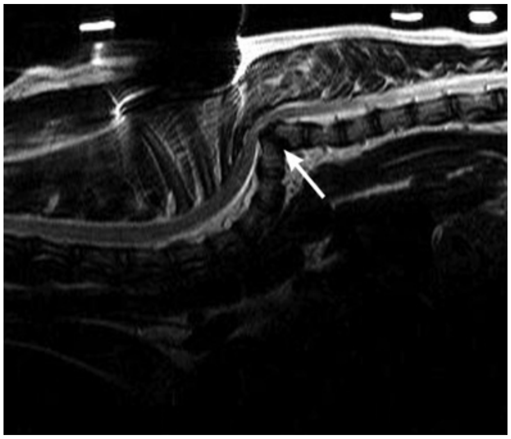


Figure 13.51 Sagittal T2-weighted MR spinal image of a French bulldog with severe kyphotic deformity and ventral spinal cord compression (arrow). (Westworth and Sturgess, 2010.[550] Reprinted with permission from Elsevier.)

clinical picture was dominated by ataxia and dysmetria of all limbs. A remarkable feature in these cases is that the spinal cord lesions could be seen on MRI similar to those seen in the Rottweiler leukoencephalomyelopathy (Fig. 13.47). The lesions were in the dorsolateral funiculi of the cervical spinal cord and were primarily demyelinating, as seen in cases of leukoencephalomyelopathy in Rottweilers. The disease is progressive and there is no treatment.

14. Lysosomal storage diseases
    a. Lysosomal storage diseases typically cause signs of a progressive multifocal encephalopathy and/or myelopathy in a young (2- to 6-mo-old) animal. Occasionally, clinical signs of a progressive myelopathy predominate. Examples are globoid cell leukodystrophy (Krabbe's disease) in dogs and mucopolysaccharidosis in cats. Lysosomal storage diseases are discussed in Chapter 7.
    b. The prognosis is poor in most cases. Sometimes, decompressive surgery in cases of mucopolysaccharidosis (with malformed vertebrae impinging on the spinal cord) will be successful.
15. Motor neuron diseases
    While this group of diseases technically falls under spinal cord disorders, they result in LMN signs and are discussed in Chapter 17.

B. Anomalous/developmental

1. Congenital vertebral malformations[8,23,31,95,142,205,223,244,247,269,287,308,345,419,429,439,454,455,461,482,492,516,550,551]
    a. Many vertebral malformations are discovered incidentally and do not cause clinical problems. Some malformations may lead to spinal cord damage and clinical signs of dysfunction by static or progressive (i.e. as the patient grows into adulthood) spinal stenosis and/or vertebral instability caused by the abnormal vertebra or vertebrae. The commonly reported vertebral malformations are:
        1. Hemivertebra (Fig. 13.51)—part of the vertebra fails to form properly, usually the vertebral body. The abnormal vertebra usually has a wedge shape. If the central part of the vertebra fails to form, a type of hemivertebra called butterfly vertebra may result. Hemivertebrae are seen most commonly in the screw-tail breeds (e.g. English and French Bulldogs, Boston Terriers, Pug dogs, etc.), but have also been described in a number of other toy- and miniature-breed dogs. The mid-thoracic region of the vertebral common is most commonly affected, with the T8 vertebra being commonly involved. The malformed vertebrae lead to varying degrees of abnormal angulation of the spine, including kyphosis, lordosis, and scoliosis. In addition to the compression of the spinal cord at the level of the malformation, instability is thought to play a role in the development of myelopathy in clinically affected dogs.
        2. Block vertebra (Fig. 13.52)—this is a failure of segmentation leading to a combined vertebra, composed of what should have been two or more single vertebrae.
        3. Spina bifida (Fig. 13.53)—this refers to a failure of fusion of the dorsal parts of the vertebra. This may occur alone and cause no clinical signs of dysfunction, but is often associated with meningeal and/or spinal cord malformations (e.g. meningocele, myelomeningocele). English Bulldogs and Manx cats appear to be predisposed to this disorder.

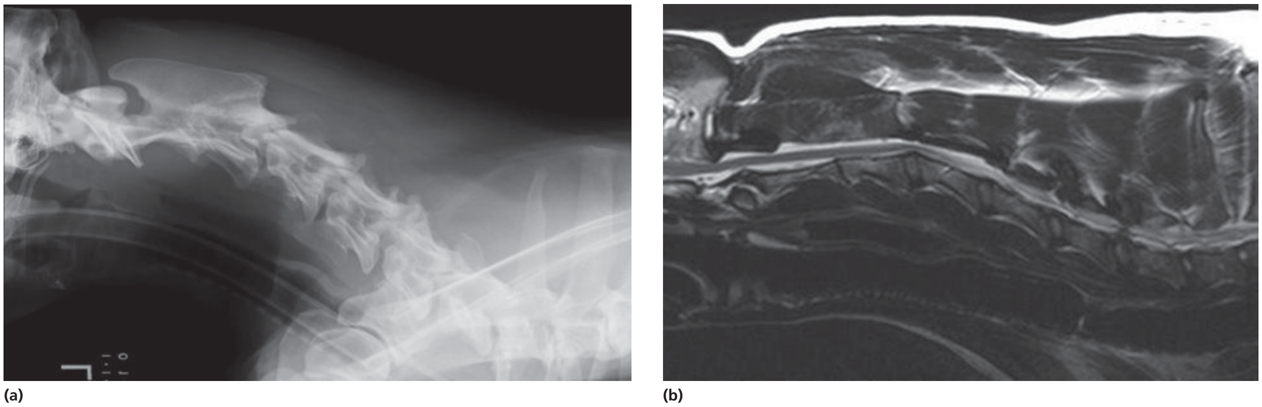


Figure 13.52 Lateral radiographic (A) and sagittal MR (B) images of a dog with a block vertebra in the cervical spine (C2–C3). (Dr. Jennifer L. Bouma, DACVR, 2014. Reproduced with permission of Dr. Jennifer L. Bouma.)

4. Stenotic vertebral canal—this can occur in association with other anomalies (e.g. hemivertebra) or as an isolated vertebral malformation. Relative stenosis refers to canal narrowing that does not cause compression of neural tissue, whereas absolute stenosis means that the stenosis does compress parenchymal tissue. Doberman Pinschers often have a relative stenosis of the cranial thoracic vertebrae (usually T3–T6). Absolute stenosis of cervical vertebrae has been described in Basset Hounds, Doberman Pinschers, and Great Danes (Fig. 13.54).
5. Transitional vertebra—this describes a vertebra that has shape characteristics of two different vertebral types. The most common examples are “lumbarization” of the sacrum or “sacralization” of the last lumbar vertebra. The clinical significance of these vertebrae is discussed in Chapter 14.
6. Atlantoaxial (AA) instability or subluxation (Video 10). In the AA joint there is no intervertebral disc and the joint is supported entirely by ligaments. Normally, there are four ligaments supporting the AA joint, keeping it stable and properly aligned. Three of these ligaments are associated with the dens (odontoid process), namely the apical ligament, two alar ligaments, and the transverse ligament (Fig. 13.55). In addition there is also the dorsal AA ligament. The pathogenesis of the disease typically revolves around a congenital

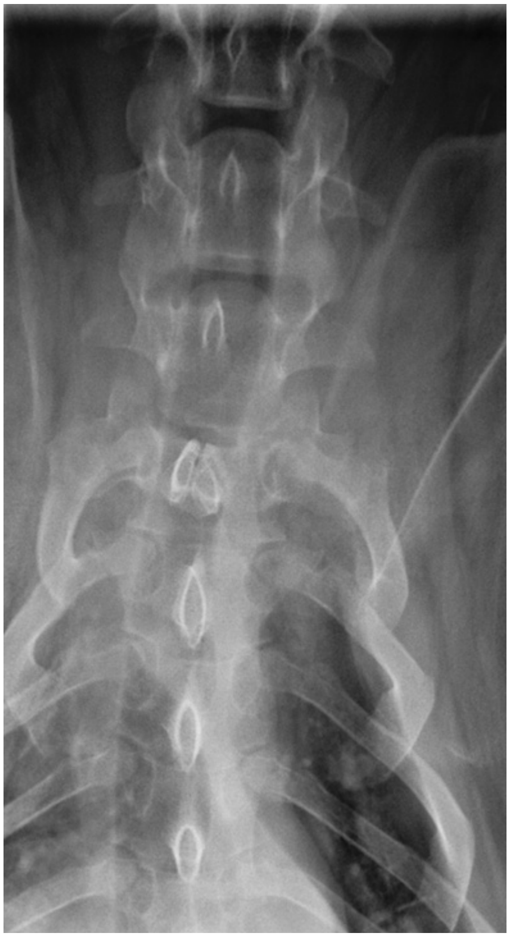


Figure 13.53 Ventrodorsal radiograph of a dog with spina bifida of a thoracic vertebra. (Westworth and Sturgess, 2010.[550] Reprinted with permission from Elsevier.)

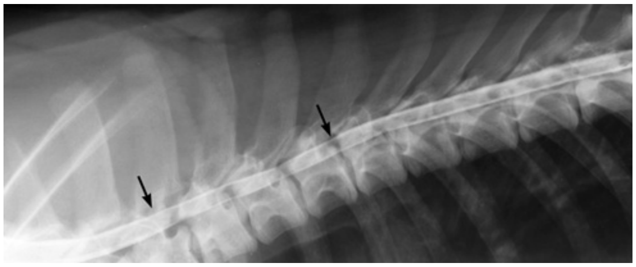


Figure 13.54 Myelographic image showing congenital spinal stenosis in the thoracic spine. (Westworth and Sturgess, 2010.[550] Reprinted with permission from Elsevier.)

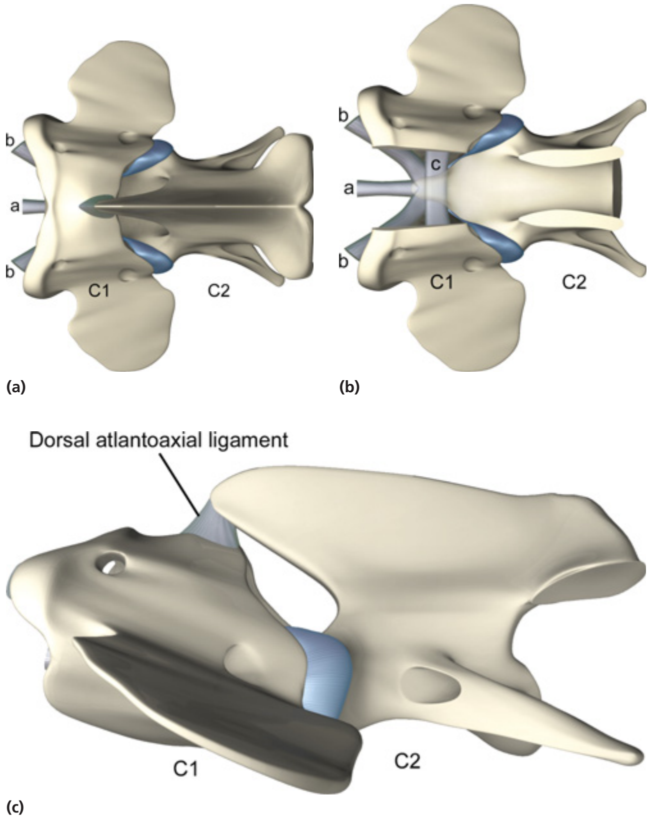


Figure 13.55 Atlantoaxial joint. (A) Dorsal view of the relationship between C1 and C2. (B) Dorsal view with the dorsal lamina of C1 removed. Note the odontoid process (dens) and the three ligaments associated with it, (A) apical ligament, (B) alar ligaments, and (C) transverse ligament. (C) Lateral view of the atlantoaxial joint showing the dorsal atlantoaxial ligament. (The Ohio State University. Reproduced with permission.)

malformation of the dens (hypoplasia or aplasia), making the AA joint unstable and causing subluxation (Fig. 13.56). Abnormal ligamentous support of the dens may also be involved. This problem is usually seen in miniature- and toy-dog breeds, often less than 2 yrs of age, but has been reported in older dogs and larger dog breeds. Commonly reported breeds with AA instability include Yorkshire Terriers, Pomeranians, Miniature and Toy Poodles, Chihuahuas, and Pekingese. It occasionally occurs in cats. The instability may lead to dorsal subluxation or luxation of the axis, with resultant compression of the cranial cervical spinal cord. Associated malformations of the atlas and/or occipital bones may be observed in some patients.

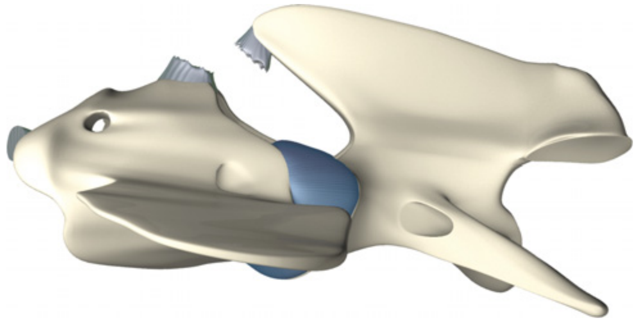


Figure 13.56 Illustration showing atlantoaxial subluxation with rupture of the dorsal atlantoaxial ligament. Note the space between the arch of atlas and the spinous process of the axis. (The Ohio State University. Reproduced with permission.)

b. Clinical signs, if present, associated with the above malformations should correspond to the anatomic location of the abnormality. In most cases, the clinically affected patient is an immature animal, but some patients may not exhibit clinical signs until adulthood. Onset of clinical signs of dysfunction may be acute or chronic. Depending on the specific abnormality or abnormalities, clinical signs may or may not progress. In some cases, the clinical signs of dysfunction are intermittent. In the case of AA instability, clinical signs can vary from neck pain with no neurologic deficits to tetraplegia with respiratory difficulty. Dogs with clinical dysfunction due to hemivertebrae typically present with evidence of a T3–L3 myelopathy of varying severity and rate of progression. Most of these dogs are less than 1 yr old at presentation, but older dogs have been reported.

c. Diagnosis of a vertebral malformation as a cause of clinical disease is based upon signalment, history, and neurologic deficits that match the location of the abnormality. Plain radiography (Fig. 13.57) and myelography have traditionally been used in diagnosis, but CT and MR imaging are being used more commonly. Stressed radiographic views are not recommended in the diagnosis as they can cause severe neurologic deterioration and death. A safer method of diagnosing AA instability in dogs is via CT or MR imaging (Fig. 13.58). It is best to position these dogs in sternal recumbency to avoid any worsening associated with prolonged cervical extension during MR imaging.

d. Treatment of patients with vertebral malformations that cause clinical signs of dysfunction is often frustrating, but some cases may respond to medical therapy (e.g. anti-inflammatory doses of glucocorticoids, neck brace for AA instability) or surgical stabilization with or without decompression. AA instability is sometimes treated nonsurgically, often involving external splinting of the neck, with or without administration of anti-inflammatory drugs (e.g. prednisone). The bandage or splint must restrict cervical ventroflexion and is more effective if it involves the head and thoracic limbs (Fig. 13.58). The bandage has to stay in place for 6–8 wks, and has to be changed at least weekly. It is important to monitor the respiratory

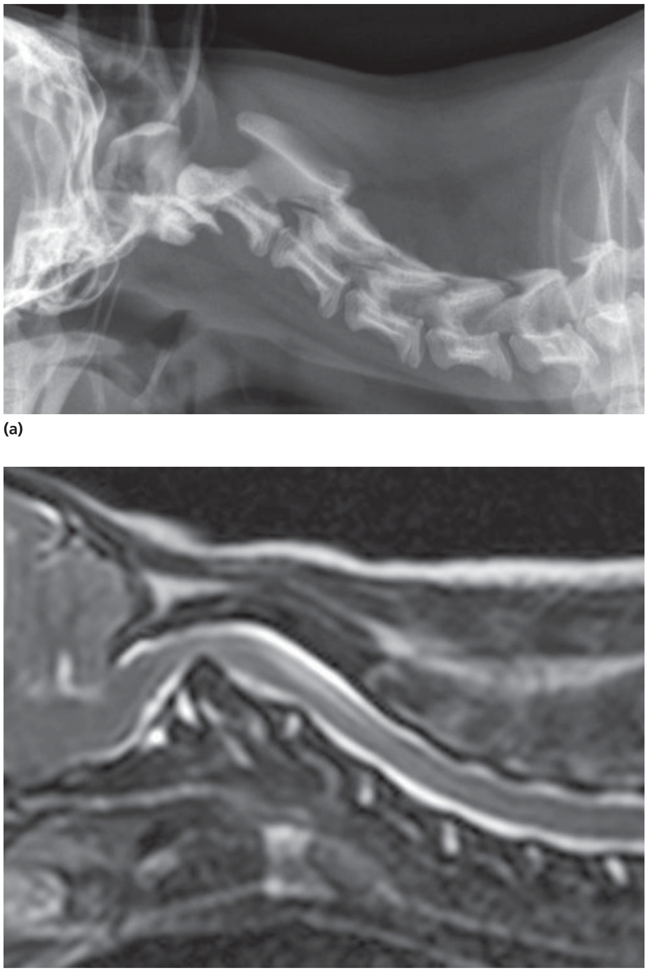


Figure 13.57 (A) Lateral radiograph of a dog's cranial cervical spine, demonstrating atlantoaxial joint subluxation. (B) Corresponding sagittal T2-weighted MR image of the same dog. Note severe spinal cord compression with hyperintensity caudal to the compressive lesion.

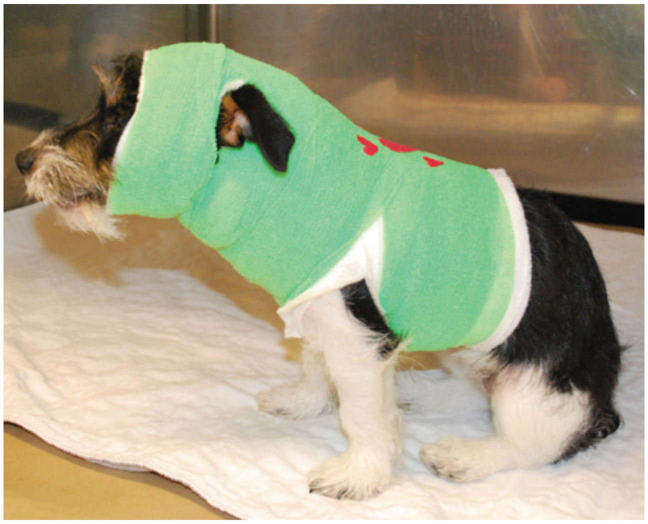


Figure 13.58 Bandage for conservative treatment of atlantoaxial subluxation. Note the cranial extension of the bandage sitting under the mandible and the caudal extension covering the thoracic region.

rate and effort after placing the bandage or splint to make sure the airways are not compromised. One retrospective study of AA dogs treated nonsurgically (all received external splinting) cited a good final outcome in 10/16 dogs (62.5%). Six of the dogs in this report (37.5%) died or were euthanized due to neurologic deterioration or lack of improvement following splint removal. In this study, the only factor significantly associated with outcome was length of clinical signs prior to therapy; dogs affected < 30 days were more likely to have positive outcomes than dogs affected > 30 days. Surgical success rates for AA instability vary in the literature from approximately 60 to 95%; however, most recent reports regarding the surgical treatment of this disorder describe a surgical success rate exceeding 80%. Similar to what has been reported for the nonsurgical management of AA instability patients, length of clinical disease presence has been negatively associated with surgical success as well. Several studies also suggest that the severity of neurologic dysfunction prior to surgery is also inversely related to outcome; the prognosis for patients with AA instability is fair to good if there are mild to moderate neurologic deficits, and guarded if the deficits are severe (e.g. tetraplegia). The surgical technique recommended by one of the authors (CD) involves a ventral approach with cancellous bone grafting and stabilization with pins and PMMA (Fig. 13.59). There are several variations of the ventral fixation. A dorsal approach which involves securing the atlas to the axis with orthopedic wires or sutures can also be performed. Recently, a dorsal tension band (Kishigami Atlantoaxial Tissue Band) was also reported. Postoperative complications involving upper-respiratory function (e.g. coughing, gagging, laryngeal paralysis) occasionally occur with the ventral approach. Aspiration pneumonia is also a potential postoperative complication that may be related to upper-airway (i.e. laryngeal) and/or pharyngeal dysfunction. Anecdotally, the author has found that relaxing the self-retaining retractors at frequent intervals (e.g. every 10 min) during surgery dramatically reduces the rate of postoperative upper-airway complications. Among the neurosurgical spinal procedures, the highest mortality is seen with AA fixation. Overall, reported perioperative mortality rates for the surgical management of dogs with AA instability vary from 0 to 30%, with most recent reports having rates of about 5–10%. Because of the proximity of the AA site to the brain-stem centers for cardiac and respiratory control, intraoperative deaths have been attributed to inadvertent damage to these medullary

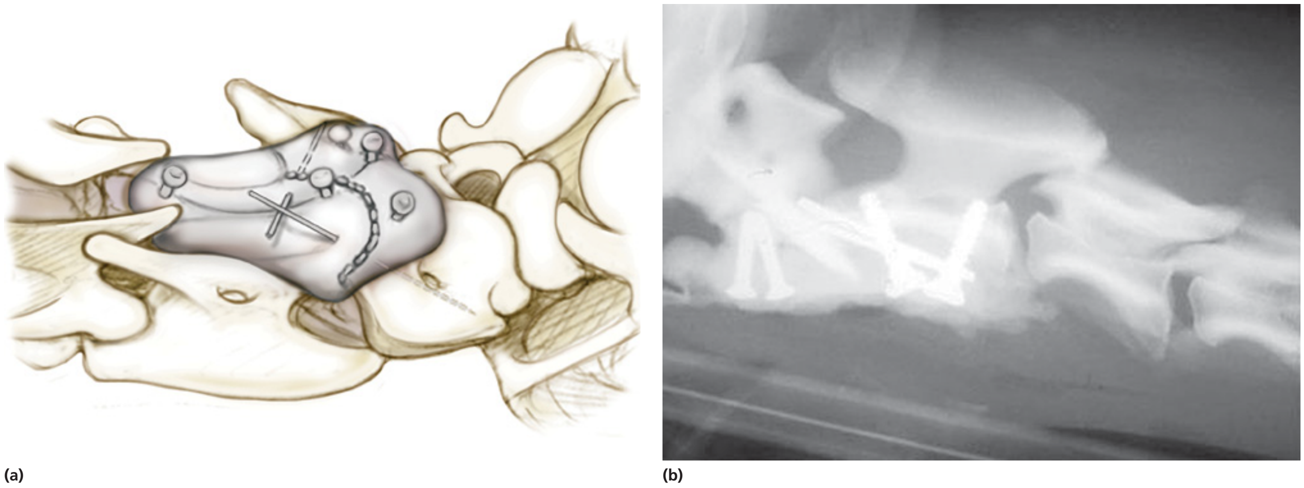


Figure 13.59 Fixation of atlantoaxial subluxation. A) Schematic illustration showing ventral placement of cortical screws in the body or C1 and C2 and transarticular pins enveloped in bone cement. B) Postoperative radiograph of a dog showing the fixation. The cement should only cover the necks of screws to avoid esophageal and tracheal obstruction. (Platt, SR, da Costa, RC. Cervical spine. In: Tobias KM, Johnston SA. *Small Animal Surgical Practice*; 2012. Reproduced with permission.)

regions. Implant failure and infection are also possible.

There are limited reports regarding the surgical management of dogs with hemivertebrae experiencing clinical signs of myelopathy. However, stabilization of the abnormal vertebral segment, with or without decompression, has been successful in most of the cases reported (Fig. 13.60).

2. Stenotic vertebral canal[287]
   In contrast to the congenital condition, this is progressive until skeletal growth is completed. This may be due to inborn errors of skeletal growth or other, as yet unidentified, factors. The stenosis can be relative or absolute, similar to the congenital condition.
3. Cartilaginous exostoses[10,32,38,70,81,102,151,172,181,196,201,216,242,287,294,305,324,333,378,379,390,433,456,484]
   a. Also known as osteochondroma/osteochondromatosis, this is an uncommon condition in which nodules of cartilage, with or without bone, proliferate in the growth plate areas of various bones. The vertebrae, ribs, and long bones of the limbs are most frequently affected. Multiple lesions (multiple cartilaginous exostoses, or MCE) are seen most commonly, but solitary growths occasionally occur. This disease typically occurs in young dogs and adult cats. There is some evidence that this is a heritable condition in dogs. In cats, MCE has been associated with the feline leukemia virus (FeLV).
   b. Clinical signs of myelopathy occur when exostoses of the vertebrae impinge on the spinal cord. Most dogs with MCE affecting the spinal cord are presented for clinical signs of myelopathy before 1 yr of age. However, dogs with MCE may be young adults (more than 1 yr old) by the time the mass or masses result in clinical signs of disease. Some dogs may develop neurologic dysfunction at an older age, due to neoplastic transformation of one or more exostoses. Cats with MCE tend to be adults at the time clinical signs

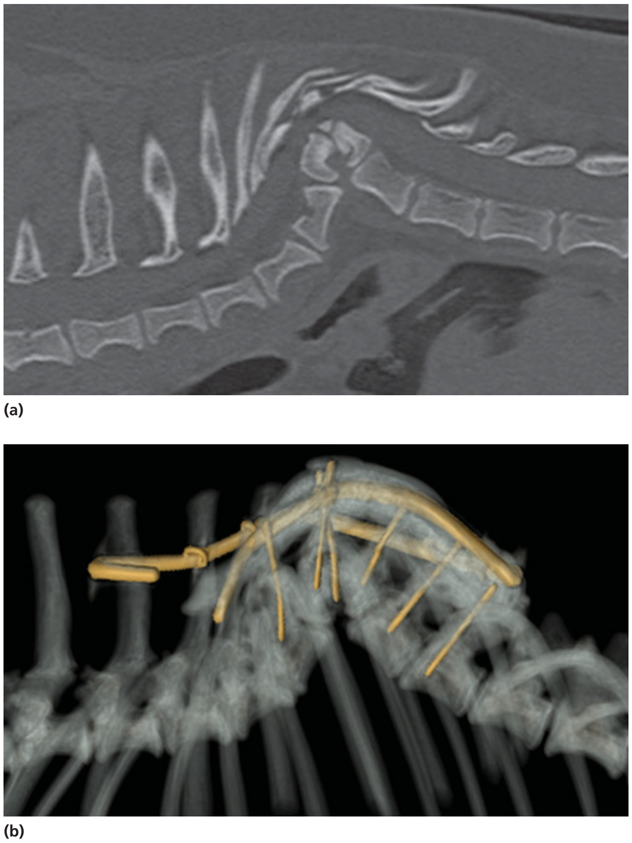


Figure 13.60 Preoperative (A) and postoperative (B) 3D CT reconstructed image of a dog with hemivertebra treated surgically.

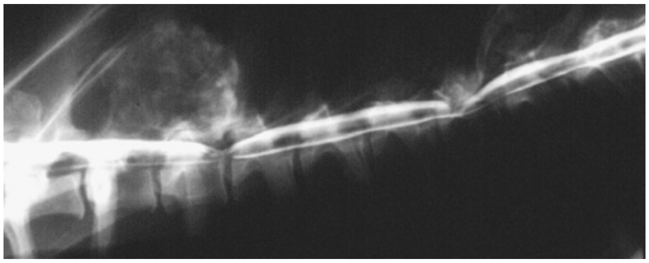


Figure 13.61 Lateral myelographic image of a dog with multiple cartilaginous exostoses of the thoracic spine.

of myelopathy are evident. The clinical signs depend upon the region(s) of the spinal cord that is (are) compressed.

c. A tentative diagnosis is made via visualizing the characteristic lesions on spinal imaging; the masses are usually evident on plain radiography and myelography (Fig. 13.61), but CT (Fig. 13.62) and MR imaging provide more detailed information in regard to the extent of vertebral involvement and spinal cord compression. Definitive diagnosis is attained via histopathologic examination of the nodules.

d. Prognosis with surgical resection of compressive vertebral masses in a skeletally mature dog has traditionally been regarded as generally good, because growth of exostoses was thought to be arrested at the time of skeletal maturity. However, there is some evidence in dogs suggesting that progressive growth of exostoses after skeletal maturity may be more common than previously believed, warranting a guarded to poor prognosis in some cases. The disease is considered aggressive in cats, and has a poor prognosis. Malignant transformation of exostoses in adult animals has been described. Such transformation may also be more common in dogs than previously appreciated, sometimes occurring several years after diagnosis of cartilaginous exostoses.

4. Meningoceles/myelomeningoceles

Meningoceles and myelomeningoceles are protrusions of meninges and CSF, with or without parenchymal tissue, respectively. They are often associated with spina bifida. They occur most commonly in the lumbosacral region and are discussed in Chapter 14.

5. Spinal dysraphism[93, 161, 162, 202, 287, 352, 434, 502, 517]

a. Myelodysplasia is a catchall term that refers to a number of abnormalities of embryological development, including duplication and absence of cord structures, as well as syringomyelia and hydromyelia. A specific form of myelodysplasia, referred to as spinal dysraphism, is thought to be a hereditary disease in Weimaraner dogs. This condition occasionally occurs in other dog breeds. Most of the abnormalities are located along the median plane of the spinal cord in these dogs.

b. Clinical signs of a T3–L3 myelopathy are usually apparent by 4–6 wks of age. A "bunny hopping" pelvic limb gait is the most characteristic feature of spinal dysraphism. Proprioceptive deficits in the pelvic limbs are also common, whereas paraparesis is uncommon. The condition is also typically nonprogressive, even when hydromyelia/syringomyelia is present.

c. A tentative diagnosis of spinal dysraphism is made primarily based upon signalment, history, and clinical signs. Results of diagnostic tests (e.g. CSF analysis, radiography, myelography, CT, MRI) are typically normal, depending upon the specific spinal abnormalities and the specific tests performed (e.g. hydromyelia/syringomyelia may not be apparent on myelography, but will likely be visible with MRI).

d. There is no treatment for spinal dysraphism. Since the clinical signs are usually not severe, and the disorder is not progressive, the prognosis for life as a functional pet is good.

6. Syringomyelia (hydromyelia)[18, 42, 72, 82, 84, 120, 189, 190, 195, 211, 213, 230, 241, 254, 267, 272, 287, 332, 334, 364, 442–444, 457, 502, 508, 554–557, 560]

a. Technically, hydromyelia is a fluid dilatation of the central canal and syringomyelia is a fluid dilatation within the spinal cord outside the central canal that may or may not communicate with the central canal. Distinguishing between hydromyelia and syringomyelia is often impossible in the living patient and is clinically unimportant. For purposes of consistency, the term syringomyelia is used to refer to this disorder in this textbook. The vast majority of syringomyelia cases in dogs appear to be secondary to Chiari-like malformation syndrome (CLM), the canine analog of human Chiari type I malformation. Although CLM with syringomyelia has been reported in a number of dog breeds, the most commonly affected breed is the CKCS. CLM and syringomyelia are discussed in detail in Chapter 7, so syringomyelia will be only briefly discussed here. Syringomyelia may be associated with other congenital spinal cord (e.g. spinal dysraphism) and/or brain (e.g. Dandy–Walker syndrome, hydrocephalus, quadrigeminal cyst) malformations, but may also be caused by inflammatory and neoplastic processes that obstruct the flow of CSF. It can also occur secondary to spinal cord trauma. This condition can also occur as a solitary disorder of an unknown etiology (i.e. idiopathic).

In human beings, the majority of syringomyelia cases are associated with abnormalities of the caudal medullary/cerebellar region of the brain, such as Chiari type I malformation (most commonly), intra-arachnoid cysts, and Dandy–Walker syndrome. It is

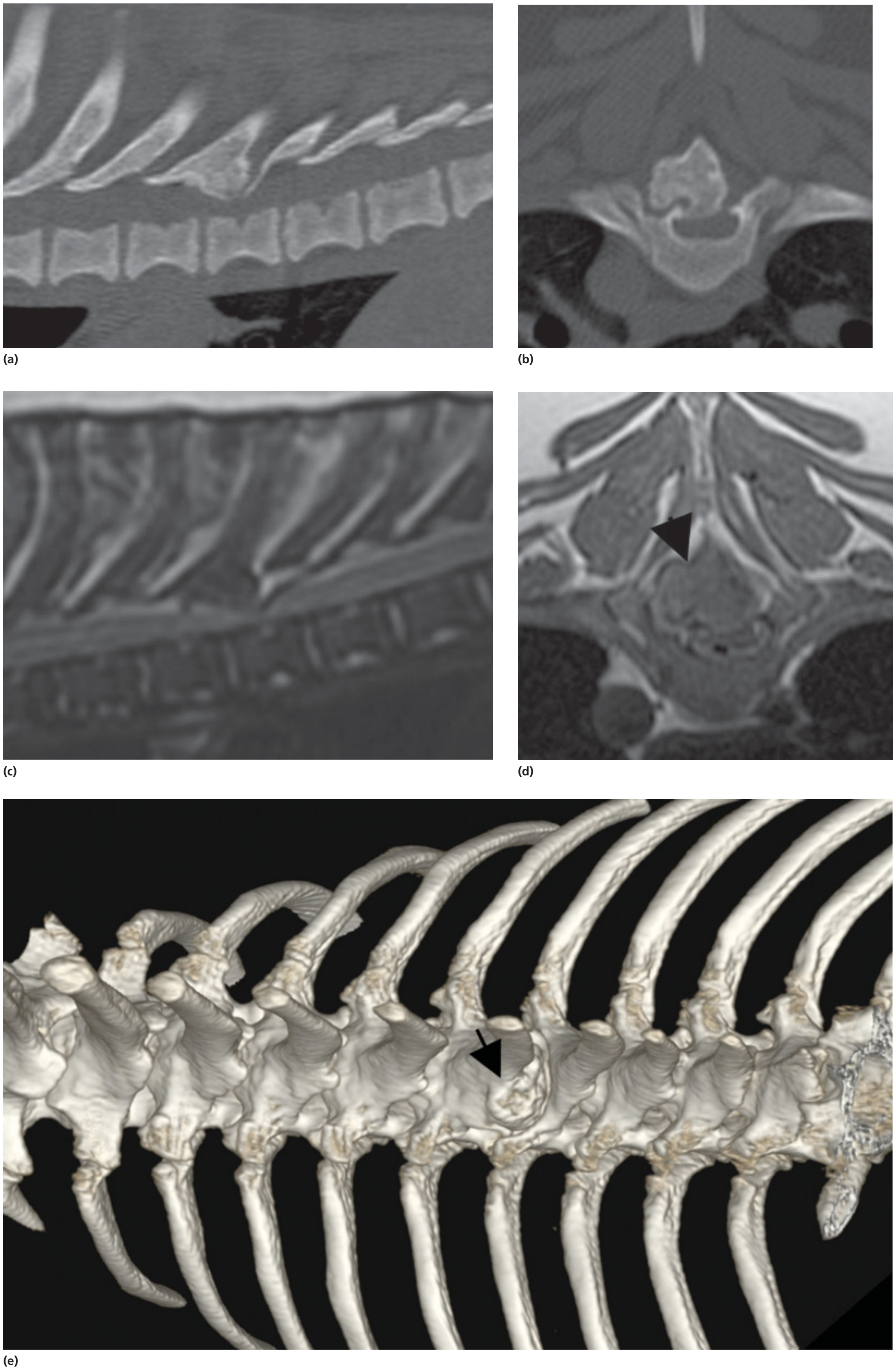


Figure 13.62 Images of a dog with cartilaginous exostosis in the thoracic vertebral column. (A) Sagittal reconstructed computed tomography (CT) scan. (B) Transverse CT at the center of the lesion. (C) Sagittal T2-weighted MR image showing compression of the spinal cord. (D) Transverse T1-weighted MR image showing the osseous proliferation (arrowhead). (E) Reconstructed CT image showing the location of the lesion (arrow). Courtesy Dr. Peter Dickinson, University of California, Davis.

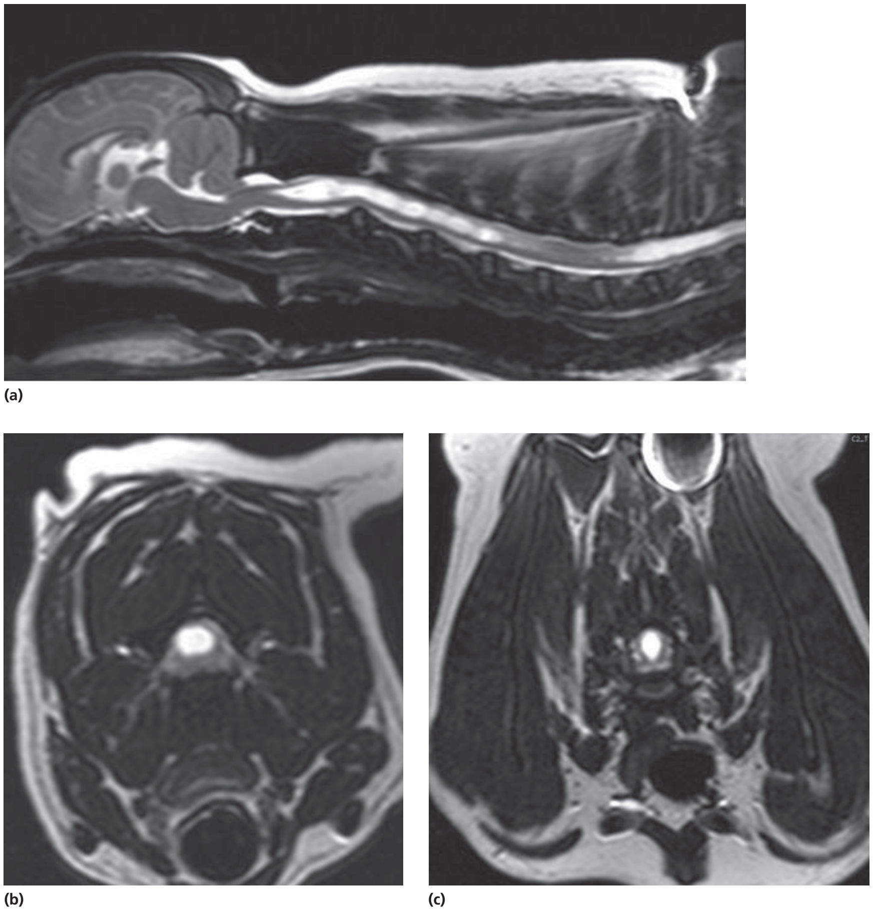


Figure 13.63 Sagittal (A) and transverse T2-weighted images of a dog with syringomyelia of the cervical (B) and cranial thoracic spinal cord (C).

believed that these hindbrain anomalies are not merely coincidental malformations that occur concomitantly with syringomyelia, but that they may actually cause the syringomyelia by disrupting normal CSF flow mechanisms. In addition, abnormalities of the cranial cervical spine have been described to occur concomitantly with Chiari type I malformation in people. The authors have encountered a number of young dogs with syringomyelia that have cranial cervical compressive lesions (typically dorsal compression at C1/C2) which may or may not occur concurrently with CLM (Fig. 13.63).

b. Clinical signs of a mild myelopathy (typically cervical) may be acute or chronic and may or may not be progressive. In many of the reported cases associated with CLM, onset of clinical signs of neurologic dysfunction occurred in adulthood. However, dogs with CLM-related syringomyelia are being increasingly diagnosed at younger ages (< 1 yr); whether this reflects an increased awareness of the disease, an increase in its severity, or a combination is unknown. The age range of clinical disease onset is very broad, possibly reflecting the multitude of suspected etiologies for the condition. This age range may also reflect different rates of fluid accumulation and subsequent spinal cord dysfunction among dogs. Scoliosis, especially of the cervical region (i.e. torticollis), and spinal hyperesthesia are frequent clinical findings in cases of syringomyelia. In syringomyelia cases due to CLM, syrinx width was correlated with both pain and scoliosis in one study. The development of scoliosis has been proposed to be due to asymmetric damage to LMNs that supply epaxial/hypaxial musculature caused by the accumulated fluid. An alternative and more likely hypothesis is that the scoliosis is a sensory phenomenon due to asymmetric damage to dorsal horn gray matter by the accumulated fluid (A. de Lahunta, personal communication). Proprioceptive deficits occur with some frequency but limb paresis is quite uncommon.

Persistent scratching at the neck and shoulder area is a characteristic feature of syringomyelia, especially in the CKCS breed.

c. Diagnosis may be difficult or impossible to achieve with myelography. Occasionally during myelography, the contrast medium will enter the central canal (canalogram) and provide a diagnosis. More often, however, the spinal cord will either appear subjectively wider than normal or normal on myelography. CT or MRI (ideally) is much more likely to demonstrate the cavitary lesions. The authors prefers MR imaging for dogs suspected of having hydromyelia/syringomyelia, as this imaging modality is more likely to identify Chiari-like malformations (sagittal view) as well as the fluid-filled spinal cord lesions (Fig. 13.64). CSF is often either normal or indicative of mild inflammation in most cases of syringomyelia; CSF should be evaluated to help rule out potential underlying causes (e.g. inflammatory/infectious disease) or concurrent disorders. It is important to rule out other diseases because it has been shown that up to 70% of normal (asymptomatic) Cavalier King Charles Spaniels have syringomyelia.

d. Medical and surgical treatment options for syringomyelia are discussed in detail in Chapter 7.

7. Dermoid sinus (pilonidal sinus)[25,43,44,68,99,100,126,164,233,234,279,287,330,367,416,427,474]

a. A failure of separation of the neural tube from the skin ectoderm during embryogenesis is believed to be the basis for this disorder. A sinus tract with a small cutaneous opening on the dorsal midline extends ventrally to various depths, sometimes to the level of the subarachnoid space. This is encountered most commonly in Rhodesian Ridgeback dogs, but has been reported in other breeds. Other breeds reported with dermoid sinus include Ridgeback crossbreed, Thai Ridgeback dog, Cocker Spaniel (American and English), Shih Tzu, Siberian Husky, Golden Retriever, Boxer dog, Chow Chow, Great Pyrenees, Boerboel, Fox Terrier, Rottweiler, Brittany Spaniel, Springer Spaniel, English Bull Terrier, and Yorkshire Terrier. The sinus is most often located in the cervical, cranial thoracic, and sacrocaudal regions, but can occur anywhere along the spine. Dermoid sinuses have also been reported in the head region. The sinus tract is lined with squamous epithelium and adnexa (hair follicles and sebaceous glands). Dermoid sinus is thought to be a heritable condition, especially in the Rhodesian Ridgeback dog, in which the percentage of affected dogs is reported to be 5.3%. The exact mode of inheritance is undetermined at this point. The ridge trait appears to be inherited in an autosomal dominant mode and the presence of the ridge predisposes dogs to develop dermoid sinus. Dermoid sinuses have been classified as types I–IV or I–V, depending on the extent of penetration of tissue beneath the subcutaneous layer (Fig. 13.65). Types I and II extend to the supraspinous ligament (deeply type II is a closed fibrous band), whereas type III is more superficial and type IV extends to the vertebral canal (with or without an obvious laminal defect) and attaches to the dura mater. Type V has been proposed more recently, but this entity is a true cyst,

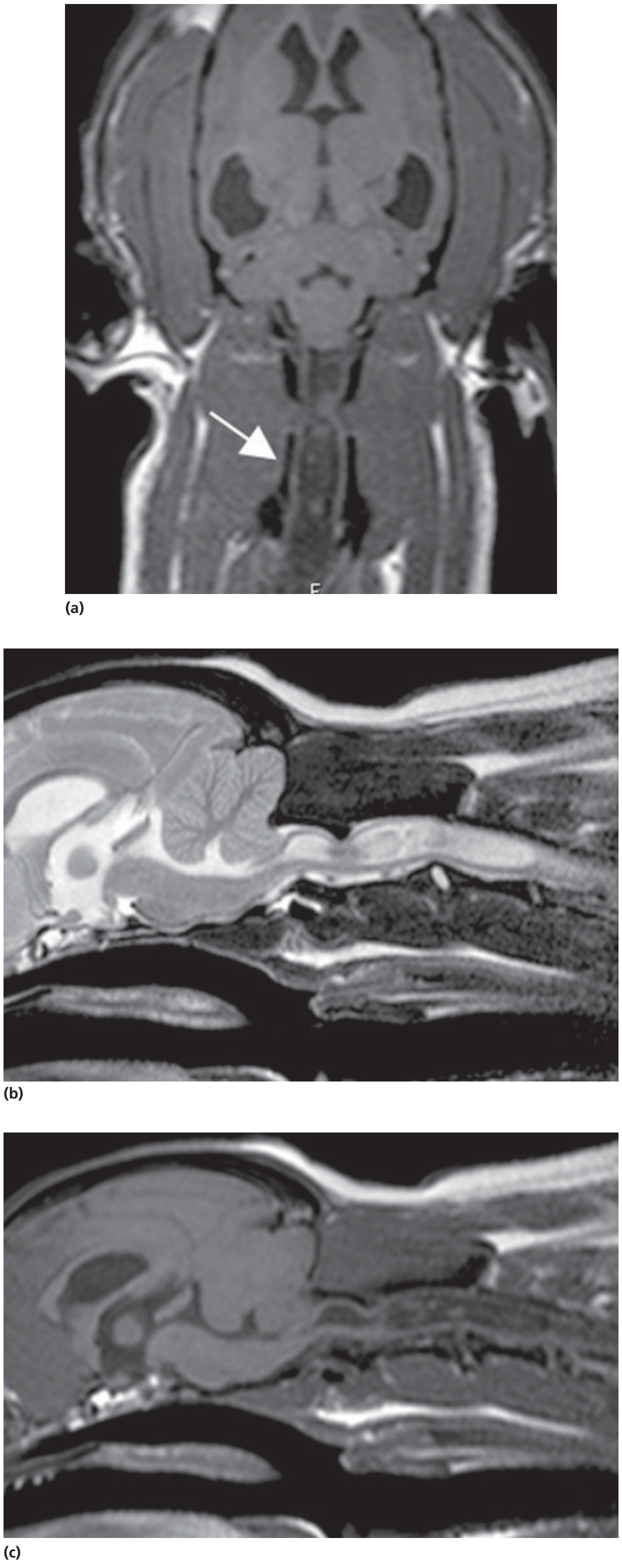


Figure 13.64 MR images of a dog with severe syringomyelia secondary to CLM. (A) Dorsal T1-weighted MR imaged showing the large syrinx (arrow). (B) Sagittal T2-weighted showing the extent of the syringomyelia. Note the dorsal compressive lesion between the first and second cervical vertebrae and the cerebellar herniation. (C) Corresponding T1-weighted MR image.

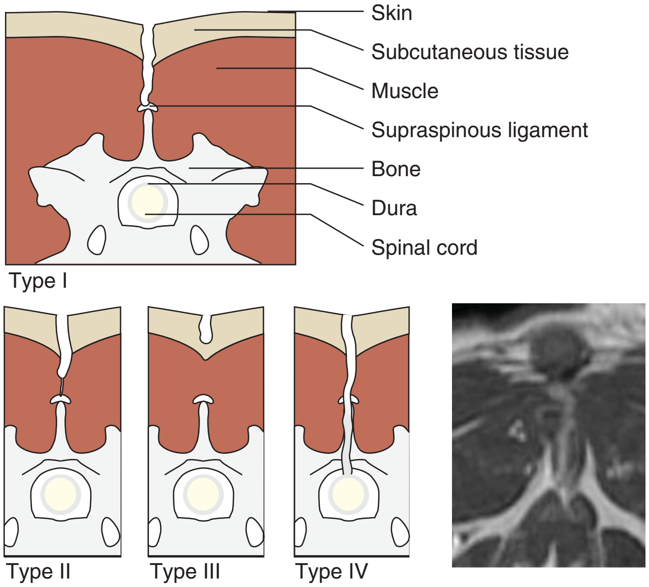


Figure 13.65 Diagram of the four types of dermal sinus tracts (I–IV), illustrating the extent of tissue depth involved. For comparison, a cervical transverse T2-weighted MRI of a type IV dermal sinus tract is shown. Note the serpentine appearance of the tract as it courses ventrally through a laminal defect to the dura mater. (MRI courtesy of Dr. Jim Lavely, in Westworth and Sturges, 2010.[550] Reproduced with permission from Dr. Jim Lavely.)

with no tract or skin opening and should be referred to as a dermoid cyst.

b. Clinical signs may vary from irritation due to bacterial infection of the sinus (most commonly) to evidence of meningitis and myelitis in cases that involve sinus communication with the meninges and spinal cord. Onset of clinical signs usually occurs at a young age, but can occur at any age. A thick fibrous cord (the sinus) can often be palpated subcutaneously on the dorsal midline.

c. Diagnosis is based upon signalment, history, clinical signs, and demonstration of a sinus tract via imaging. Myelography or other imaging modalities (CT or MRI) may also be used to demonstrate or rule out communication of the sinus with the subarachnoid space. There is controversy in the literature regarding the use of fistulograms, due to the risk of introducing an infection into deeper tissues. But if a fistulogram is planned, only contrast agents safe for myelography should be used if communication of the sinus with the subarachnoid space is suspected or known.

d. Treatment includes broad-spectrum antibiotics based upon culture and sensitivity results, and complete surgical excision of the sinus tract. Prognosis varies with the extent of neurologic dysfunction (if any) and whether the entire sinus tract is successfully removed. In general the prognosis is guarded to good.

8. Spinal arachnoid diverticula (cysts)[19,34,69,159,185,194,210,220,222,258,287,342,355,389,409,411,415,449,458,475,477,487,538,545,550] (Video 27)

a. The common name for this disorder, arachnoid cyst, is a misnomer, because the lesions are actually CSF-filled diverticula of the subarachnoid space, rather than true cysts. These lesions have also been described as meningeal cysts, leptomeningeal cysts, spinal arachnoid pseudocysts, arachnoid cavitations, and arachnoid diverticula. Proposed causes of these anomalous fluid accumulations are numerous, including congenital malformation, trauma, inflammation (arachnoiditis), and neoplasia. However, an underlying etiology is rarely found for spinal arachnoid cysts. Interestingly, in a large recent report, 21.3% of dogs had concurrent diseases (e.g. intervertebral disc disease, vertebral malformations, myelitis) in close proximity with the diverticula, which might have influenced the development of diverticula. The accumulated fluid causes compression of adjacent spinal cord parenchyma, resulting in clinical signs of myelopathy. Spinal arachnoid cysts are typically solitary, dorsally or dorsolaterally located, focal accumulations of fluid that occur at either the cranial cervical (most commonly over C2/C3 vertebral segments) or caudal thoracic regions of the spinal cord. Multiple or bilobed spinal arachnoid cysts are frequently encountered, however, especially in the cervical region of Rottweilers. Ventrally located or circumferential spinal arachnoid cysts have also been reported. A recent report described 122 cases of arachnoid diverticula. Fifty-two percent of the diverticula were located in the cervical region, whereas 48% were in the thoracolumbar region. The most common location in the cervical region was C2–C3 followed by C5–C6. In the thoracolumbar region the majority were located between T9–T10 and T13–L1. The majority of diverticula were located dorsally (83.2%). The second most common location was ventrally (6.4%).

b. Spinal arachnoid diverticula have been described in a considerable number of dogs and several cats. Rottweilers appear to be particularly predisposed. In this breed, dorsally located fluid accumulations in the cranial cervical regions are common. In the thoracolumbar region, a predisposition is seen in small-breed dogs, particularly Pugs and French Bulldogs. The age at onset of clinical signs of neurologic dysfunction is quite variable, ranging from several months to 13 yrs of age. Most reported dogs developed signs of myelopathy in young adulthood, except in Pugs that average 5–6 yrs of age at presentation. A strong male predisposition has been recently found. Slowly progressive ataxia and paresis (paraparesis or tetraparesis, depending on lesion location) are typical clinical features of this disorder. Dogs with dorsally or

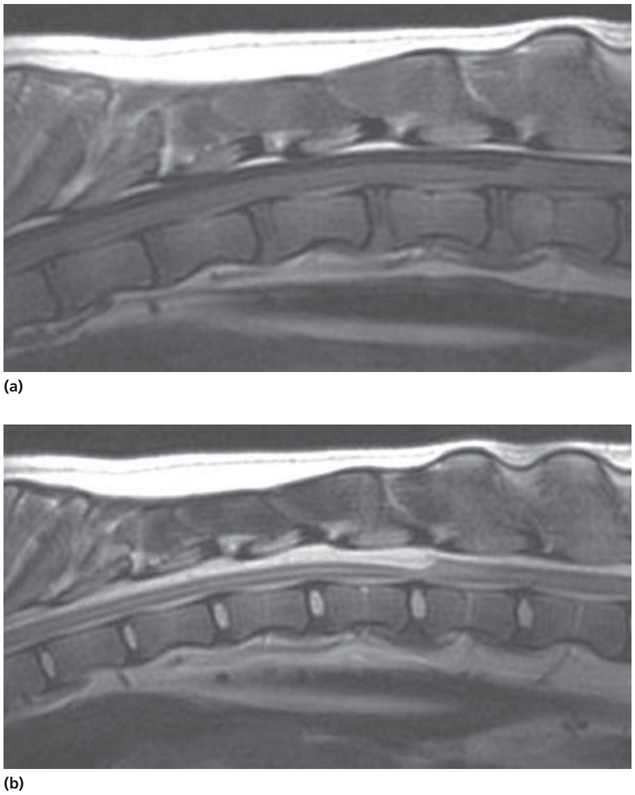


Figure 13.66 Sagittal T1-weighted (A) and T2-weighted MR images of a dog with spinal arachnoid diverticulum (Dr. Peter Gordon, 2014. Reproduced with permission from Dr. Peter Gordon.)

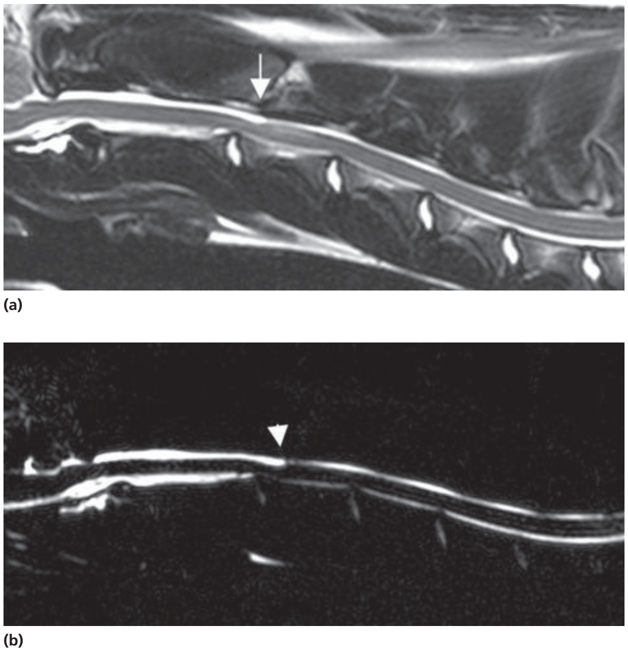


Figure 13.67 MR images of a dog with an arachnoid diverticulum between C2 and C3 (arrow). (A) Sagittal T2-weighted image and (B) MR myelogram sequence (heavy T2 or HASTE). Note that the diverticulum is more easily visualized in the MR myelogram sequence.

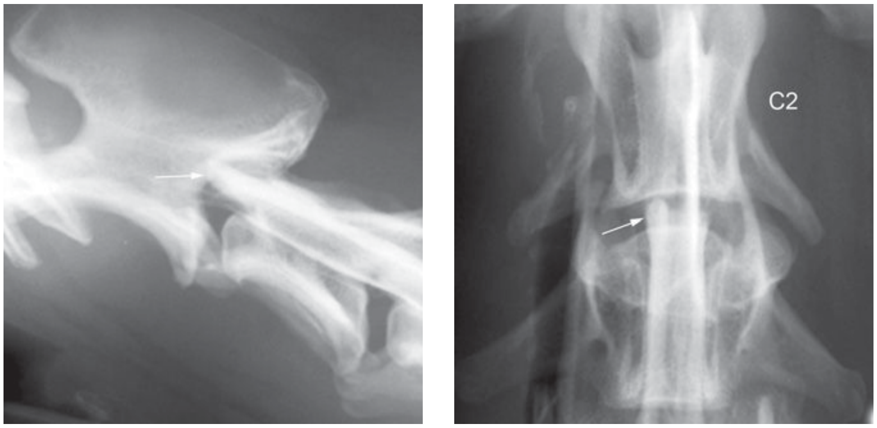
dorsolaterally located cranial cervical lesions (often Rottweilers) typically exhibit tetraparesis with pseudohypermetria, primarily in the thoracic limbs (presumably via interference of the "cyst" with spinocerebellar tracts or because of severe UMN spasticity). Spinal hyperpathia does not appear to be a prominent clinical feature of this disorder, but has been reported to occur in 18.9% of dogs. Urinary and fecal incontinence has been reported with this disorder in approximately 8% of dogs, primarily with thoracolumbar diverticula.

c. The diagnosis of spinal arachnoid diverticulum is based primarily on spinal imaging; earlier reports focused on myelographic findings. Both CT myelography and MR imaging (Fig. 13.66) have also been successfully used to identify these lesions, and provide more detailed information regarding lateralization and potential associated abnormalities (e.g. syringomyelia). It is important to use MR myelogram sequences (heavy T2-W images) to facilitate visualization of the diverticulum (Fig. 13.67). The typical myelographic or MRI appearance is a bulbous, contrast-filled (or CSF-filled) diverticulum continuous with the contrast column (or CSF) in the subarachnoid space, with a characteristic teardrop shape (Fig. 13.68). In some cases the MR imaging appearance is not clear, and in those cases CT myelography may facilitate visualization (Fig. 13.69). CSF analysis is typically normal in the majority of cases. Approximately 20% of dogs show albuminocytologic dissociation and 10% can show mild mononuclear pleocytosis. Histopathology of resected "cyst wall" reveals meningeal tissue (dura-arachnoid).

d. Medical management (i.e. glucocorticoid therapy) may be attempted initially. In a few cases the signs can be managed for long periods and the disease appears to become stable. Surgical management is typically the treatment of choice. Surgical management involves resecting a portion of the meninges comprising the "cyst" wall, thereby relieving the pressure exerted on the underlying spinal cord parenchyma. From the limited data available, surgical treatment of spinal arachnoid cysts in dogs and cats appears to have a good prognosis. It appears that 60–85% of cases have good outcomes. There is some evidence that marsupialization of the cyst wall to surrounding tissues at surgery may help prevent recurrence. At least 10–20% of cases have recurrence of signs.

C. Neoplastic[47, 52, 54, 55, 77, 96, 101, 116, 144, 154, 155, 168, 171, 188, 200, 207, 208, 216, 239, 253, 263, 266, 278, 280, 284, 286, 287, 297–299, 302, 314, 316, 317, 321, 323, 325, 334, 344, 349, 350, 358, 369, 372, 374, 376, 382, 391, 392, 395, 408, 418, 422, 426, 441, 445, 450, 460, 469, 491, 498, 503–505, 514, 528, 530, 537, 542, 543, 561, 565, 566]

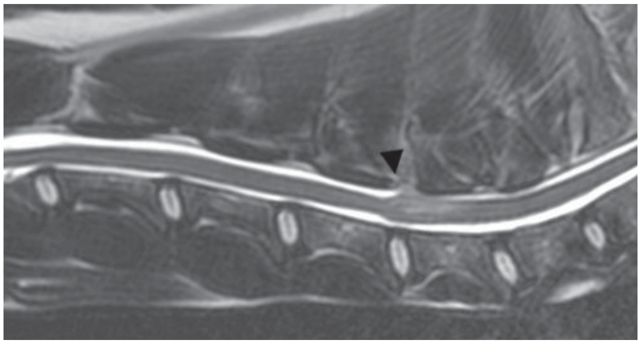
(Video 28)



(a) (b)

Figure 13.68 Lateral (A) and ventrodorsal (B) myelographic images of a spinal arachnoid diverticulum in the cervical region of a dog. (Dr. P Scrivani, Cornell University, 2014. Reproduced with permission from Dr. P Scrivani.)

1. There are a large number of tumors that can affect the spinal cord of dogs and cats. As with brain tumors (see Chapter 7), tumors affecting the spinal cord can be conceptually divided into primary and secondary tumors. Primary tumors include those neoplasms that arise from spinal cord parenchyma (e.g. neurons, glial cells) or associated meningeal/ependymal tissue. Secondary tumors include primary or metastatic vertebral neoplasms, malignant nerve sheath tumors (MNSTs; see Chapter 17 also), and metastases to the extradural space or the cord parenchyma (intramedullary metastases). As with brain tumors, primary tumors are more common than metastatic tumors. It is often clinically useful to classify spinal cord neoplasms based upon the relationship between the tumor and the meninges. Spinal cord tumors are typically classified as extradural, intradural/extramedullary, or intramedullary (Fig. 13.70). Since some spinal tumors occupy more than one of these locations (e.g. may be both extradural and intradural/extramedullary), the additional location category of mixed compartment has been suggested. In one large retrospective study of 399 histopathologically confirmed spinal cord tumors in dogs, 48% were extradural, 13% were intradural/extramedullary, 6% were intramedullary, and 33% were mixed compartment. Spinal cord tumors exert their pathologic effects by compression and/or invasion of the spinal cord, as well as producing peritumoral edema, inflammation, and hemorrhage. Examples of some of the more commonly encountered spinal cord tumors in dogs and cats are as follows:
   a. Extradural tumors—this category includes primary and secondary (metastatic or local invasion) vertebral and soft-tissue tumors. Primary vertebral tumors such as osteosarcoma, chondrosarcoma, myeloma (plasma cell tumor), fibrosarcoma, and hemangiosarcoma are common extradural tumors encountered in dogs. Other vertebral tumors reported in cats include fibrosarcoma, undifferentiated sarcoma, and plasma cell tumors. The most common primary vertebral body tumor in dogs is also osteosarcoma. Carcinomas account for the majority of secondary vertebral tumors in dogs. It may be difficult in some cases to ascertain whether a vertebral tumor is primary or metastatic.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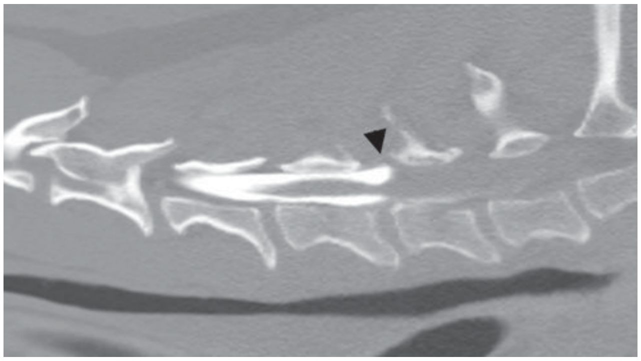
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Figure 13.69 Images of a dog with cervical arachnoid diverticulum. (A) Sagittal T2-weighted MR image. (B) CT-myelogram image. Note that the diverticulum does not have the typical tear-drop appearance on MRI (arrowhead). CT-myelography facilitates visualization (arrowhead) and confirmation.

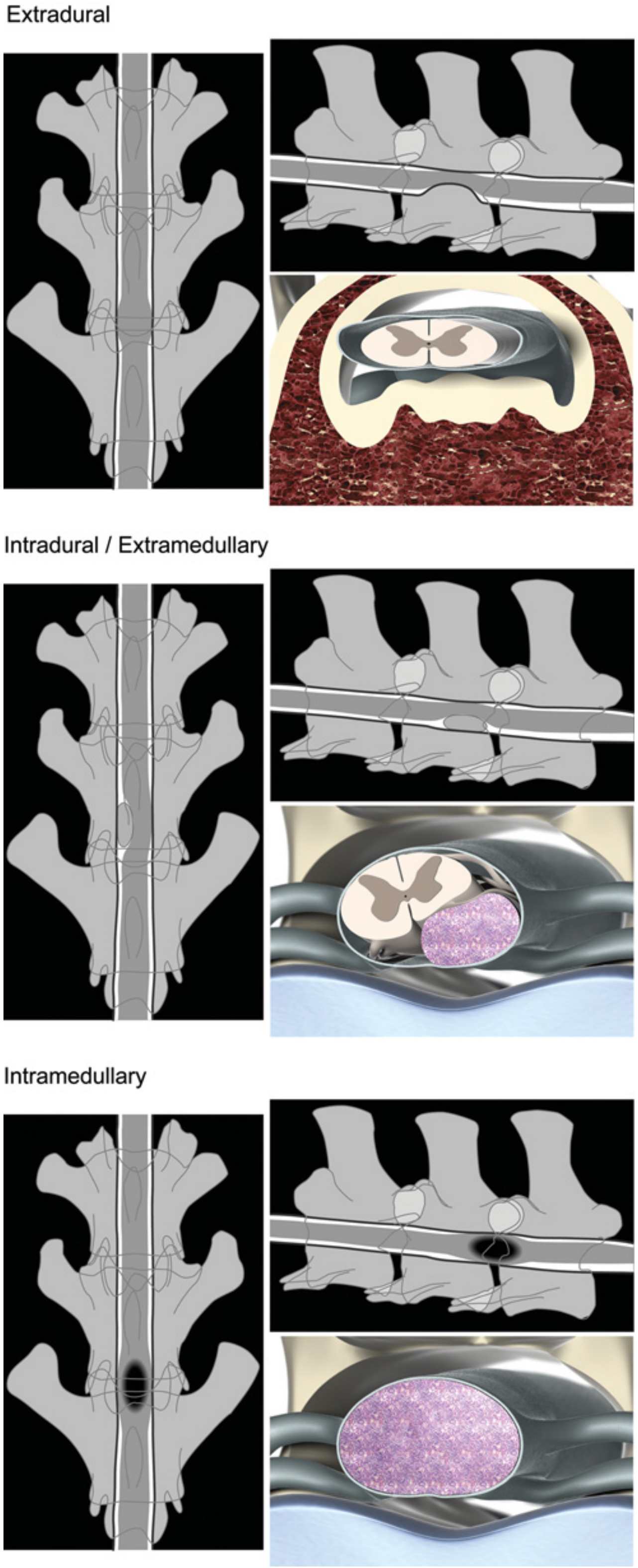
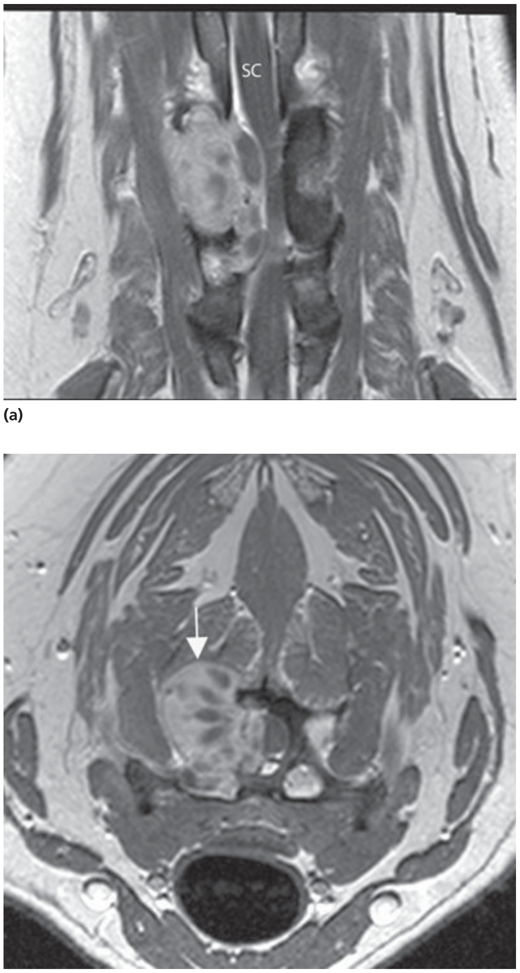


Figure 13.70 Representation of the classification of the spinal neoplasia into extradural, intradural/extramedullary, and intramedullary. (The Ohio State University. Reproduced with permission.)

Other tumors may occur in the epidural space, without directly involving the vertebrae. Common among these are sarcomas, most frequently osteosarcoma and hemangiosarcoma. Lymphosarcoma can be primary or metastatic, and is often located in the extradural space, particularly in cats. Lymphosarcoma is the most common spinal tumor of cats, according to a number of sources in the literature. Meningioma and MNST usually are typically located intradurally, but occasionally will exhibit an extradural pattern on myelography or other imaging modalities (CT/MRI). Metastatic carcinomas (e.g. mammary carcinoma, prostatic carcinoma) may localize to the extradural space. A number of fatty tumors have been reported to affect the spinal cord in dogs, including lipoma, myelolipoma, infiltrative lipoma, and liposarcoma. These all generally occur in an extradural location, although a myxoid liposarcoma was reported to occur in an intradural extramedullary location in a dog. Extradural tumors represent the most frequently diagnosed category of spinal neoplasia (Fig. 13.71).

   b. Intradural/extramedullary tumors—meningiomas and MNSTs are the two most common neoplasms in this category, with meningiomas predominating. An uncommon blast-cell tumor of young dogs called nephroblastoma also typically displays an intradural/extramedullary pattern on spinal imaging (Fig. 13.72).
   c. Intramedullary tumors—these infrequently encountered neoplasms include primary and metastatic intramedullary tumors. In a recent large case series, ependymoma and astrocytoma were the most common primary tumors. The most common intramedullary metastatic tumors were hemangiosarcoma and transitional cell carcinoma. Lymphoma is another common intramedullary tumor (Fig. 13.73).
   d. Mixed compartment tumors—these tumors tend to occur in more than one of the three typical compartments listed above. MNST is the most common type of neoplasm in this category, followed by lymphosarcoma, and malignant fibrous histiocytoma. There are isolated reports of spinal germ cell tumors in dogs, one of which fit the criteria for a teratoma (differentiated to the level of three separate germ cell derivatives: endoderm, mesoderm, and ectoderm). These tumors were primarily intramedullary, but also occupied intradural and extradural compartments.

2. In general, most patients with spinal neoplasia are older (e.g. more than 5 yrs), but some tumors (lymphosarcoma, nephroblastoma) are seen commonly in young animals. Spinal tumors appear to be much more common in larger dogs vs. small-breed dogs. Boxers and Golden Retrievers were shown to have a higher prevalence of spinal meningiomas. The median age of cats with spinal lymphosarcoma is 2–3 yrs. Spinal nephroblastomas in



(a)

(b)

Figure 13.71 Dorsal (A) and transverse (B) T1-weighted MR images of a dog with an extradural mass (arrow) at the level of the 5th cervical vertebra. The mass was a sarcoma. SC = spinal cord.

dogs are typically diagnosed between 6 mos and 3 yrs of age (median age 14 mos in one report). These uncommon neoplasms have been ascribed multiple names, including neuroepithelioma, medulloepithelioma, and ependymoma. It is unlikely that this neoplasm is an ependymoma, and most evidence supports the use of the term nephroblastoma. German Shepherd dogs and retrievers appear to be predisposed to developing nephroblastoma. Interestingly, dogs with primary intramedullary tumors (e.g. ependymoma) had a mean age of 5 yrs at diagnosis, whereas dogs with secondary intramedullary tumors averaged 10 yrs.

Spinal tumors classically cause progressive signs of a myelopathy, but acute or subacute development of spinal cord dysfunction often occurs, especially with feline lymphosarcoma and intramedullary neoplasms. The rapid onset of clinical signs may be due to such factors as pathologic fracture of a cancerous vertebra, acute hemorrhage

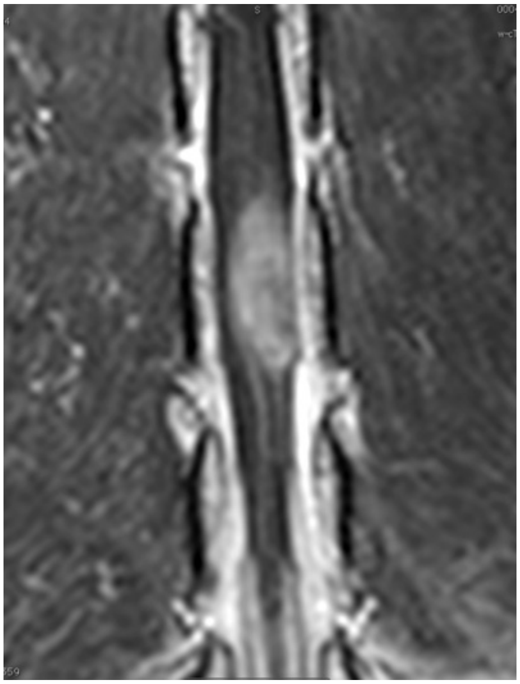
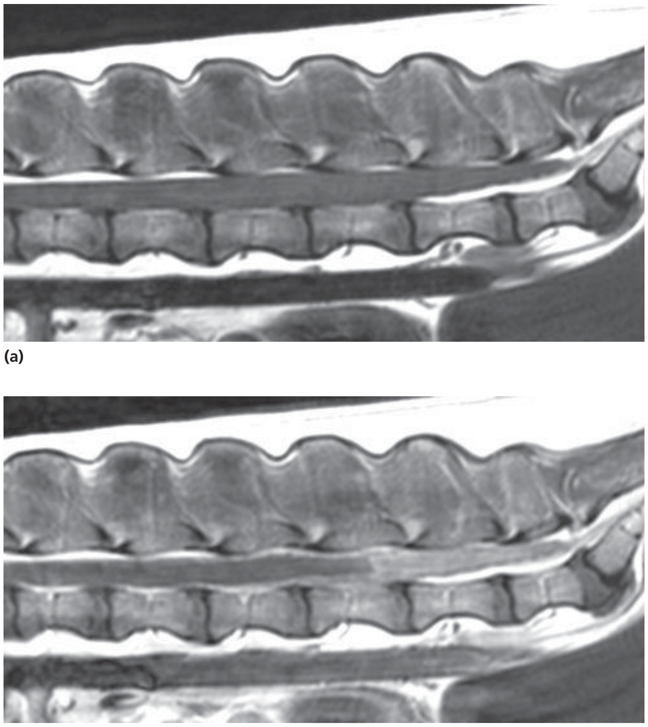


Figure 13.72 Dorsal MR image T1-weighted (post contrast administration) of a presumed nerve sheath tumor in the lumbar spine that was intradural/extramedullary in location.



(a)

(b)

Figure 13.73 MR images of a dog with an intramedullary spinal cord lymphoma. (A) Sagittal T1-weighted image pre contrast. (B) Sagittal T1-weighted post administration of intravenous contrast showing enhancement of lesion between L5 and L7.

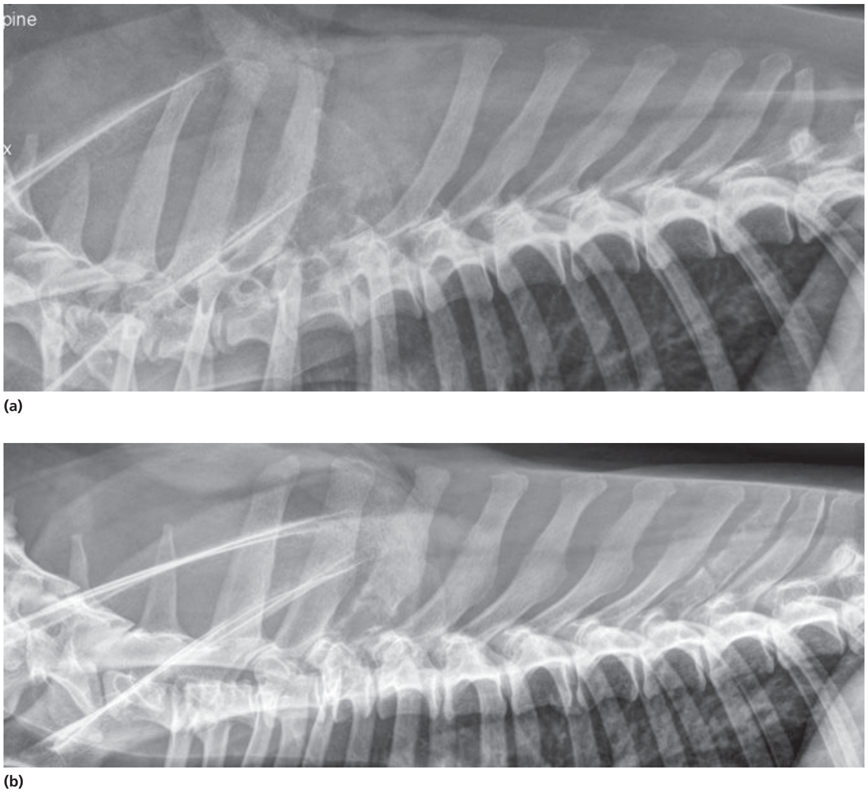


Figure 13.74 Radiographs of two dogs with osseous neoplasia in the cranial thoracic spine. (A) Note severe lysis of the spinous process and lamina of T4. (B) Note lysis of the T3 and T8 spinous processes.

or necrosis of a tumor, or rapid growth of a neoplasm with subsequent damage to spinal cord parenchyma (more likely with intramedullary tumors). Spinal cord tumors are typically solitary, and can occur anywhere along the length of the spine. Meningiomas and MNSTs arise most frequently in the cervical spinal cord, with MNSTs being especially prominent in the cervical intumescence area. Many primary and metastatic osseous tumors occur in the cranial thoracic area and this region should always be investigated when spinal neoplasia is suspected, which would be any large breed dog with chronic or subacute onset of paraparesis (Fig. 13.74). Feline lymphosarcoma is found more often in the thoracolumbar spine than the cervical spine. The vast majority of reported nephroblastomas of young dogs have been located between T10 and L2 vertebral levels.

A prominent feature of extradural and intradural/extramedullary spinal neoplasia is spinal hyperesthesia, which often precedes the onset of proprioceptive and voluntary motor deficits. Spinal hyperesthesia is often not a prominent clinical feature in patients with intramedullary spinal tumors, probably due to the lack of meningeal involvement. However, in a recent study with 53 dogs with intramedullary neoplasms, spinal hyperesthesia was found on palpation in 90% of cases. It is the clinical impression of the authors, though, that dogs with extramedullary tumors are significantly more painful. In MNSTs of the cervical intumescence, a history of unilateral thoracic limb lameness (on the side of the tumor) preceding the development of clinical signs of myelopathy is common. These cases can be mistaken as having orthopedic disease for prolonged periods of time. In the authors' experience, one of the key signs to suggest nerve involvement is the presence of severe or focal muscle atrophy.

3. A tentative diagnosis of spinal neoplasia is typically based upon signalment, history, clinical signs, and the results of spinal imaging. Bloodwork abnormalities are unlikely, but hyperglobulinemia and proteinuria may be evident in cases of myeloma. Electrophoresis can also be performed when suspected of multiple myeloma. Most cats with spinal lymphosarcoma are FeLV positive, have leukemic bone marrow, and have multicentric neoplasia. Many cats also have renal involvement, thus bone marrow and ultrasound-guided kidney biopsies can assist in the diagnosis of lymphosarcoma. With the possible exception of spinal lymphosarcoma, CSF evaluation rarely reveals neoplastic cells, and may reveal increased protein levels, with or without elevated cell counts (more likely with tumors with meningeal involvement). When lymphoma is suspected (in cases of lymphocytic pleocytosis or possible neoplastic lymphocytes in the CSF), flow cytometry or polymerase chain reaction (PCR) for lymphocyte antigen receptor rearrangement (PARR) can be used to confirm the diagnosis. Testing for PARR requires a higher

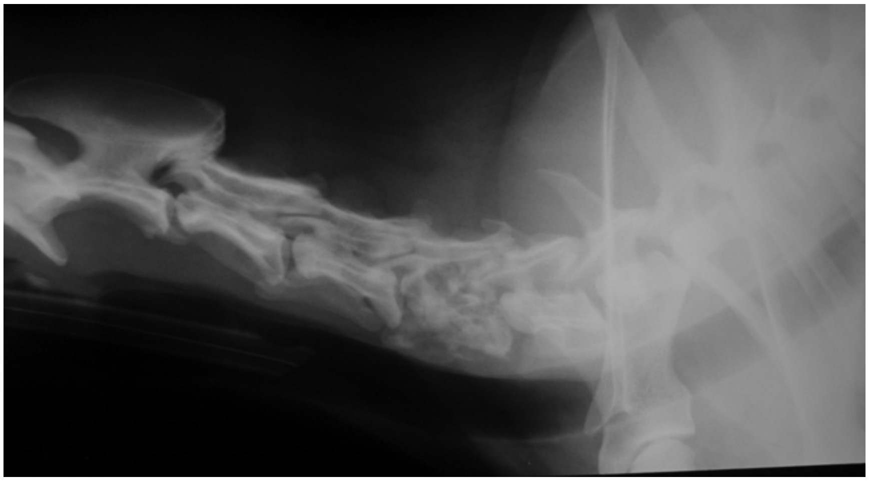


Figure 13.75 Lateral radiograph of a dog's cervical spine, demonstrating an osteosarcoma lesion involving the C5 vertebral body.

concentration of lymphocytes than what is required for flow cytometry but it can also be done on slides. In cases of vertebral neoplasia, bony lysis with loss of cortical outlines is often seen on imaging of affected vertebrae, with or without evidence of bony proliferation (Fig. 13.75). It is important to evaluate the vertebral structures very carefully, because multiple myeloma tends to cause marked bone lysis with minimal proliferation (see Fig. 13.91). In the majority of soft-tissue spinal neoplasms, plain radiographs of the spine are normal. Myelography, CT, or MR imaging (Fig. 13.76) are usually helpful both in the diagnosis of spinal tumors and therapeutic

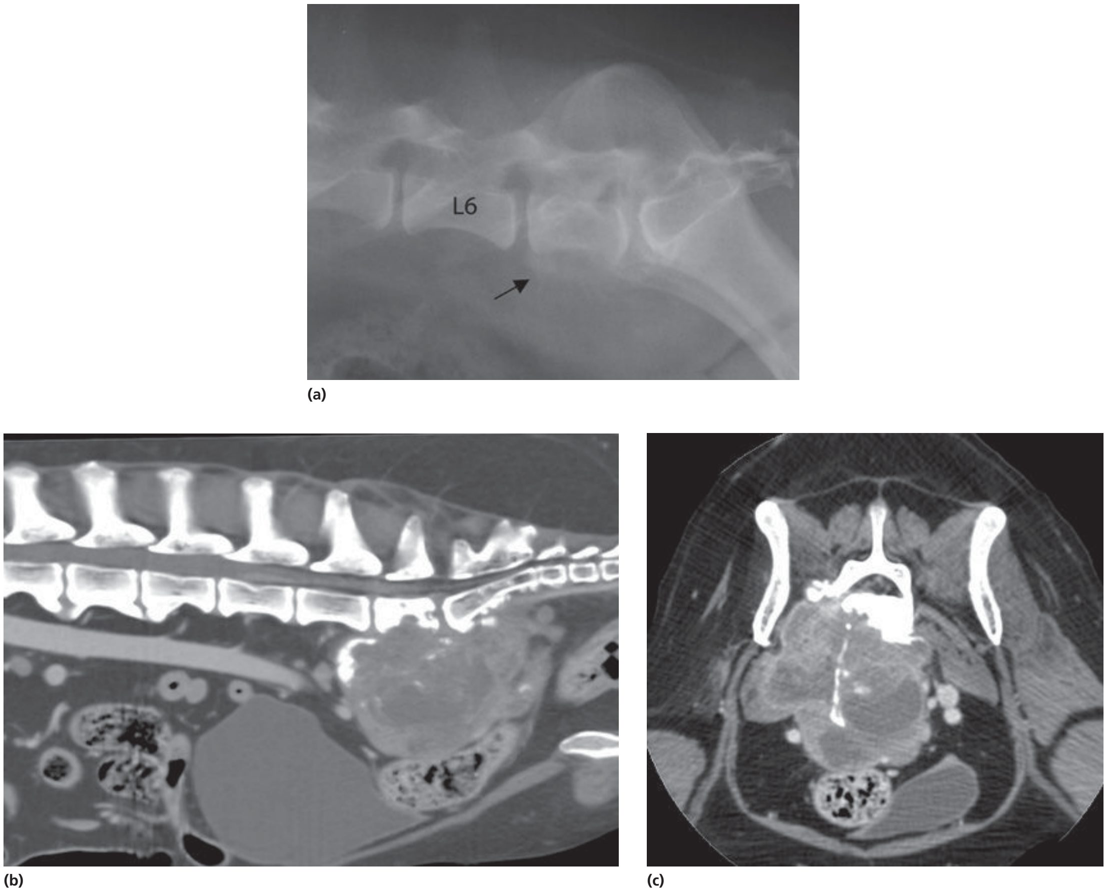


Figure 13.76 Images of a dog with an aggressive sarcoma involving the L7 and S1 region. (A) Lateral radiograph showing an osseous lesion with bony and soft tissue proliferation at L7–LS1. (B) Sagittal CT image showing a large soft tissue mass extending dorsally towards L7 and S1. (C) Transverse CT image showing lysis of the vertebral body of L7 and involvement of the nerve roots in the right. Note severe ipsilateral muscle atrophy.

planning. An intramedullary myelographic pattern may be misleading, as an intradural/extramedullary mass with attendant cord swelling may cause an identical pattern on myelography or advanced imaging (e.g. CT or MRI). Intradural/extramedullary spinal tumors will occasionally infiltrate the spinal cord parenchyma (mixed compartment mass), which may contribute to the development of an intramedullary imaging pattern (Fig. 13.77).

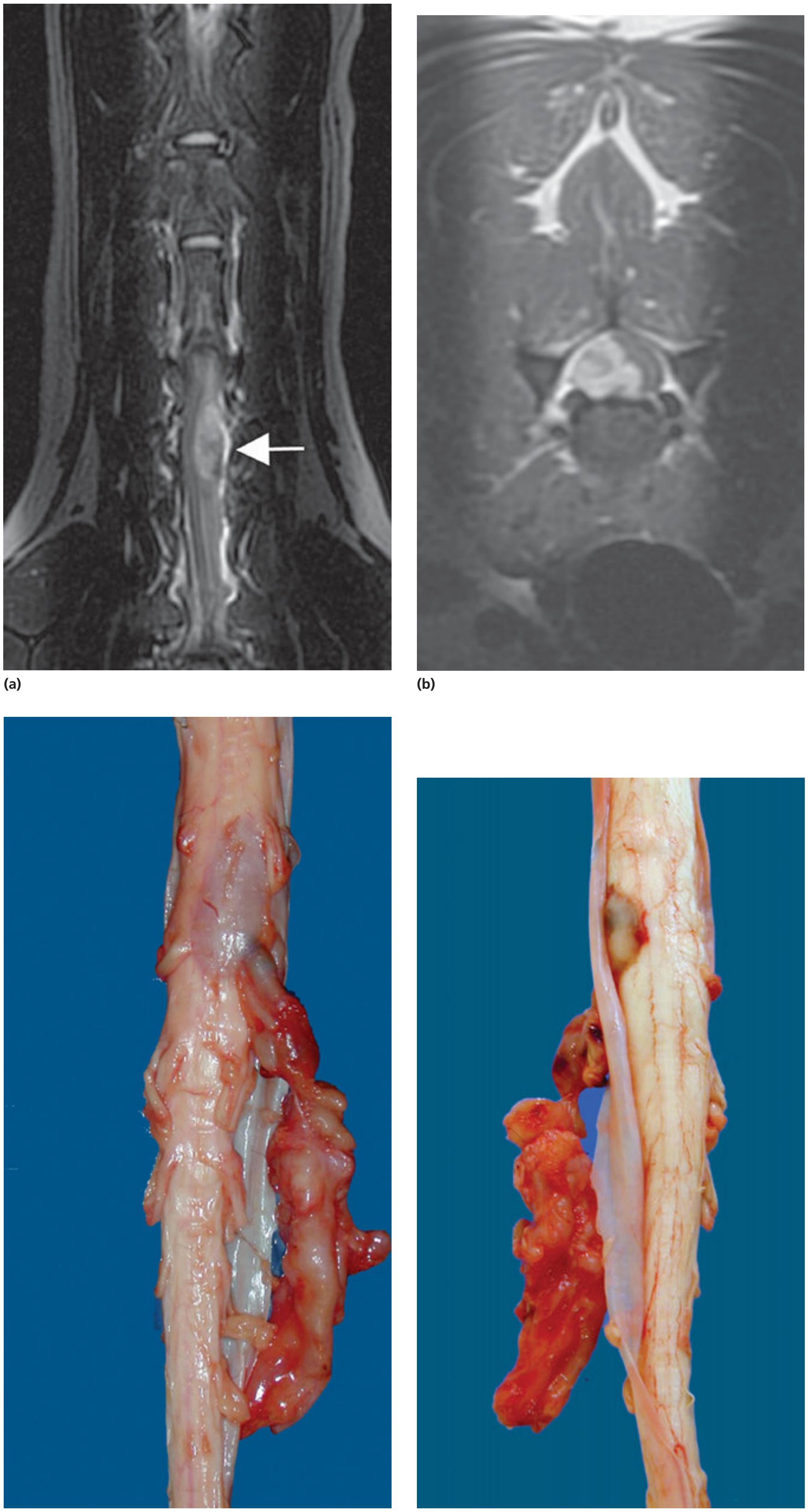
It is important to realize that both meningiomas and MNSTs tend to be associated with an intradural extramedullary pattern. Also, both tumors appear to have a predilection for the cervical spinal cord. In some cases of MNST, an enlarged intervertebral foramen evident on radiographs, CT or MRI, and/or an enlarged nerve root identifiable with CT or MRI, may help in distinguishing a tumor as being an MNST, rather than meningioma. The absence of such distinguishing imaging results, however, does not rule out the possibility of MNST. Myelography has been shown to be more useful than CT or MRI to differentiate intradural/extramedullary from intramedullary tumors. A definitive diagnosis of spinal tumors in all cases requires a histopathologic evaluation of affected tissue. This is facilitated with surgical intervention. However, fluoroscopic, US or CT-guided needle biopsy may provide a diagnosis in some cases (Fig. 13.78).

4. As with brain tumors, therapy for dogs and cats with spinal tumors can be divided into supportive and definitive treatments. Supportive therapies are directed against secondary sequelae of the spinal tumor (e.g. cord edema, pain), whereas definitive therapies are aimed at elimination of neoplastic tissue. Supportive therapy consists of anti-inflammatory doses of glucocorticoids (e.g. prednisone, 0.5 mg/kg, PO, q 12 hrs), which can be increased or decreased as needed, with or without additional pain-relieving drugs (e.g. narcotics). Definitive therapy consists primarily of surgery and megavoltage radiation therapy, similar to brain tumor definitive therapy (see Chapter 7). Chemotherapy is indicated for lymphosarcoma and myeloma. There are no reports describing the use of chemotherapy for other spinal neoplasms (e.g. gliomas) in dogs and cats.

The prognosis for dogs and cats with spinal neoplasia treated with supportive therapy alone is poor. Although data are lacking, these patients will likely be euthanized because of progressive spinal cord dysfunction within several weeks to several months, depending on the tumor type. For most canine and feline spinal tumors, there is a lack of meaningful prognostic information based upon large numbers of cases in which definitive therapy was pursued. With the exception of lymphosarcoma, there is a notable absence of prognostic information pertaining to feline spinal neoplasia. In one report, prognostic data concerning nonlymphoid spinal neoplasia in 11 cats were described. Several of the cats experienced prolonged remissions following surgical intervention, including one cat with osteosarcoma, one with chondrosarcoma, one with an MNST, and one with meningioma, with survival times of approximately 57 mos, 12 mos, 73 mos, and 47 mos, respectively. The MST for four additional cats with meningioma was approximately 6 mos after surgery. Although based on a small number of cases, nonlymphoid spinal neoplasia may often be associated with a favorable prognosis in cats treated surgically. There is some evidence to suggest that osteosarcomas may be less aggressive in cats, compared with dogs.

The prognosis for most cases of vertebral neoplasia in dogs (e.g. osteosarcoma, chondrosarcoma) is considered poor. Surgical decompression may provide some temporary relief of clinical signs. However, vertebral neoplasms often cause such extensive bony destruction by the time of diagnosis that any further destabilization due to surgical intervention (e.g. laminectomy) may hasten the development of a pathologic fracture/luxation. Radiation therapy and chemotherapy are usually unsuccessful in the treatment of these tumors. In one report of dogs with vertebral tumors treated via various methods (e.g. surgery, radiation therapy, chemotherapy), the MST was 135 days. Sustained remissions (more than 1 yr) are likely in patients with plasma cell tumors (myeloma) of the vertebrae that are treated with chemotherapy. Although chemotherapy and/or radiation therapy is the recommended definitive therapy for spinal lymphoma, the majority of both feline and canine cases will be euthanized within 3 mos due to progressive or recurrent disease, despite therapy. One report described the outcome in 17 dogs treated with surgery alone or surgery followed by radiation therapy. Surgery alone yielded a MST of 19 mos. Radiation therapy after surgical treatment was reported to significantly increase the survival time, ranging from 18 to 78 mos. No reports described the survival time with radiation therapy alone.

The prognosis for surgical removal/debulking of canine spinal MNSTs appears to be poor. Median postoperative survival is approximately 5–6 mos, with a disease-free interval of only about 1 mo. The efficacy/inefficacy of postoperative radiation therapy for spinal MNSTs has not yet been established for dogs or cats. There are several reports of the successful surgical removal of nephroblastomas in young dogs, only a few of which report long-term follow-up; it is thought that recurrence of the tumor is likely within 6–12 mos in some cases. A case series reported an MST of 374 days with surgery and radiation therapy. There is also some evidence that spinal nephroblastomas may at times invade the spinal cord parenchyma and those cases have shorter survival. Adjunctive therapy (i.e. radiation therapy, chemotherapy) for this neoplasm remains to be investigated. Intramedullary spinal neoplasia is uncommon. The prognosis for dogs and cats with these tumors is considered poor. A report described the survival time for 22 dogs with intramedullary tumors.


(a)

(b)

(c)

(d)

Figure 13.77 Images of dog with primary nerve sheath tumor in the brachial plexus that extended into the spinal cord. (A) Dorsal T2-weighted imaged of the cervical spine showing an oval area of hyperintensity (arrow). (B) Transverse T1-weighted image post contrast enhancement showing a large mass within the spinal cord. (C) Ventral image of the spinal cord showing a large mass involving the nerves peripherally and extending proximally invading the spinal cord. (D) Dorsal view of the spinal cord with the dura mater open showing mass within the spinal cord. (From da Costa RC. In: Daleck CR, de Nardi AB, Rodaski S. *Oncology in Dogs and Cats*; 2009 (in Portuguese). Guanabara Koogan. With permission.)

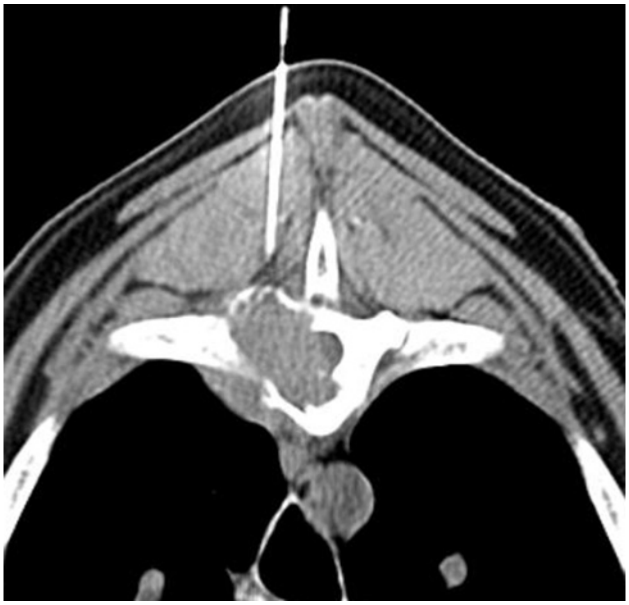


Figure 13.78 CT-guided biopsy of a spinal mass in the thoracic spine.

The MST was only 20 days (23 days for primary tumors, 16.5 days for metastatic tumors).

There are a number of reports of the surgical removal of lipomatous spinal cord masses in dogs. Although the overall success rate of surgery appears to be favorable, even with infiltrative lipomas and liposarcomas, postoperative radiation therapy may be advisable with these latter two tumor types in order to achieve good long-term results.

D. Nutritional

1. Feline hypervitaminosis A[86, 287, 423]
    - **a.** This is an uncommon disease of adult cats (2–10 yrs old) fed a diet with excess vitamin A. These diets typically consist primarily of liver. Confluent exostoses of multiple bones, including cervical and thoracic vertebrae, form the basis for clinical signs.
    - **b.** Clinical signs of neck pain and rigidity, lameness, and reluctance to move are common. The cervical vertebral exostoses can compress spinal nerves, leading to hyperesthesia.
    - **c.** Changing the diet may halt further progression of the disease, but the prognosis for recovery is poor.
2. Methionine deficiency-related spinal myelinopathy[287, 407, 481, 500]
    - **a.** A unique myelopathy has been described in hunting dogs in Europe. English Foxhounds, Harriers, and Beagles have been reported to develop a diffuse myelopathy that is associated with being fed a diet composed primarily or exclusively of ruminant (cow and sheep) stomachs for at least 6 mos. The predominant lesion is spinal cord demyelination, with relatively mild axonal damage. Affected dogs have significantly lower serum methionine levels and significantly higher liver methionine synthetase activity, in comparison with age-matched controls fed a balanced diet. The dietary-induced methionine deficiency is believed to cause a disruption of spinal cord myelin integrity.
    - **b.** Adult hunting dogs between 2 and 7 yrs of age have been described with this disorder. A gradual onset of mild paraparesis and pelvic limb ataxia is typical, and the gait often worsens with exercise. There is often exaggerated flexion of the pelvic limbs during ambulation. Another characteristic feature of this disorder is a loss of panniculus (cutaneous trunci) reflex caudal to the thoracolumbar junction area of the spine.
    - **c.** Diagnosis of this condition is based primarily upon dietary history combined with characteristic clinical signs of a progressive T3–L3 myelopathy. Bloodwork and urinalysis results are within normal limits, as are results of CSF analysis and myelography. Serum methionine levels are abnormally low and liver methionine synthetase levels are abnormally elevated. In dogs that were euthanized for this condition, histopathologic evidence of demyelination with minor axonal damage is appreciated throughout white matter of the spinal cord as well as some brain-stem areas.
    - **d.** Treatment of the condition is switching affected dogs to a balanced diet. The prognosis for full recovery is favorable after institution of sound feeding practices.

E. Inflammatory/infectious

1. Discospondylitis[66, 252, 287, 512]

   This is an infection of the intervertebral disc and surrounding vertebral endplates that is usually caused by bacteria. The most common bacteria incriminated are *Staphylococcus* spp. Other bacteria and fungal organisms have also been reported to cause discospondylitis. A pathologically similar, but radiographically distinct, disorder called vertebral physitis, has also been described. Any vertebral level can be affected, but the L7–S1 space is one of the most common. This disease is discussed in more detail in Chapter 14.
2. Meningitis/meningomyelitis[12, 29, 48, 65, 80, 103, 145, 152, 158, 175, 179, 214, 250, 262, 282, 287, 310, 334, 335, 361, 362, 385, 425, 435, 436, 459, 463, 464, 468, 501, 513, 518–520, 533, 539, 547]
    - **a.** Noninfectious causes—granulomatous meningoencephalomyelitis (GME) is discussed in detail in Chapter 7. Occasionally, clinical signs of myelopathy predominate in GME patients, especially signs of cervical myelopathy. A number of other inflammatory conditions, in which clinical signs of myelopathy predominate and for which no infectious organism has been identified have been described:
        1. Corticosteroid responsive (aseptic) meningitis, also known as steroid responsive meningitis-arteritis—this is an immune-mediated disease

with the inflammatory process targeting the leptomeninges and associated vessels. The etiopathogenesis is unknown but the immunopathogenesis is characterized by markedly increased IgA levels in CSF and serum, increased B-cell/T-cell ratio in the blood and CSF, a suggested Th2-mediated immune response, and autoantibodies in the CSF and serum, which are not specific for the disease and thought to be an epiphenomenon. Elevated IL-8 levels and increased chemotactic activity in the CSF can explain the invasion of neutrophils in the leptomeninges in SRMA. This usually occurs in young (less than 2 yrs old), medium- to large-breed dogs, and may be the most common type of meningitis encountered in veterinary practice. A few breeds are predisposed, Boxers, Beagles, Bernese Mountain dog, Golden Retrievers, German Shorthaired Pointers, and Nova Scotia Duck Tolling Retrievers appear to be predisposed to developing this aseptic meningitis (Fig. 13.79). Clinical signs most often include severe neck pain and fever, without other signs suggesting systemic disease. Neurologic signs are uncommon in acute presentations. Affected dogs are reluctant to walk and a stiff gait may be seen. A chronic, protracted form has been reported, which is associated with deficits compatible with a cervical or multifocal myelopathy. A peripheral neutrophilia may be apparent on a complete blood count (CBC). The CSF in these cases may appear hemorrhagic, cloudy, or xanthochromic (Fig. 13.80). CSF analysis reveals a neutrophilic pleocytosis with elevated protein levels (Fig. 13.81). The neutrophils are nondegenerate and CSF culture results are negative. Concurrent autoimmune nonerosive polyarthritis appears to be very common with this disorder; in one study, five of 11 dogs (46%) with autoimmune polyarthritis and spinal hyperesthesia had evidence of aseptic meningitis on CSF analysis. Treatment with immunosuppressive doses of prednisone (2–4 mg/kg/day) usually results in rapid improvement. These patients should be slowly weaned off the prednisone over a number of months (e.g. 3–6 mos), but, in the authors' experience, approximately one-half of these dogs will require some level of long-term immunosuppressive therapy; most of the dogs requiring such extended therapy can be weaned to a very low dose of drug. There are anecdotal

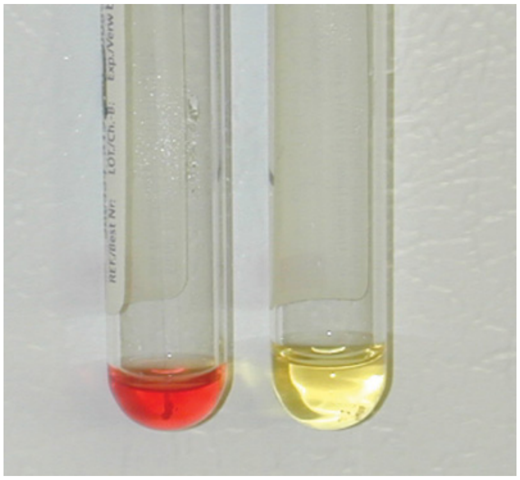


Figure 13.80 Cerebrospinal fluid of a dog with corticosteroid responsive meningitis collected from the cervical and lumbar regions showing hemorrhagic and xanthochromic appearances.

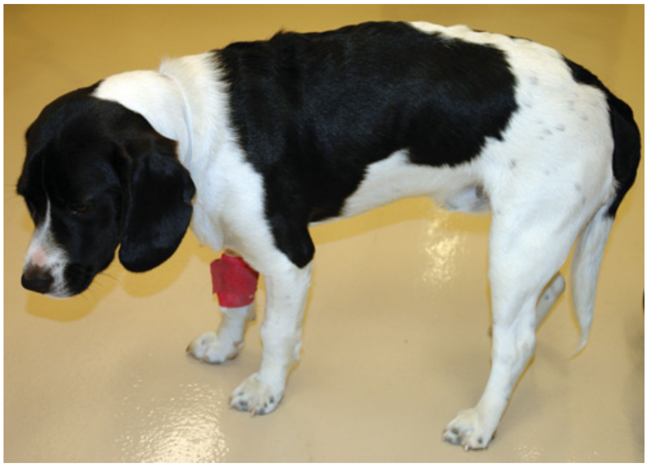


Figure 13.79 Posture of cervical pain in a Beagle with steroid responsive meningitis-arteritis.

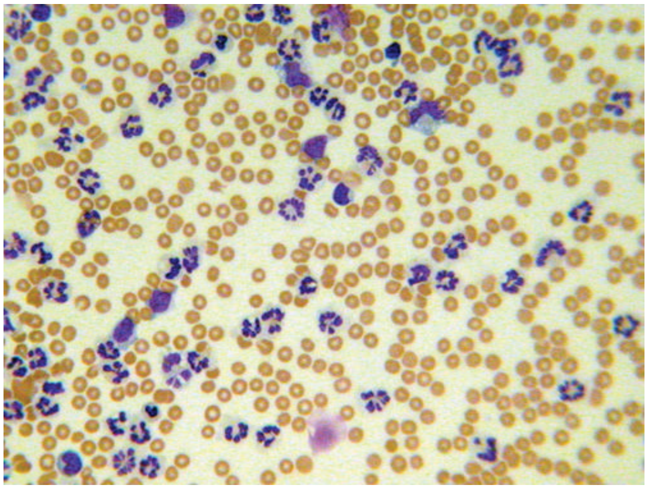


Figure 13.81 Cerebrospinal fluid from a dog with steroid responsive meningitis. Cytologic appearance of neutrophilic pleocytosis with hemorrhage in the background.

reports of successfully using other immunomodulatory drugs for this disorder (e.g. azathioprine, cyclosporine), especially for cases of relapse. The prognosis for control of clinical signs with this disease is typically excellent. A major rule-out for a suppurative pleocytosis is bacterial meningitis (see Chapter 7). Concurrent therapy with broad-spectrum antibiotics may be warranted if the diagnosis is questionable.

2. Myelitis and meningomyelitis—myelitis refers to an inflammatory process involving only the spinal cord but not the meninges, whereas meningomyelitis would be an inflammation of both the spinal cord and the meninges. Clinically, the distinction between the two diseases is based on the presence or absence of spinal pain. Dogs with pure myelitis will have no spinal pain as the spinal cord (and brain) have no nociceptors. Myelitis and meningomyelitis are not common spinal conditions compared with meningoencephalitis or other spinal disease, but it is important to keep them on the list of differentials, because CSF analysis is required to diagnose them. Clinical signs associated with meningomyelitis depend on the affected region of the spinal cord and include paresis or paralysis, pain, and proprioceptive deficits. Both subacute (3–7 days) and chronic presentations are seen. One consistent feature of myelitis is the asymmetry in the neurologic deficits. It is not as asymmetric as seen in vascular diseases such as fibrocartilaginous embolic myelopathy, but it is close. Spinal reflexes may or may not be reduced depending on the lesion localization. There are few reports in the literature. In the largest cases series (28 cases), the breeds more commonly affected were hounds or toy breeds. Meningomyelitis of unknown etiology and granulomatous meningomyelitis were the most common presumptive diagnoses. A diagnosis of meningomyelitis is supported by CSF analysis and MRI (Fig. 13.82). Typically, the diagnosis of noninfectious meningomyelitis (also known as meningomyelitis of unknown cause) is achieved after ruling out infectious agents with serology, PCR, and CSF culture investigations. The treatment for meningomyelitis of unknown etiology is based on the use of corticosteroids and other immunosuppressive agents if necessary (see Chapter 7 for a treatment of noninfectious meningoencephalitis).
3. Pyogranulomatous meningoencephalomyelitis—a severe, usually rapidly (over 2–3 wks) progressive disorder, primarily involving the caudal brain stem and cranial cervical spinal cord, has been described in mature pointer dogs. Inflammatory lesions occur in the meninges and parenchyma of the brain and spinal cord. Clinical signs typically suggest a painful cervical myelopathy. Other reported signs include trigeminal and facial nerve paralysis, vestibular dysfunction (e.g. head tilt, nystagmus), Horner's syndrome, seizures, vomiting, and bradycardia. A predominantly neutrophilic pleocytosis with elevated protein levels is a characteristic CSF finding. While some dogs respond temporarily to antibiotic therapy, the prognosis is poor.

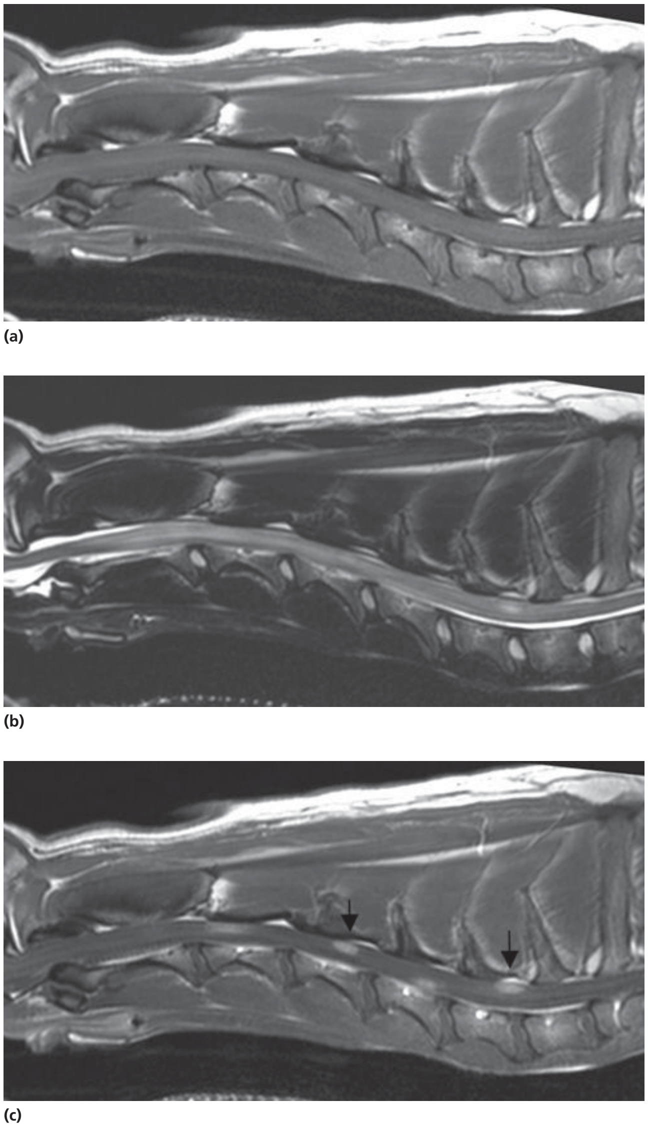


Figure 13.82 Meningomyelitis in a dog. (A) Sagittal T1-weighted image of the cervical spine. (B) Sagittal T2-weighted image showing diffuse hyperintensity in the spinal cord. (C) Postcontrast sagittal T1-weighted image showing multiple focal areas of contrast enhancement (arrows).

4. Aseptic meningitis/polyarthritis of Akita dogs—two of eight young (less than 8 mos old) Akita dogs

with a syndrome similar to juvenile rheumatoid arthritis of people had evidence of aseptic meningitis. One pup responded poorly to immunosuppressive therapy and one pup was euthanized (no therapy attempted).

5. Feline polioencephalomyelitis—this is an uncommon subacute to chronic disorder of both young and adult cats. A nonsuppurative inflammatory process of unknown etiology (viral suspected) leads to neuronal, axonal, and myelin loss in both the brain and the spinal cord. Clinical signs of myelopathy (ataxia and paresis of pelvic limbs or all four limbs) predominate, but intention tremors and focal seizure activity may be observed. Leukopenia may be demonstrated by a CBC. Antemortem diagnosis is difficult and the prognosis is poor.

b. Infectious causes (see also Chapter 7)—appropriate references dealing with diagnosing and treating infectious diseases should be consulted for more detail. All of the following infectious diseases may result in clinical signs of myelopathy, with or without signs suggesting brain dysfunction:

1. Viruses, such as canine distemper virus, feline coronavirus (FIP).
2. Bacteria, such as *Staphylococcus* spp., *Streptococcus* spp., coliforms—an apparently rare disease syndrome called spinal epidural empyema has been reported to cause a severe myelopathy in a number of dogs and one cat. The route of infection of the epidural space may be either hematogenously or direct (e.g. bite wound, foreign body). The majority of cases were imaged via myelography, which showed evidence of extensive purulent epidural fluid accumulation, typically over several vertebral lengths. These purulent accumulations can be more focal and can also be multifocal along the length of the spinal cord. Both MRI and CT have been used to image this condition in veterinary medicine, and MR imaging is the preferred modality. Hallmarks of this disorder are spinal hyperesthesia, fever, and often rapidly progressing paresis or plegia. Lethargy and anorexia have also been described in many of the reported cases. Peripheral neutrophilia apparent on a CBC is a consistent laboratory finding in patients with spinal epidural empyema. A moderate neutrophilic pleocytosis with elevated protein concentration is likely on CSF analysis. CSF culture is typically negative, but cultures from blood and epidural fluid are often positive. There may or may not be radiographic evidence of vertebral osteomyelitis or discospondylitis. The key to the successful management of this disorder appears to be rapid diagnosis and aggressive medical and surgical treatment. Although somewhat controversial, spinal epidural empyema is considered by most sources as a surgical emergency, with delayed diagnosis and treatment often leading to poor outcomes. Despite the high level of morbidity and mortality associated with this condition, successful outcomes are likely if expedient surgical decompression and treatment with broad-spectrum antibiotics (based on culture/sensitivity result) is undertaken. The patient's neurologic status has to be considered because dogs with mild neurologic deficits and spinal pain can be successfully managed with appropriate antibiotics.
3. Fungi, such as *Cryptococcus*, coccidioidomycosis.
4. Rickettsiae, such as *Ehrlichia*, *Rickettsia*, Rocky Mountain spotted fever.
5. Protozoa, such as *Toxoplasma*, *Neospora*.
6. Parasitic, such as *Dirofilaria*, *Cuterebra*.
7. Algae, such as *Prototheca*.

F. Ischemic/vascular

1. Fibrocartilaginous embolic myelopathy (FCEM)[1,2,24,71,94,133,134,137,156,198,219,224,257,287,315,320,334,365,383,386,387,448,467,500,515,524,529,531,568,569] (Videos 29 and 30)

   a. This is a common syndrome caused by the embolization of arterial and/or venous supply to an area of the spinal cord. The embolizing material has been identified as fibrocartilage and is believed to originate from the NP of the intervertebral disc (Fig. 13.83).

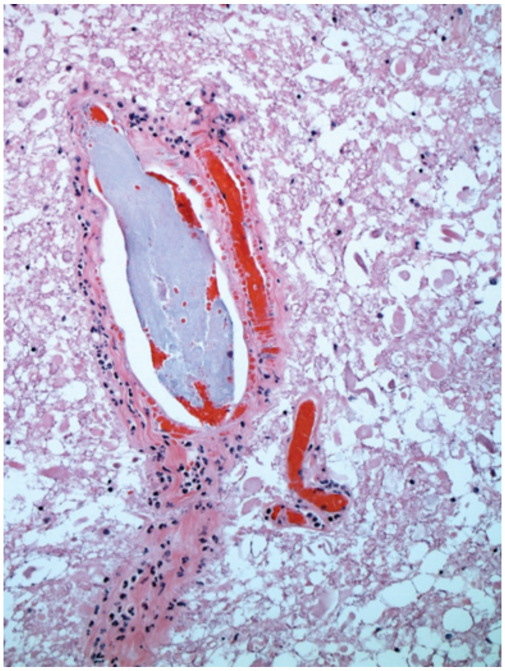


Figure 13.83 Fibrocartilage material within a spinal cord vessel from a dog with confirmed fibrocartilaginous embolic myelopathy.

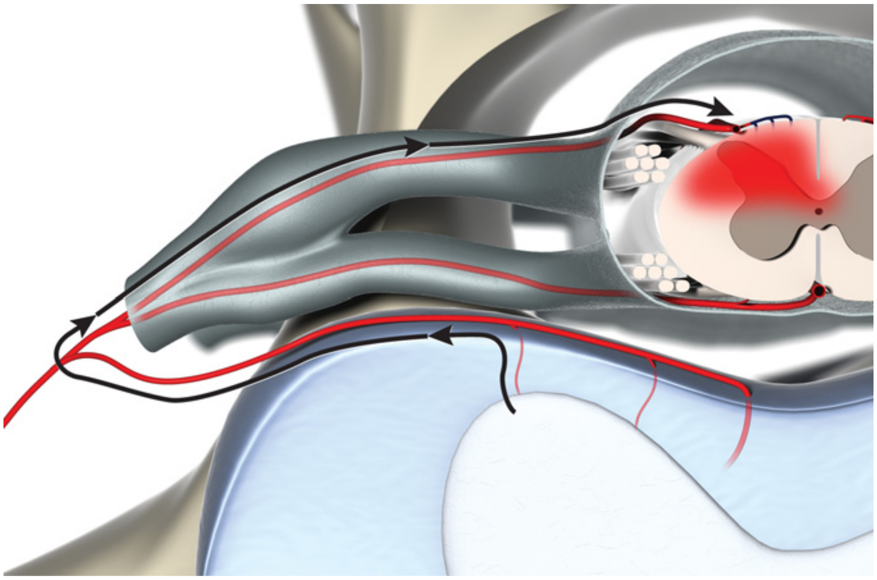


Figure 13.84 Diagram demonstrating one of the possible theories for development of fibrocartilaginous embolic myelopathy. Neovascularization over the annulus fibrosus can lead to penetration of fibrocartilage material into the vascular system leading to spinal cord embolism. (The Ohio State University. Reproduced with permission.)

The mechanism or mechanisms by which this material reaches the spinal cord vasculature from the disc is/are unknown. Theories center around either venous entry of disc material (e.g. extrusion either directly into a venous sinus or venous system of vertebral bone marrow, a Schmorl's node) with retrograde movement into the spinal arterial system or direct entry to the spinal cord arterial system (e.g. into normal surrounding vasculature or neovascularization over the annulus fibrosus associated with concomitant type II disc degeneration) (Fig. 13.84).

b. This disease usually affects nonchondrodystrophic dogs, principally of large and giant breeds, but smaller nonchondrodystrophic dogs (e.g. Shetland Sheepdogs, Miniature Schnauzers) and a number of cats have been reported. In addition, FCEM has been described in a few chondrodystrophic small-breed dogs. Approximately 20% of FCEM patients are dogs less than 20 kg. One study reported that FCEM is the most common cause of myelopathy in Miniature Schnauzers (Fig. 13.85). Age of onset of clinical signs ranges from the juvenile to the elderly, but most dogs presenting with FCEM are young to middle-aged (1- to 7-yr-old) adults. A number of juvenile (8–13 wks old) Irish Wolfhounds with FCEM were described in one report. Most of the reported cats with FCEM have been middle-aged to older at presentation (median age 10 yrs), and the majority were domestic shorthaired cats. Male cats seem to be slightly more predisposed (male to female ration 1.3:1). Most of the reported feline FCEM cases have involved the cervical spinal cord, with the C6–T2 region being the most commonly affected. The FCEM patient typically presents with a history of peracute to acute onset and progression of clinical signs. Most patients will reach peak severity of neurologic dysfunction within 24 hrs, many within 6 hrs or less. Very rarely, animals with FCEM may develop dysfunction over several days. Owners often observe the affected dog to cry out in apparent pain during exercise or a mild traumatic event, shortly before the onset of neurologic dysfunction. Approximately 50% of dogs develop the spinal cord infarction during some sort of intense physical activity (running, playing). These dogs are often not in any detectable pain by the time they are presented to the clinician. In one study, it was found that spinal hyperesthesia could be elicited in 21% of dogs with FCEM.

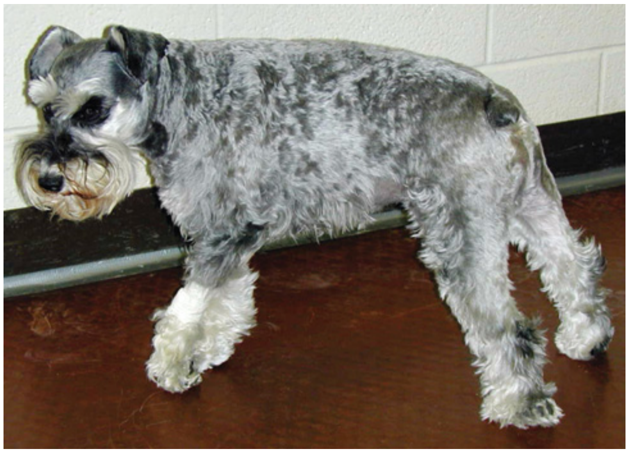


Figure 13.85 Miniature Schnauzer with fibrocartilaginous embolic myelopathy (FCEM). Note proprioceptive positioning deficits on left thoracic and pelvic limbs. Asymmetry is the clinical hallmark of FCEM.

It is the authors' experience that spinal hyperesthesia can often be elicited in FCEM patients that are examined shortly after the onset of neurologic dysfunction. These dogs are typically quite distressed, so the distinction between true spinal pain and anxiety is challenging. Exercise and/or trauma have been reported in 43–79% of cats with FCEM. Clinical signs of myelopathy will vary, depending upon both the location and severity of the spinal cord ischemic injury. Deficits are often moderate to strongly asymmetric and the clinical signs are typically not progressive after the first 24 hrs of infarction. One clinical feature frequently seen in dogs with FCEM in the thoracolumbar or lumbosacral region is a strong asymmetry of the cutaneous trunci reflex (i.e. a difference of several vertebral bodies between the cut-off in the left and right sides). The most common locations for FCEM in dogs are L4–S3 (44–50%), followed by T3–L3 (27–42%). In cats the most common location is C6–T2. Cats can have very severe presentations (typically more severe than dogs) and may even display signs of Horner's syndrome with cervical infarctions. Cats also seem to have other forms of ischemic myelopathy besides FCEM. A recent report described a hyaline arteriopathy (causing thrombosis) as the cause of ischemic myelopathy in five cats. The majority had involvement of the cervical spinal cord, which was mostly symmetric (as opposed to the asymmetry frequently seen with FCEM). The condition was also recurrent, which lead to euthanasia of all cats.

c. Diagnosis of FCEM is based upon history, signalment, clinical signs, and ruling out other causes of acute myelopathy. Main differentials are IVDD, trauma and myelitis. Results of plain radiography, CSF evaluation, and myelography are typically normal. Myelographic evidence of spinal cord swelling (intramedullary pattern) and nonspecific CSF abnormalities (e.g. elevated protein level, mild pleocytosis, xanthochromia) may be seen in some cases. The preferred method of imaging for patients with suspected spinal cord infarcts is MRI (Fig. 13.86); focal, sharply demarcated, hyperintense parenchymal lesions (suspected to be edematous, infarcted tissue) on T2-W and FLAIR images are characteristic. These lesions are isointense or hypointense to spinal cord on T1-W images and may display varying degrees of contrast enhancement (usually mild when present); the presence or absence of contrast enhancement may be related to the timing of MR imaging after the infarct occurs, often occurring about a week after injury in humans with FCEM. The FCEM lesions are often primarily within the gray matter of the spinal cord and unilateral in location. In one study of 52 dogs with suspected FCEM, 11 dogs (21%) did not have any lesions apparent on MR imaging. The appearance of lesions on MR imaging in this study was not associated with the timing of imaging after infarction (in people, ischemic lesions may not be apparent on MRI within the first 48 hrs of the infarct), but was significantly associated with the severity of neurologic dysfunction; ambulatory dogs were much more likely to have normal MRI results than non-ambulatory dogs. This study also found a positive association between disease severity and lesion extent on MR imaging. The lesions were measured both in length (sagittal images, expressed as a ratio over C6 or L2 vertebral length for cervical/cervicothoracic and thoracolumbar/lumbosacral lesions, respectively) and cross-sectional area (in the transverse images, expressed as a percentage of the cross-sectional area of the spinal cord in the area of infarction).

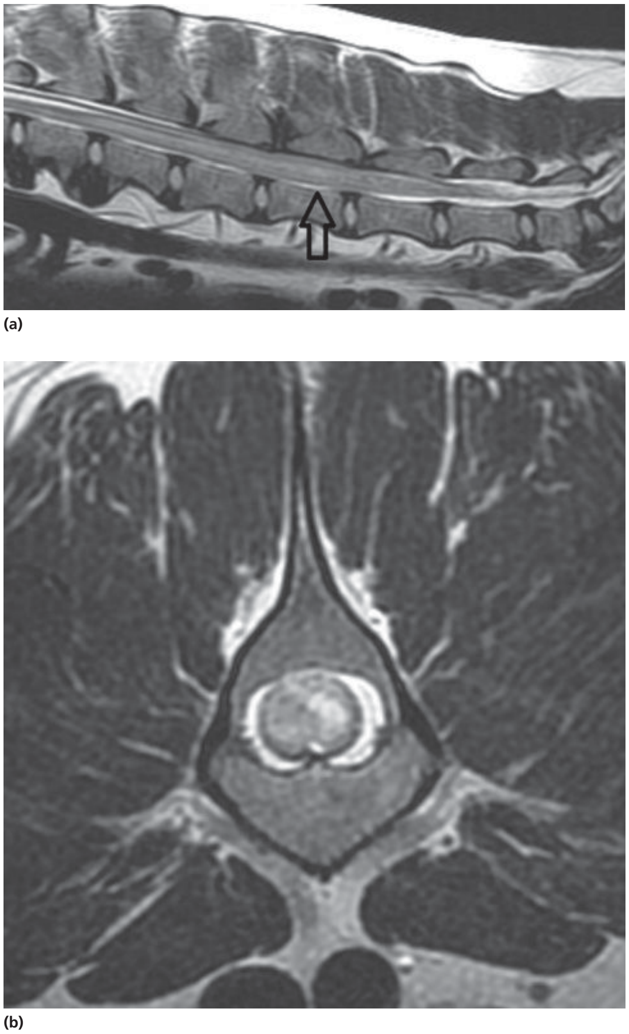


Figure 13.86 Sagittal (A) and transverse (B) T2-weighted MR images of a dog with an FCEM lesion in the caudal lumbar region. Note spinal cord hyperintensity and swelling in the sagittal image and the asymmetric hyperintensity in the transverse image.

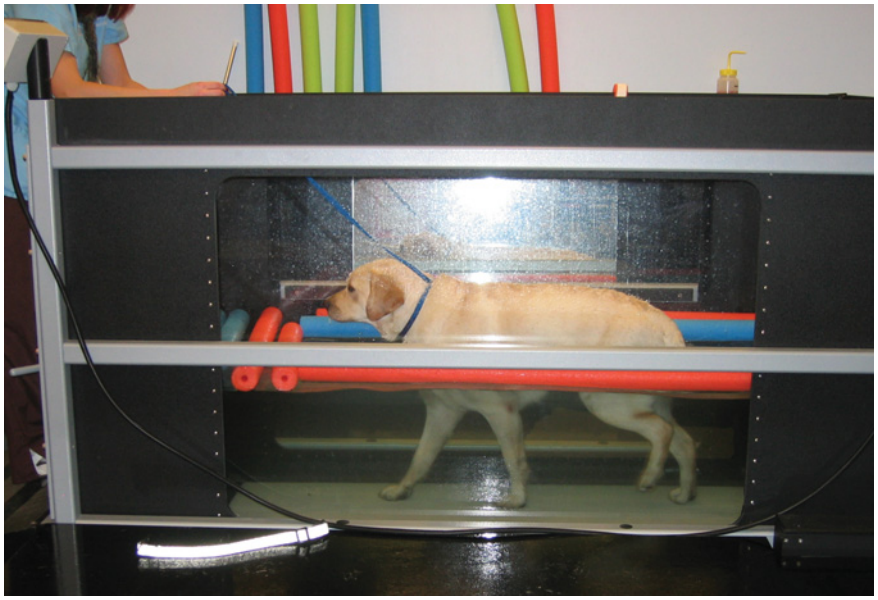


Figure 13.87 Physical therapy with underwater treadmill is a useful modality to hasten the recovery of dogs with FCEM.

d. The treatment of FCEM is controversial. Several reports suggest treating dogs using the same protocols used for spinal trauma, but the mechanisms of injury are quite distinct. To the authors' knowledge, no study has systematically investigated the treatment of FCEM with corticosteroids. Contrary to patients with spinal cord trauma, the recovery of FCEM patients is much faster, making an objective evaluation of steroid treatment very subjective. One of the authors (RdC) has treated dogs with and without corticosteroids and has not seen any difference in outcome, thus use of corticosteroids appears unnecessary for this disease. Vasodilators have been used but there is no evidence supporting a beneficial effect. There is some evidence that controlled physiotherapy (e.g. underwater treadmill) has a positive impact on neurologic recovery in dogs with FCEM (Fig. 13.87). Most dogs will show dramatic improvement in the first 3 to 7 days post FCEM. Development of collateral circulation and reperfusion may be responsible for this improvement. For nonambulatory dogs, especially of large and giant breeds, the prognosis for recovery is often guarded. Negative prognostic indicators reported include loss of DPP (nociception), severe LMN damage, and owner reluctance to pursue prolonged physical therapy. Some reports disagree with the assertion that LMN damage portends a worse prognosis than UMN spinal cord damage in FCEM cases. The degree of owner reluctance to pursue physical therapy is often associated with the size of the dog (e.g. prolonged physical therapy and bladder management for a paralyzed Great Dane may not be feasible for many owners). While earlier reports reported poor recovery rates and high mortality (up to 64%), it is the authors' opinion that, currently, the prognosis is quite positive, compatible with contemporary reports. In a recent report of 50 dogs, 42 (84%) had successful outcomes. In this study, the extent of the lesion as measured on MR images was predictive of outcome; dogs with a lesion length/vertebral length ratio (sagittal images; see previous discussion) of < 2 or a cross-sectional (transverse images) lesion area/spinal cord area percentage of < 67% were significantly more likely to recover, compared with dogs that had higher values for these parameters. Severity of neurologic signs at presentation was also significantly associated with a negative outcome in this study. The median time to maximal neurologic recovery for these dogs was 3.75 mos. In the report on miniature Schnauzers, only 22% of the cases were euthanized. While many of the surviving dogs regained functional status, most retained some neurologic deficits. As many dogs remain with asymmetric paresis for prolonged periods, paw protection is important to allow them to ambulate without injuring themselves (Fig. 13.88).

The prognosis for FCEM in cats seems similar to dogs (although older reports also suggested a guarded to poor prognosis). In a recent report with 19 cats, 15 (79%) recovered and most returned to have a normal lifestyle. The median time to recover ambulation for cats has ranged from 3.5 to 11.5 days. In addition to the reports of suspected or confirmed

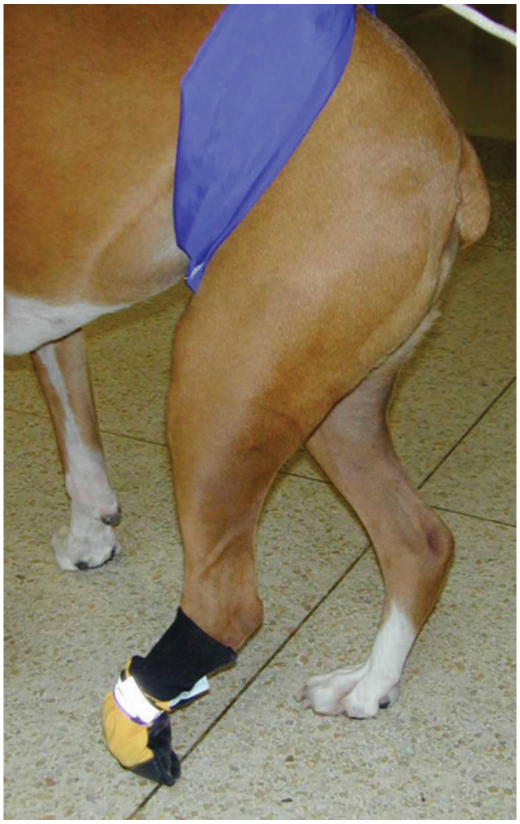
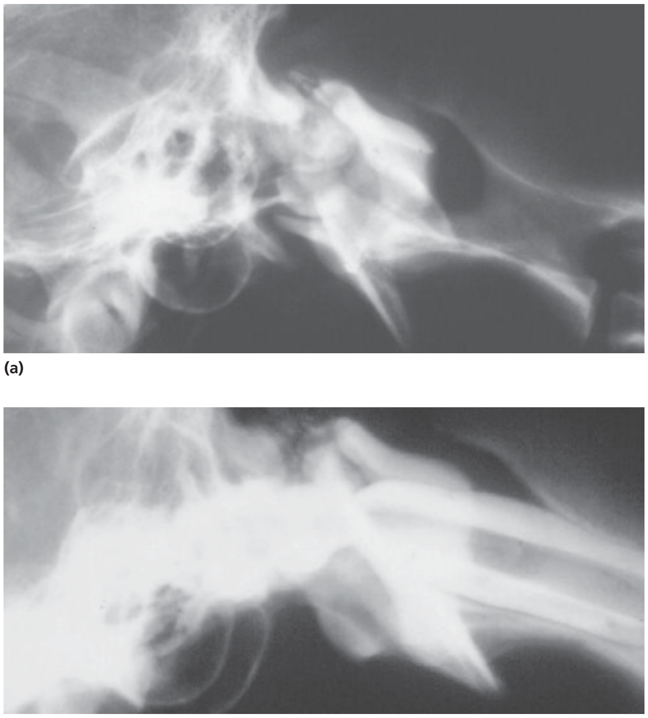


Figure 13.88 Protective boot in place in a Boxer dog recovering from FCEM.



(a)

(b)

Figure 13.89 Lateral premyelographic (A) and postmyelographic (B) images of a dog's cervical spine, demonstrating a dorsal compressive tumoral calcinosis lesion between the occiput and C1 vertebra. From: Dewey CW, Coates JR, Miscellaneous spinal disorders. In: D Slatter (ed.), *Textbook of Small Animal Surgery.* 3rd ed. Philadelphia: W.B. Saunders; 2002. Reprinted with permission.)

feline FCEM cases, one of the authors (CW) and colleagues have described MR imaging and clinical features of 11 acutely nonambulatory tetraparetic cats with suspected cervical infarcts (all based on characteristic MRI lesions). These were all older cats, with a median age of 15 yrs. Eight cats had evidence of a C1–C5 myelopathy and three had evidence of a C6–T2 myelopathy. Six of the eight cats with C1–C5 lesions had cervical ventroflexion and were unable to hold up their heads or move their head and neck voluntarily. The cats with C1–C5 myelopathy had very similar asymmetrical MRI lesions in the ventral gray matter at the C1–C2 vertebral level. Nine cats had pre-existing medical conditions that may have predisposed them to spinal cord infarction, including cardiomyopathy, hypertension, hyperthyroidism, and chronic renal failure. Though some of these cats may have had FCEM as a cause for infarction, there may be other potential causes for spinal cord infarction in cats. Eight of these 11 cats regained ambulatory function within 2 mos of presentation.

2. Traumatic feline ischemic myelopathy[500]

A syndrome of acute pelvic limb paralysis from ischemic myelopathy, associated with evidence of abdominal injury, has been described in cats. The ischemic cord damage is thought to be due to vasospasm and/or thrombosis of lumbar arteries that supply spinal branches to the cord. The proposed cause is compressive injury to the abdomen from an automobile tire. Treatment of this disorder has not been reported.

G. Toxic

Both strychnine and the exotoxin tetanospasmin from *Clostridium tetani* act at the spinal cord level to produce clinical signs of muscle rigidity. These similar disorders are discussed in Chapter 18, since they present clinically as disorders of muscle tone.

H. Miscellaneous

1. Tumoral calcinosis (calcinosis circumscripta)[143, 287, 336, 351, 507]

An idiopathic disorder of young, large-breed dogs has been described, in which partially calcified fibrous masses develop in periarticular connective tissue along the spine (Fig. 13.89). These are often solitary masses at the AA or upper thoracic intervertebral levels. This disorder is histologically distinct from solitary osteochondromas. Clinical signs of myelopathy depend upon lesion location and extent. Prognosis is favorable with surgical removal.

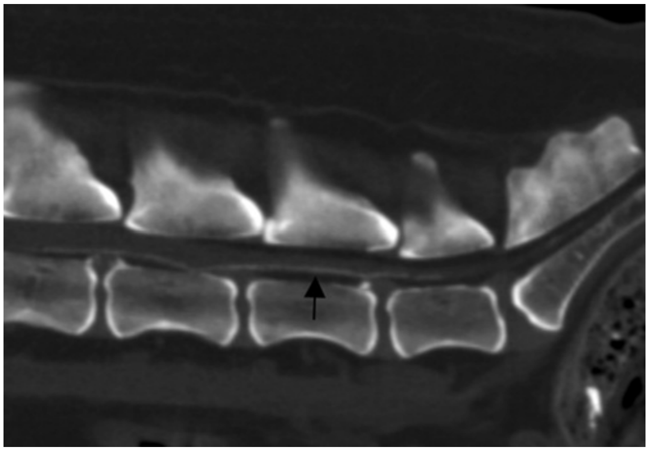


Figure 13.90 Sagittal CT image of the lumbosacral region showing dural ossification (arrow). (Courtesy of Drs. Camila Trevisan and Francisco Shigeru Hato Jr. *Hospital Veterinário Cães e Gatos 24h*; 2014. Osasco, Brazil.)

2. Dural ossification[287, 559]
   This is an idiopathic deposition of bony plaques on the inner surface of the dura mater, especially in older dogs. Radiographically, these plaques appear as radiopaque lines (Fig. 13.90), and are best seen at the intervertebral foraminal level. This is almost always an incidental finding, as it is rarely incriminated as causing clinical disease.
3. Spondylosis deformans[273, 281, 287, 289, 404]
   In the vast majority of cases, this is a common degenerative process of the spine, with no clinical significance (it can be considered a radiographic "distractor"; Fig. 13.91). Exostoses form around the ventral vertebral endplate margins, sometimes resulting in a bony bridge between adjacent vertebrae. This is a noninflammatory condition believed to be associated with degenerative changes in the annulus fibrosus of the intervertebral discs, and is possibly due to chronic mild instability at affected disc spaces. Osteophytes vary from small spurs to bone bridges across the disc space, leaving at least part of the ventral surface of the vertebral body unaffected. (Fig. 13.92) A recent retrospective study of 2041 dogs found spondylosis in 367 (18.1%) of them. This can be observed in adult animals of various sizes and ages, but tends to be more prominent in middle-aged to older medium- to giant-breed dogs. The margins of the exostoses are usually smooth and only proliferate ventrally and laterally (Fig. 13.93). Spondylosis is often associated with type II disc protrusions, especially at the lumbosacral junction, but by itself it is not an important clinical entity. There is no association between spondylosis deformans and the occurrence or location of type I disc extrusions in dogs, and it is not considered a clinically important phenomenon in such cases. This syndrome must be distinguished from discospondylitis (see Chapter 14) and disseminated idiopathic skeletal hyperostosis (DISH). Recently, a study suggested that spondylosis as well as DISH may predispose dogs to adjacent segment disease, predisposing them to the development of compressive myelopathies secondary to intervertebral disc disease.

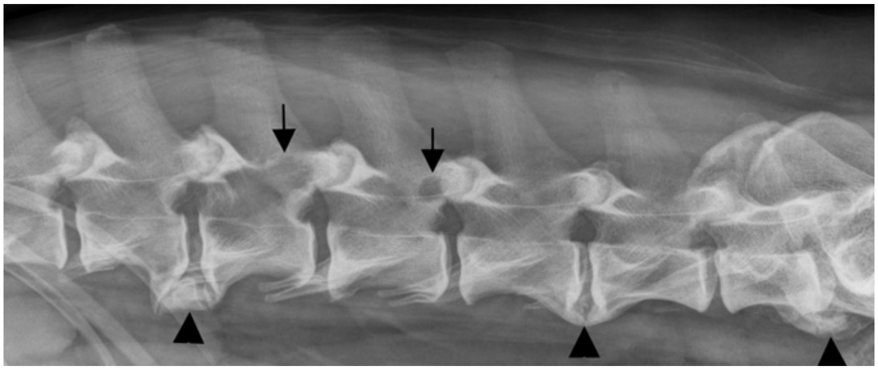


Figure 13.91 Multiple areas of spondylosis (arrowhead) in the lumbar spine of a dog. Note also several lytic lesions (arrows) caused by multiple myeloma which was the cause of the dog's neurologic signs.

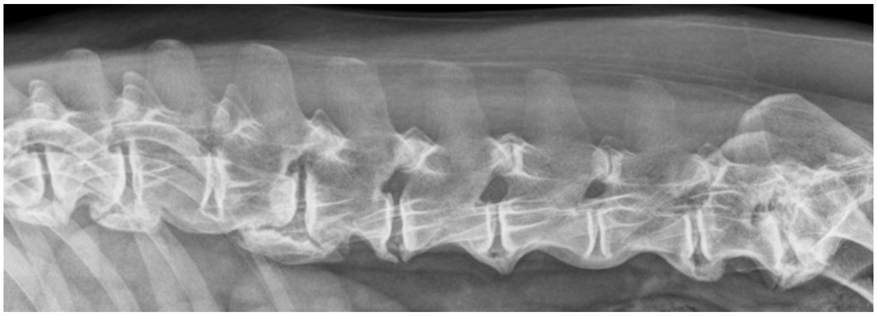


Figure 13.92 Severe appearance of spondylosis in the lumbar spine of a dog. Note that the central part of the vertebral body is spared of the osseous proliferation.

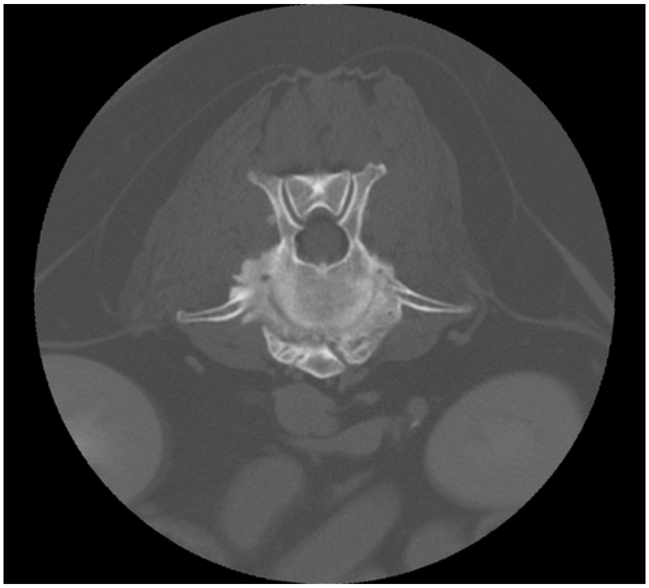


Figure 13.93 Transverse CT image of the dog in Fig. 13.92. Note that the osseous proliferation is located in the ventral and lateral aspects of the vertebral body. No proliferation is seen within the vertebral canal.

4. Disseminated idiopathic skeletal hyperostosis (DISH)[85, 273, 375, 562]

   This idiopathic disorder refers to extensive periarticular calcification and ossification throughout the body, including the vertebrae. It is thought that, for some unknown reason, DISH patients have an exaggerated bony proliferative response to minor bone stresses. In the same report of 2041 dogs mentioned previously, it was found that, though initially thought to be a rare condition, 78 dogs (3.8%) had DISH. Among these 78 dogs, 53 (67.9%) also had spondylosis. The most common location for DISH were T6–T10 and L2–L6 vertebral regions. Boxers and Flat-coated Retrievers were predisposed to both DISH and spondylosis, though Boxers were significantly more affected. Out of the 69 dogs with DISH, 28 (40.6%) were Boxers. It is important to differentiate DISH from spondylosis deformans. DISH is a systemic disorder characterized by fibrocartilaginous proliferation followed by endochondral ossification within soft tissues of the axial and appendicular skeleton. Ossification of DISH appears to affect an area rather than specific anatomic structures, as it develops not only at entheses but also along the surfaces of ligaments, short fibers, and in neighboring connective tissue, suggesting a possible biomechanical component to its poorly understood etiopathogenesis. Spondylosis deformans develops in an effort to stabilize the disc space following degeneration of the annulus fibrosus, with focal new bone formation in association with vertebral disc articulations. Lesions of spondylosis typically spare at least part of the ventral surfaces of adjacent vertebral bodies, and that is the most important radiographic difference with DISH. The characteristic radiographic appearance of vertebrae in patients with DISH is “flowing” ossification primarily at the ventrolateral aspect of the spine, extending for at

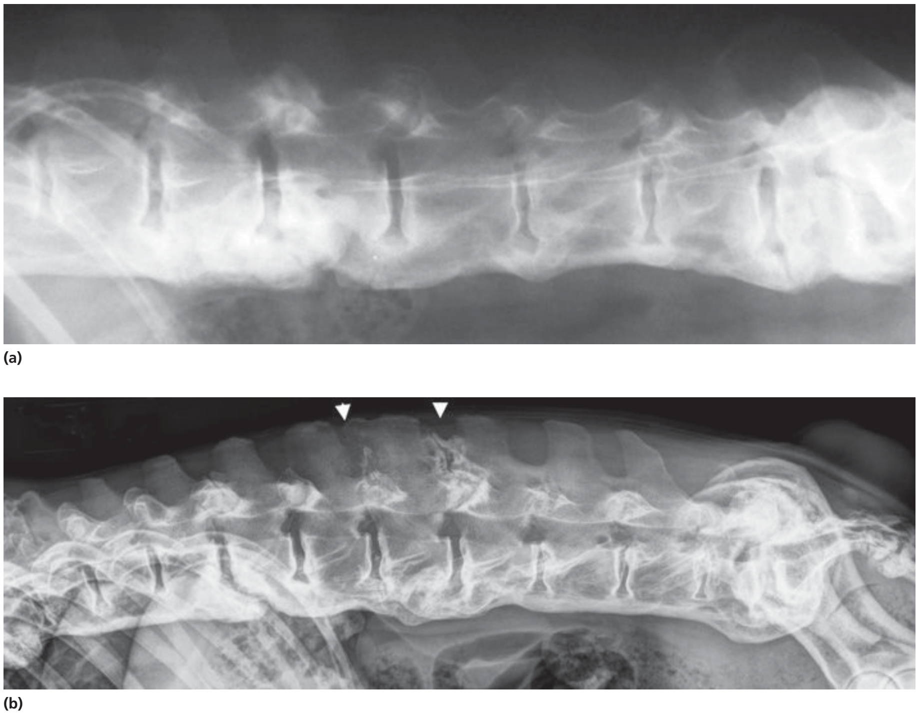


Figure 13.94 (A) Lateral thoracolumbar radiograph demonstrating DISH in a dog. Note that the osseous proliferation involves the entire vertebral body. (B) Some dogs with DISH also have osseous proliferation in the dorsal aspect of the vertebral column (arrowheads)

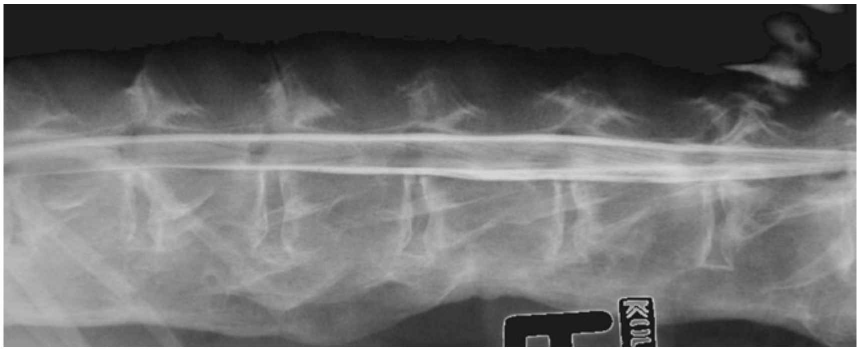


Figure 13.95 Myelographic appearance of the lumbar spine in a dog with severe DISH. No evidence of spinal cord compression is seen.

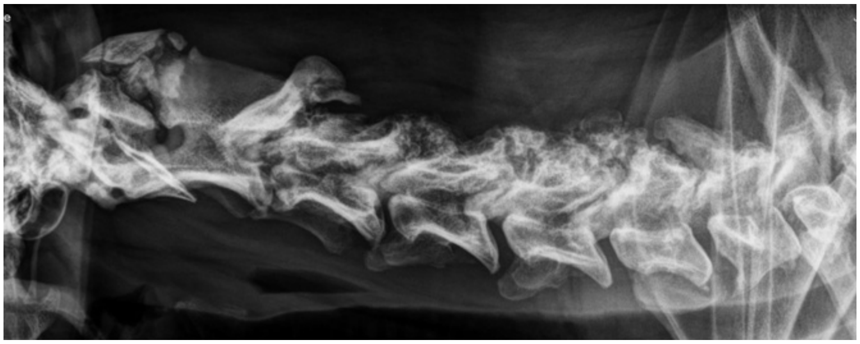


Figure 13.96 Lateral radiograph of dog with atypical DISH. There is abundant irregular new bone formation in the dorsal aspect of the vertebral column surrounding the articular and spinous processes. (Ciepluch *et al.*, 2014.[85] Reproduced with permission from Wiley.)

least four contiguous vertebrae (Fig. 13.94). The osseous proliferation does not invade the vertebral canal and as such does not cause spinal cord compression or neurologic deficits (Fig. 13.95). Spinal pain and lameness have been reported, although it is probably quite rare. There may also be ossification of the interspinous ligaments dorsally. Ossification at areas of ligamentous attachments (enthesiophytes) is also characteristic. Despite the extensive periarticular formation of new bone, the joints themselves are normal (i.e. no degenerative joint disease). Uncommon presentations may involve bone proliferation in the dorsal structures of the vertebral column (Fig. 13.96). Clinical signs of gait abnormalities and decreased joint mobility reflect the restrictive effects of the periarticular bone formation. As it typically does not lead to clinical signs, there is no therapy for this disease. If nerve root compression is documented with advanced imaging, analgesics (e.g. gabapentin) or surgical decompression of nerve roots may be necessary.

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Video Resources

Video resources are available on the companion website: www.wiley.com/go/dewey/neurology

See videos 10, 11, 12, 23, 24, 25, 26, 27, 28, 29 and 30.

CHAPTER 14

Disorders of the Cauda Equina

Curtis W. Dewey & Ronaldo C. da Costa

Clinical signs of cauda equina dysfunction

The variety of terms used to describe this area of the spine can lead to confusion. In this text, the cauda equina is defined as the leash of nerve roots derived from the terminal spinal cord segments from L7 caudally (Cd1–Cd5) that travels through the vertebral canal in the lumbosacral area (i.e. there are only nerves, the peripheral nervous system in this region, Fig. 14.1). The lumbosacral area, or lumbosacral junction, is defined as the bone (e.g. L7 vertebra, sacrum) and connective tissue (e.g. L7–S1 articular facet joint capsules, interarcuate ligament, disc) enclosing the cauda equina. The end of the spinal cord in cats and small-breed dogs is more caudal and can extend to the lumbosacral area. As with myelopathies, clinical signs associated with cauda equina dysfunction depend upon the location ("sided-ness") and extent of the lesion. Typical signs of dysfunction associated with cauda equina disorders are listed below. The clinician should bear in mind that lesions of the spinal cord segments which give rise to the cauda equina can result in identical clinical signs of dysfunction, as will lesions of their respective nerve roots. In general, though, diseases affecting the spinal cord cause a more severe presentation than those affecting only the nerve roots or spinal nerves.

A. Hyperesthesia, paresthesia/dysesthesia
   1. Hyperesthesia (pain) may arise from compression and/or inflammation of meninges and nerve roots of the cauda equina, from the bony components of the lumbosacral area, from the L7–S1 disc, and from L7–S1 articular facet joint capsules. Hyperesthesia may be manifested in a number of ways. Some patients exhibit obvious discomfort when rising or sitting down. Others may be reluctant to jump or to climb stairs. A unilateral or bilateral pelvic limb lameness, which may be exacerbated by increased activity, may also indicate hyperesthesia in the area of the lumbosacral joint and cauda equina. With some conditions, the patient may appear to be in constant pain (e.g. discospondylitis, vertebral tumor), whereas in others, careful palpation of the lumbosacral area is required to elicit a painful response from the patient.
   2. Paresthesia and dysesthesia are two similar terms that describe abnormal sensations caused by irritation or trauma to sensory nerves or nerve roots. Human patients describe such sensations as pricking, burning, and tingling. These occur without any known external sensory stimulus. It cannot be proven whether such sensations occur in dogs and cats with cauda equina disorders, but historical complaints and clinical signs often suggest the existence of this phenomenon. Dogs and cats with cauda equina disorders will sometimes stare or bite at areas around the rump and pelvic limbs.

B. Proprioceptive deficits—interference with afferent proprioceptive fibers at the level of the cauda equina can produce various degrees of proprioceptive deficits to the pelvic limbs. This can be as mild as delayed proprioceptive positioning reactions or as severe as pelvic limb weakness with dragging the dorsal aspect of the toes ("knuckling"). The deficits may or may not be symmetric.

C. Voluntary motor deficits—motor deficits to the muscles innervated by the sciatic nerve and caudal (coccygeal, or tail, innervation) nerves may be clinically detectable, as the cord segments and nerve roots of the cauda equina give rise to these nerves. Pelvic limb weakness may be apparent with damage to sciatic nerve contributions, and decreased to absent tail tone and movement may occur with damage to caudal segments and/or nerve roots. In some cases, the patient may be observed to exhibit an abnormally low tail carriage or a tail deviated to one of the sides, which are often noticed by the owner. Importantly, paraplegia (complete loss of motor function) is *not* seen with compressive lesions affecting only the nerves in the lumbosacral region.

D. Abnormal reflex activity—decreased to absent withdrawal (flexor) and gastrocnemius reflexes may be appreciated. The

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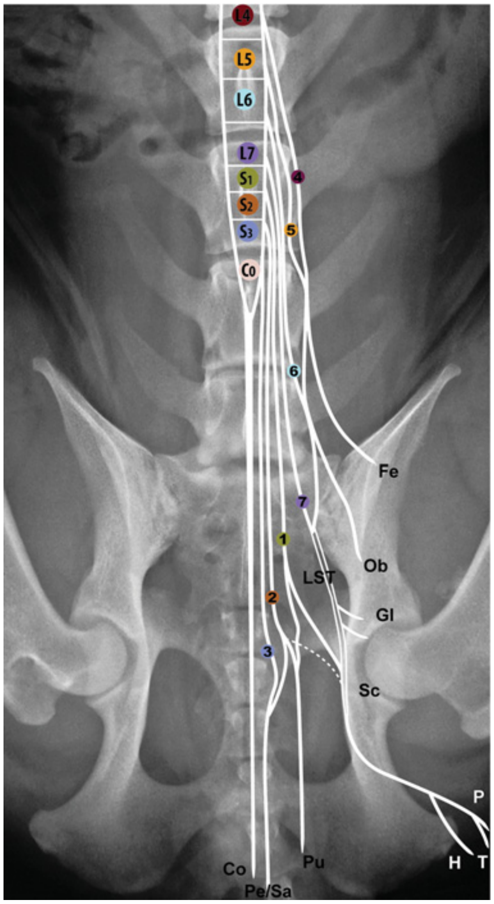

Figure 14.1 Ventrodorsal radiograph of the lumbosacral area of a dog. The overlay outlines the approximate location of the spinal segments, the caudal extent of the spinal cord and the origin of the spinal nerves comprising the cauda equina. (Meij and Bergknut, 2010.[63] Reproduced with permission from Elsevier.)

patellar reflex is typically normal or may appear hyperreflexive. Caudal thigh muscles normally inhibit the action of the quadriceps muscle group when the patellar reflex is elicited. Removal of this tonic antagonistic influence by disrupting the nerve supply to the caudal thigh muscles may result in an apparently hyperactive patellar reflex (i.e. patellar pseudohyperreflexia). A decreased to absent perineal reflex may result from cauda equina lesions.

E. Urinary and fecal abnormalities—varying degrees of urinary and fecal incontinence may occur with damage to sacral segments and/or roots. Bladder dysfunction is classically lower motor neuron in nature (see Chapter 16). These signs are typically seen with more severe presentations and are less reversible.

F. Nociceptive (deep pain perception) deficits in areas of the pelvic limbs (see Chapter 17 for autonomous zones), perineum, and tail may occur with severe lesions of the cauda equina.

Table 14.1 Cauda equina disorders of dogs and cats.

Degenerative	Degenerative lumbosacral stenosis Type I degenerative disc disease
Anomalous/developmental	Congenital vertebral malformations Developmental vertebral malformations Congenital malformations of the cauda equina Pilonidal sinus Sacral osteochondrosis Synovial cysts Arachnoid diverticulum ("cysts")
Neoplastic	Primary tumors Secondary tumors
Infectious/inflammatory	Discospondylitis Vertebral physitis Abscess
Ischemic/vascular	Intermittent neurogenic claudication
Traumatic	Indirect trauma (contusion) Direct trauma (laceration)

Disorders affecting the cauda equina in dogs and cats (Table 14.1)

A. Degenerative

1. Degenerative lumbosacral stenosis[1–3, 6–10, 12–15, 17–20, 22, 25, 26, 28, 32, 35–37, 42–47, 54, 56, 60–64, 66, 67, 70, 71, 73, 74, 77–79, 81–84, 86, 87, 89, 92, 93, 97, 100] (Video 31)
   a. This is a common disease syndrome that typically affects adult (usually middle-aged to older) large-breed dogs. According to some reports, there is a male predilection for this disease. The German Shepherd dog appears to be particularly predisposed to degenerative lumbosacral stenosis. The pathophysiology involves the following:
      1. type II degeneration and subsequent protrusion of the L7–S1 intervertebral disc into the vertebral canal (Fig. 14.2, Fig. 14.3)
      2. ventral subluxation of S1 (lumbosacral instability) and misalignment of the articular processes

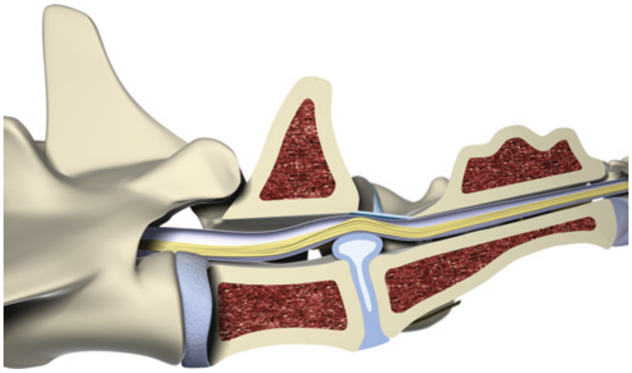

Figure 14.2 Schematic illustration of intervertebral disc protrusion at L7–S1 compressing the cauda equina. (The Ohio State University. Reproduced with permission.)

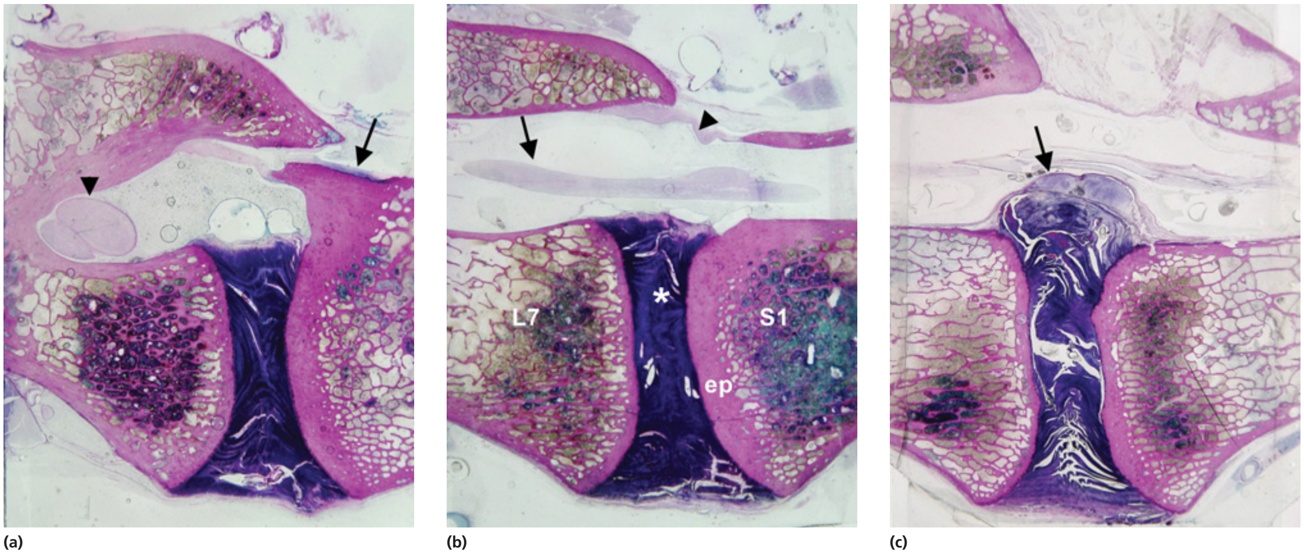

Figure 14.3 Histological sections of the lumbosacral region of the dog. (A) A parasagittal section showing the L7 spinal root ganglion in the dorsal radix (arrowhead) of the intervertebral foramen and the articular cartilage (arrow) of the facet joint. (B) A midsagittal section illustrating the dural sac (arrow), the interarcuate ligament (arrowhead), and the spinal unit consisting of the endplates (ep) and the intervertebral disc (*). (C) Midsagittal section in a dog with degenerative lumbosacral stenosis demonstrating intervertebral disc degeneration with type II disc protrusion (arrow) and dorsal displacement of the dural sac. (Meij and Bergknut, 2010.[63] Reproduced with permission from Elsevier.)

3. congenital vertebral anomalies (e.g. symmetric or asymmetric transitional vertebrae)
4. proliferation of the soft tissues surrounding the cauda equine (e.g. hypertrophy of the interarcuate ligament [ligamentum flavum], the joint capsule, and epidural fibrosis)
5. sacral osteochondrosis
6. vascular compromise of the blood supply to the spinal nerves.

Ventral spondylosis is often appreciated at the lumbosacral junction in these patients, but by itself, this radiographic finding has little clinical significance.

Reasons for this chronic degenerative process are unknown. In German Shepherd dogs as well as other large-breed dogs, the presence of transitional vertebrae at the lumbosacral junction has been associated with the development of degenerative lumbosacral stenosis. In one study, dogs with transitional lumbosacral vertebrae were eight times more likely to develop degenerative lumbosacral stenosis than dogs without such anomalous vertebrae; in this same study, dogs with transitional lumbosacral vertebrae also developed clinical signs of degenerative lumbosacral stenosis 1–2 yrs earlier than dogs with lumbosacral stenosis that did not have these abnormal vertebrae. The German Shepherd breed was also found to be eight times more likely to develop degenerative lumbosacral stenosis than other large breeds in this investigation. In addition, German Shepherd dogs have been shown to have different orientation of vertebral articular processes (facets) in the caudal lumbar and lumbosacral regions of the spinal column and a greater degree of facet joint tropism in this region, compared with other large-breed dogs. Facet joint tropism means an asymmetry in the angle of orientation between left and right facets at a given level of articulation. A morphologic and morphometric study compared the anatomy of the lumbosacral region of 733 German Shepherds with 334 large-breed dogs of other breeds. The authors found that German Shepherds had a significantly smaller vertebral canal (i.e. stenosis) and a higher step between L7 and S1. All these anatomic differences as well as the propensity for German Shepherd dogs to have transitional lumbosacral vertebrae and sacral osteochondrosis may partly explain the breed prevalence for degenerative lumbosacral stenosis. A possible genetic etiology has also been recently proposed in German Shepherds.

b. Clinical signs are variable, but lumbosacral pain is an early and consistent finding. Pain may be manifested in a number of ways (e.g. reluctance to rise or sit) and pelvic limb lameness can be unilateral or bilateral. Pain and lameness may be acute or chronic and may be persistent or episodic. These clinical signs may be misinterpreted as being due to orthopedic disease, most notably hip dysplasia. Many of these dogs have radiographic evidence of hip dysplasia, making this a

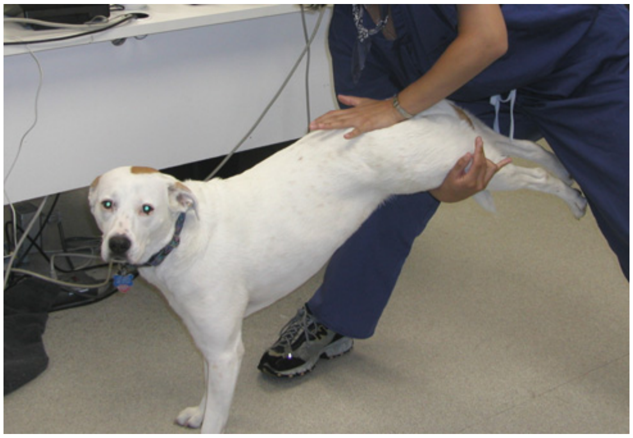

Figure 14.4 Lordosing the lumbosacral spine while applying dorsal pressure often elicits a painful response in dogs with degenerative lumbosacral stenosis.

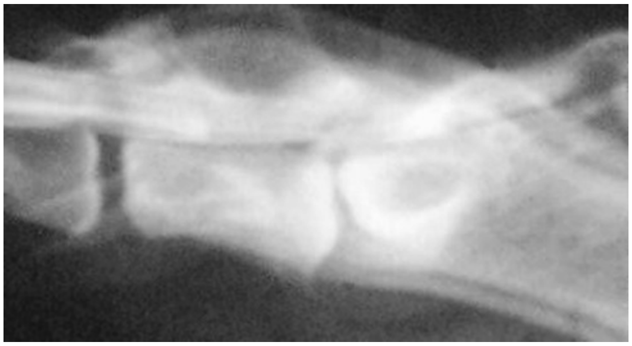

Figure 14.5 Lateral myelographic view of a cat's lumbosacral region. Since the spinal cord usually ends at the S1 level in cats, a mildly protruded L7–S1 intervertebral disc is evident on this image.

particularly easy trap to fall into when the only obvious clinical sign of an abnormality is pain and/or pelvic limb lameness. If untreated, clinical signs of dysfunction may progress to proprioceptive loss in the pelvic limbs, voluntary motor weakness (in the distribution area of the sciatic nerve), and urinary/fecal incontinence, usually in that order. In the authors' experience, deficient pelvic limb withdrawal reflexes are most apparent at the hock level in cases of degenerative lumbosacral stenosis; flexion at the hip and stifle regions often appears normal. Although typically indicative of progressively severe cauda equina compression, urinary and/or fecal incontinence occasionally comprise the initial primary clinical complaint in cases of degenerative lumbosacral stenosis. Careful palpation of the lumbosacral area, including lordosing the caudal spine while pressing on the lumbosacral area, will usually elicit a pain response in affected patients (Fig. 14.4). Elevation of the tail is a good way to isolate the lumbosacral region from the pelvis. It causes stenosis of the lumbosacral foramen and distension of the nerve roots, consistently eliciting pain. Most dogs afflicted with this disease also have obvious deficits on proprioceptive positioning tests of the pelvic limbs. Importantly, all dogs with lumbosacral disease should have a rectal exam performed as neoplasms in the pelvic canal can invade the lumbosacral region and cause signs of cauda equina dysfunction.

c. Diagnosis of degenerative lumbosacral stenosis is based upon signalment, historical and clinical findings, and results of diagnostic imaging of the lumbosacral region. The definitive diagnosis of degenerative lumbosacral stenosis is made by imaging the lumbosacral area and demonstrating compression of the cauda equina. Although degenerative changes at the lumbosacral junction (e.g. spondylosis, misalignment of the sacrum with the L7 vertebra) may often be appreciated on plain radiographs of the region, additional imaging is necessary to demonstrate cauda equina compression. A number of procedures have been advocated, including myelography, epidurography, vertebral sinus venography, discography, computed tomography (CT), and magnetic resonance imaging (MRI). Since the terminal thecal sac (subarachnoid space) of the spinal cord in large-breed dogs often ends cranial to the lumbosacral junction, myelography (Fig. 14.5) may not consistently provide useful information. Vertebral sinus venography is considered both a technically difficult and an unreliable imaging procedure. Discography (Fig. 14.6) is an accurate imaging method for degenerative lumbosacral stenosis but provides information primarily limited to the intervertebral disc. Epidurography is also considered a relatively accurate contrast procedure to identify cauda equina compression. Combination discography/epidurography (Fig. 14.7) has also been demonstrated to be a useful diagnostic imaging method for degenerative lumbosacral stenosis. Currently it is clear that CT (Fig. 14.8) and MRI (Fig. 14.9,

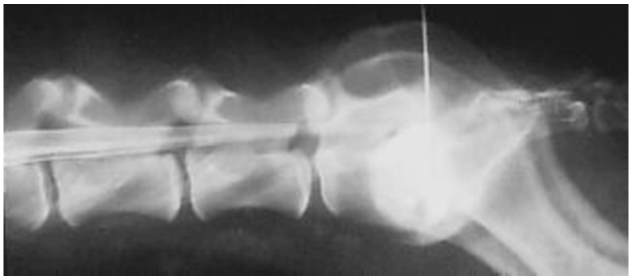

Figure 14.6 Lateral spinal radiographic image of a dog with degenerative lumbosacral stenosis. A myelogram failed to outline the lumbosacral region, so a discogram was subsequently performed. A protruded L7–S1 intervertebral disc is evident on discography.

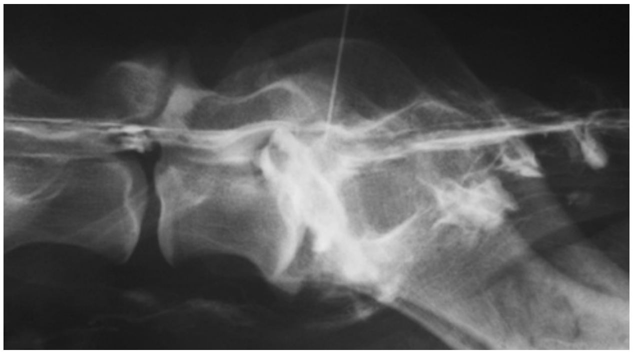

Figure 14.7 Combination discography/epidurography (lateral view) in a dog with degenerative lumbosacral stenosis (From Sharp and Wheeler, 2003. Reprinted with permission.)[85]

Fig. 14.10, Fig. 14.11) provide the most detailed structural information regarding the cauda equina, including information concerning the L7–S1 intervertebral foramina and L7 nerve roots. In one study, there was a high degree of agreement between CT and MRI findings in dogs with degenerative lumbosacral stenosis; however, the findings of neither of these modalities correlated well with what was found at surgery. Although this discrepancy may be partially explainable by differences in patient positioning during imaging vs. surgery, there are other important discrepancies between imaging findings and clinical disease that must be kept in mind. Most importantly, there is evidence that dogs without clinical signs of disease may have imaging findings consistent with a diagnosis of degenerative lumbosacral stenosis and that the degree of cauda equina compression evident on imaging does not correlate with disease presence or severity. In one study of neurologically normal dogs imaged via CT, all dogs had some level of disc protrusion at the L7/S1 disc space; the percentage of the vertebral canal height occupied by these discs varied from approximately 21 to 43%. It is apparent that evidence on imaging studies consistent with a diagnosis of degenerative lumbosacral stenosis may be an incidental finding in some dogs. It is also apparent that the extent of cauda equina compression appreciated on such imaging studies is not necessarily indicative of disease severity in patients that exhibit clinical signs of degenerative lumbosacral stenosis. In the authors' experience, middle-aged to older large-breed dogs often demonstrate hyperesthesia on palpation of the lumbosacral junction during a neurologic examination that has nothing to do with the presenting complaint or ultimate diagnosis. In other words, some dogs with degenerative lumbosacral stenosis may have subtle or inapparent clinical signs that are only elicitable on palpation. It is imperative to realize that focusing on the lumbosacral junction in some patients may lead to overlooking another spinal disorder which is primarily responsible for the clinical deficits. In patients with subtle deficits (e.g. pelvic limb proprioceptive deficits and spinal hyperesthesia), it may be worthwhile to have survey images of the thoracolumbar region (e.g. T2-sagittal MR survey) to ensure that the lumbosacral lesion is not an incidental finding. Concurrent EMG performed on the epaxial, tail, and pelvic limb musculature may improve the accuracy of diagnosis with the various imaging modalities. Tibial nerve somatosensory evoked potentials (SSEP) have also been shown to be abnormal in dogs with clinical evidence of degenerative lumbosacral stenosis. The challenges associated with the diagnosis and treatment of lumbosacral stenosis were recently highlighted in a review article.

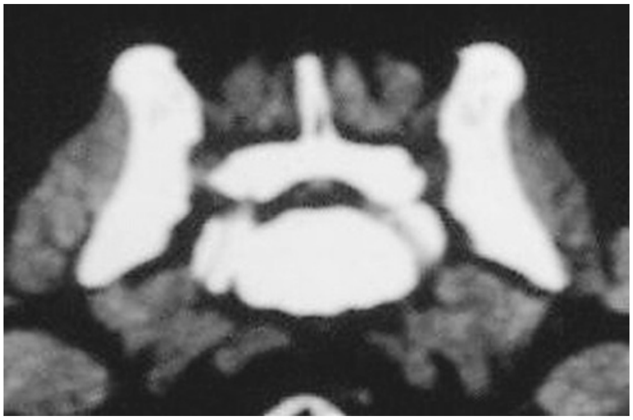

Figure 14.8 Transverse CT image of the lumbosacral region of a dog. Bilateral L7–S1 foraminal stenosis is evident.

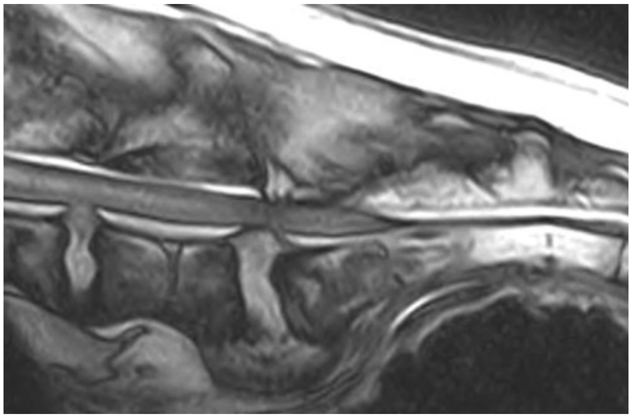

Figure 14.9 Sagittal MR image (T2-weighted) of a dog, exhibiting disc protrusions at the L6–L7 and L7–S1 intervertebral disc spaces.

d. The treatment of a patient with degenerative lumbosacral stenosis may be nonsurgical or surgical, similar to other disc-associated diseases. Treatment decisions are based primarily on severity of clinical signs,

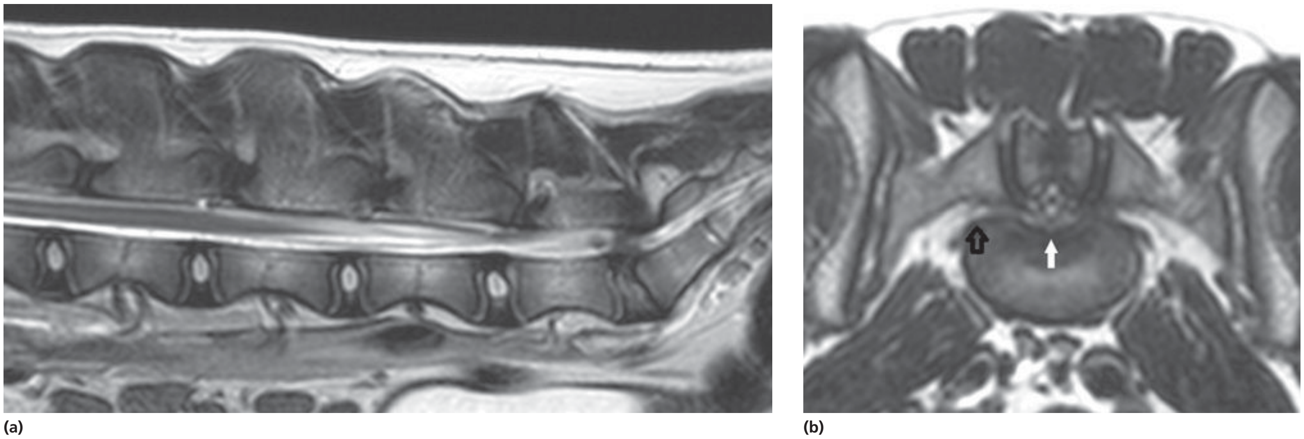

Figure 14.10 MR image of a 1-yr-old German Shepherd dog exhibiting disc protrusions with mild dorsal and ventral compression at the L7–S1 region. (A) Sagittal T2-weighted image. (B) Transverse T2-weighted image at L7–S1. White arrow shows the vertebral canal stenosis. Black arrow shows the foraminal stenosis at the entry zone.

age of the patient, and concurrent diseases; as mentioned previously, there appears to be no clear correlation between extent of cauda equina compression evident on imaging and disease severity or postoperative outcome. Nonsurgical therapy consists of enforced rest initially for a few weeks, followed by a period of regular short walks to maintain muscle mass. Additionally, anti-inflammatory medication (either nonsteroidal drugs or prednisone, not both), analgesics (such as gabapentin), and body weight reduction are recommended. Nonsurgical or conservative treatment is a reasonable initial option, primarily in older patients with multiple orthopedic or systemic conditions. Reported success rate is 55%. Epidural steroids are a popular therapeutic approach in people with lumbar and lumbosacral disc

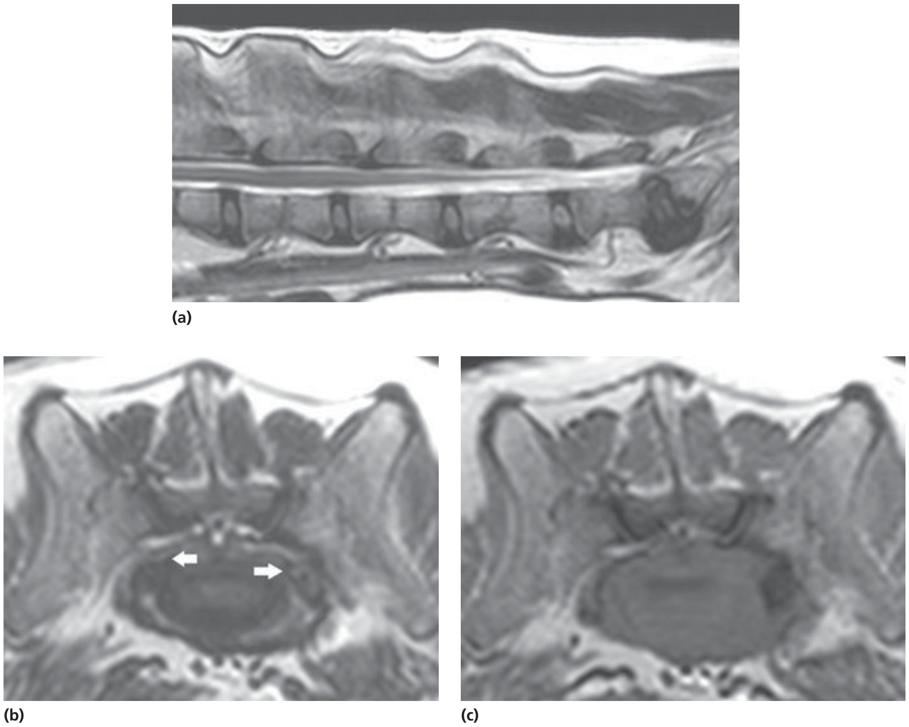

Figure 14.11 MR image of a 14-yr-old Labrador Retriever dog exhibiting disc protrusions with compression at the L7–S1 region. (A) Sagittal T2-weighted image showing severe spondylosis at L7–S1. (B) Transverse T2-weighted image at L7–S1 showing severe extensive bilateral foraminal stenosis (white arrows). Compare with Fig. 14.8. (C) Corresponding transverse T1-weighted image.

herniations. It is often used when oral therapy with anti-inflammatories and rest is not successful before considering surgery. A retrospective study evaluated the use of fluoroscopically guided epidural steroid injections in 38 dogs and found an improved outcome in 79% of dogs. The authors used methylprednisolone acetate (40 mg/mL, dose of 1 mg/kg) and three injections (day 1, day 14 and day 45). Aseptic technique is paramount for epidural infiltration due to the risk of infections. In people, nonsurgical treatment consisting of analgesics and physical therapy is the initial standard of care for patients with lumbar disc herniations and the long-term results are comparable to surgical treatment, primarily for patients with mild to moderate signs. In patients with neurologic deficits, or patients for whom pain is refractory to nonsurgical management, surgery is chosen as the preferred mode of therapy. Surgery in dogs usually consists of a dorsal laminectomy over the L7–S1 interspace (Fig. 14.12), often combined with the removal of hypertrophied soft tissue (e.g. annular disc material; Fig. 14.12C). Enlargement of the L7–S1 intervertebral foramen (foraminotomy) or removal of the articular facets (facetectomy) may also be required if compression of the L7 nerve root is appreciated. Most neurosurgeons/surgeons do not advocate the surgical stabilization of the lumbosacral joint but this may be advisable in some cases (e.g. bilateral facetectomy). In cases of lateralized foraminal stenosis, as opposed to vertebral canal stenosis, foraminotomy (surgical decompression of intervertebral foramen) may need to be performed. The prognosis for functional recovery from this disorder is generally good to excellent with surgical intervention. Successful outcomes after surgery range from 66.7–95% of cases. It appears that, although improvement in continence may occur in dogs with presurgical fecal and/or urinary incontinence (over weeks to months following surgery), resolution of incontinence is not likely to occur in most cases. Incontinence failed to resolve after

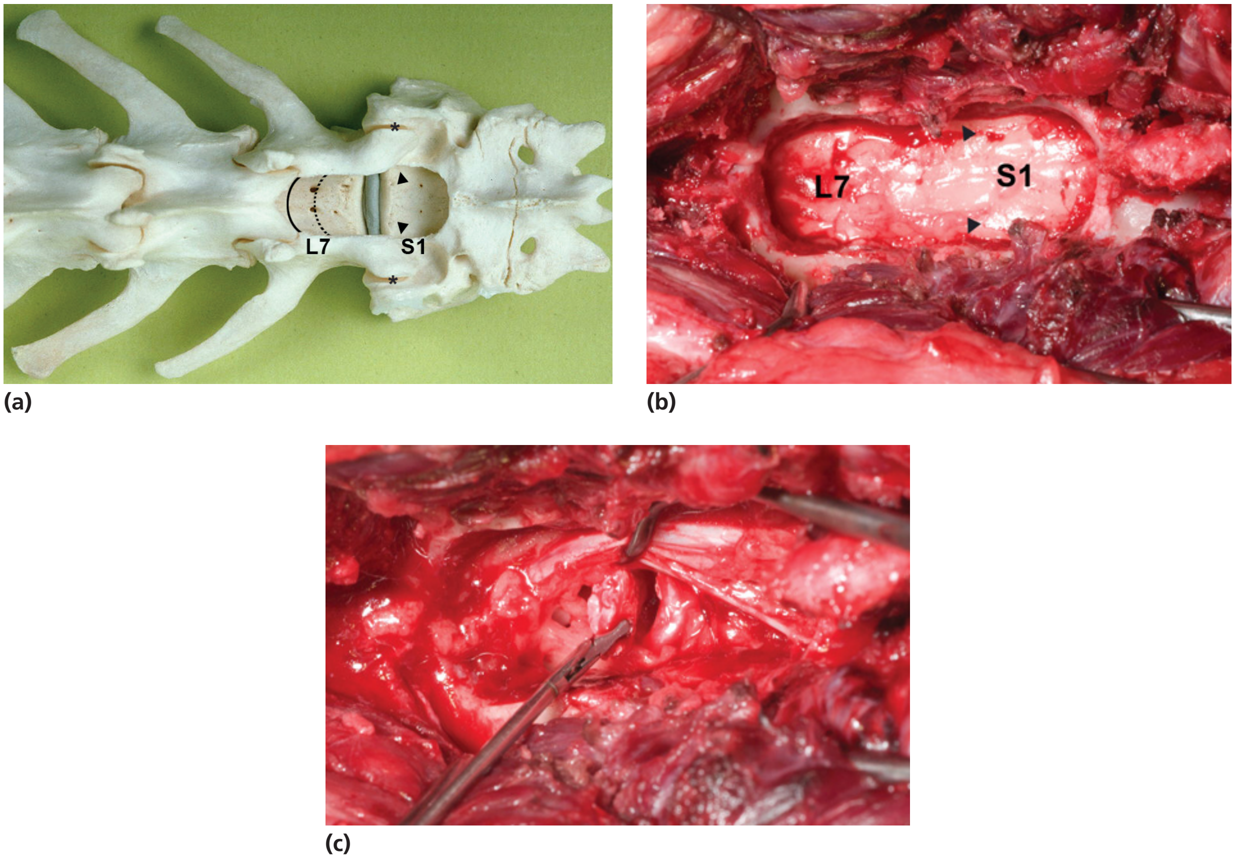

Figure 14.12 (A) Bony specimen of the canine lumbosacral spine showing the extension of dorsal laminectomy. The facet joints (*) are left intact. The laminectomy usually includes the caudal 2/3 of L7 (dashed line) but may be extended cranially (uninterrupted line). The lamina of S1 should be removed as far lateral as possible (arrowheads) to free the S1 nerves in the lateral recesses. (B) Dorsal laminectomy includes the caudal 2/3 of the L7 lamina and the complete S1 lamina. The S1 lamina should be removed as far lateral (arrowheads) as possible extending under the caudal L7 facet giving the laminectomy a keyhole appearance. (C) Following dorsal annulectomy and nucleotomy with a grasping forceps, an empty intervertebral disc remains. (Meij and Bergknut, 2010.[63] Reproduced with permission from Elsevier.)

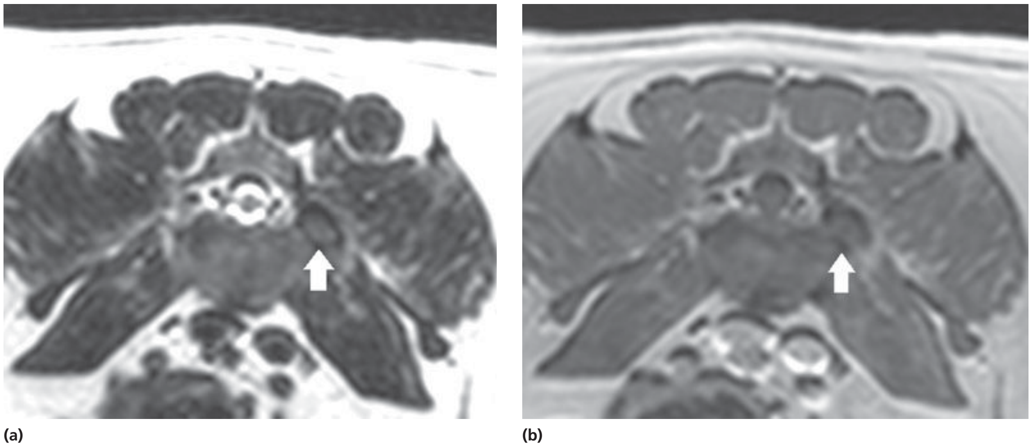

Figure 14.13 Transverse MR image of a Dachshund, exhibiting lateralized disc extrusion at L6–L7 intervertebral disc spaces (arrow). (A) T2-weighted image. (B) T1-weighted image.

decompressive surgery in 55–87% of reported cases. In one study, presurgical incontinence was the only clinical feature correlated with a poor postoperative outcome. Improvement or resolution of incontinence was found to be much less likely in dogs that had been incontinent for more than 1 mo, compared to those that had shorter histories of incontinence. Reported recurrence rates for degenerative lumbosacral stenosis vary between 3 and 18%. Recurrence is probably more likely in very active dogs (i.e. working dogs).

2. Type I degenerative disc disease[53]
   a. Occasionally, type I disc extrusions will occur in a caudal lumbar disc, leading to signs of cauda equina dysfunction (Fig. 14.13). An uncommon presentation is the disc extrusion in one of the caudal (coccygeal) disc regions (Fig. 14.14).
   b. Clinical signs of pain and dysfunction tend to occur acutely, similar to type I disc extrusions in other spinal locations. Pelvic limb "root signature" (see Chapter 13) may occur with lateralized type I disc extrusions in the caudal lumbar region (Fig. 14.13). In the authors' experience, pelvic limb root signature associated with lateralized caudal lumbar disc extrusions is most commonly seen in Cocker Spaniels. Dogs with coccygeal disc extrusion present with severe pain in the tail/sacrococcygeal/lumbosacral region without neurologic deficits. The pain is often exacerbated when the dogs elevate their tails posturing to defecate.
   c. Specifics regarding the diagnosis, treatment, and prognosis of patients with type I disc disease are discussed in Chapter 13. Diagnostic imaging other than myelography (e.g. discography, epidurography, CT, MRI) may be necessary to demonstrate a type I disc extrusion of the L7–S1 intervertebral disc.

B. Anomalous/developmental
1. Congenital vertebral malformations[11, 22, 35, 55, 56, 58, 73, 74, 76, 83, 94]

For the most part, the congenital vertebral malformations discussed in Chapter 13 can occur in the lumbosacral region. Clinical features, diagnostic and treatment options, and prognosis are similar as described for other areas of the spine. There are some vertebral malformations that are specific to the lumbosacral area:

   a. Idiopathic lumbosacral stenosis—this is an ill-defined disorder primarily in adult small to medium-sized dogs that is most likely due to abnormal embryologic formation of the neural arch. This may be a form of congenital stenotic vertebral canal (see Chapter 13). Bony abnormalities, which are probably present since birth, include abnormally thick laminae and articular

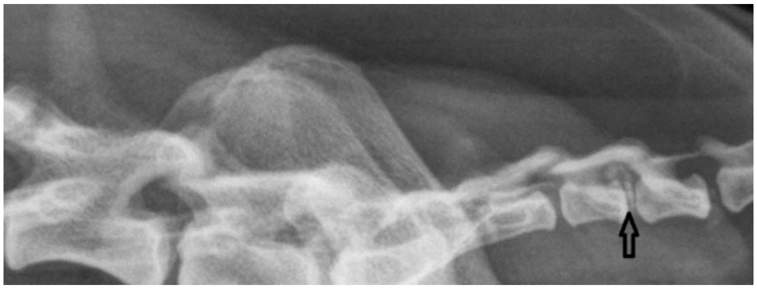

Figure 14.14 Lateral radiograph showing intervertebral disc extrusion between the first and second caudal (coccygeal) vertebrae (arrow).

facets. Mild degenerative soft tissue changes over time (e.g. thickened ligamentum flavum, facet joint capsule thickening) are thought to have profound compressive effects on the cauda equina due to the narrowed bony canal. The prognosis is generally favorable with surgical decompression.

b. Sacrocaudal (sacrococcygeal) dysgenesis/agenesis—this is a spectrum of congenital abnormalities involving both the bony and soft-tissue structures of the lumbosacral and coccygeal spine which occurs most commonly in Manx cats. The trait is inherited in an autosomal dominant fashion. There are varying degrees of abnormalities, and thus varying degrees of neurologic dysfunction associated with this disorder. Bony abnormalities include spina bifida, as well as agenesis or dysgenesis of sacral and coccygeal vertebrae. Soft-tissue anomalies associated with the cauda equina include syringomyelia/hydromyelia, meningocele and myelomeningocele (Fig. 14.15), and agenesis of spinal cord segments and nerve roots in this region. Tethered cord syndrome (discussed below) has also been reported with this disorder. Clinical deficits can vary from normal neurologic function to inability to ambulate with fecal and urinary incontinence. Clinical signs can be static or progressive. Progressive signs are probably related to the instability caused by the abnormal vertebral segments. Diagnosis is based upon signalment, history, and clinical findings, as well as results of diagnostic imaging. There are no effective treatments available for most of the anomalies, and prognosis depends mainly on the extent of the neurologic deficits.

2. Developmental vertebral conditions

a. Sacral osteochondrosis[31, 53, 59]

This condition is occasionally seen in young adult German Shepherds. It is characterized by failure of the endochondral ossification of the articular epiphyseal and physeal cartilages. This condition has been associated with degenerative lumbosacral stenosis in up to 30% of German Shepherds in one study. A 5:1 gender predisposition toward males has been reported. The diagnosis is established by lateral and ventrodorsal radiographs (Fig. 14.16). Advanced imaging (CT or MR) is useful to confirm the diagnosis and assist with surgical planning (Fig. 14.17). Dogs can be treated medically with variable degrees of success. Surgical treatment consists of dorsal laminectomy and removal of the osteochondrosis fragment, with or without dorsal annulectomy.

b. Extradural synovial cysts [4, 21, 26, 33, 80]

Extradural synovial cysts have been referred to as intraspinal synovial cysts, juxtafacet cysts, and ganglion cysts. These cysts originate from the zygapophyseal joint of the vertebral column and are located extradurally. Histologically, the cysts can be divided into synovial cysts, which are those that have a synovium-like lining of epithelial cells, and ganglion cysts, which do not have this lining and are thought to result from mucinous degeneration of the articular cartilage. The prevalence of synovial cysts in dogs is unknown, but they are not uncommon. Even

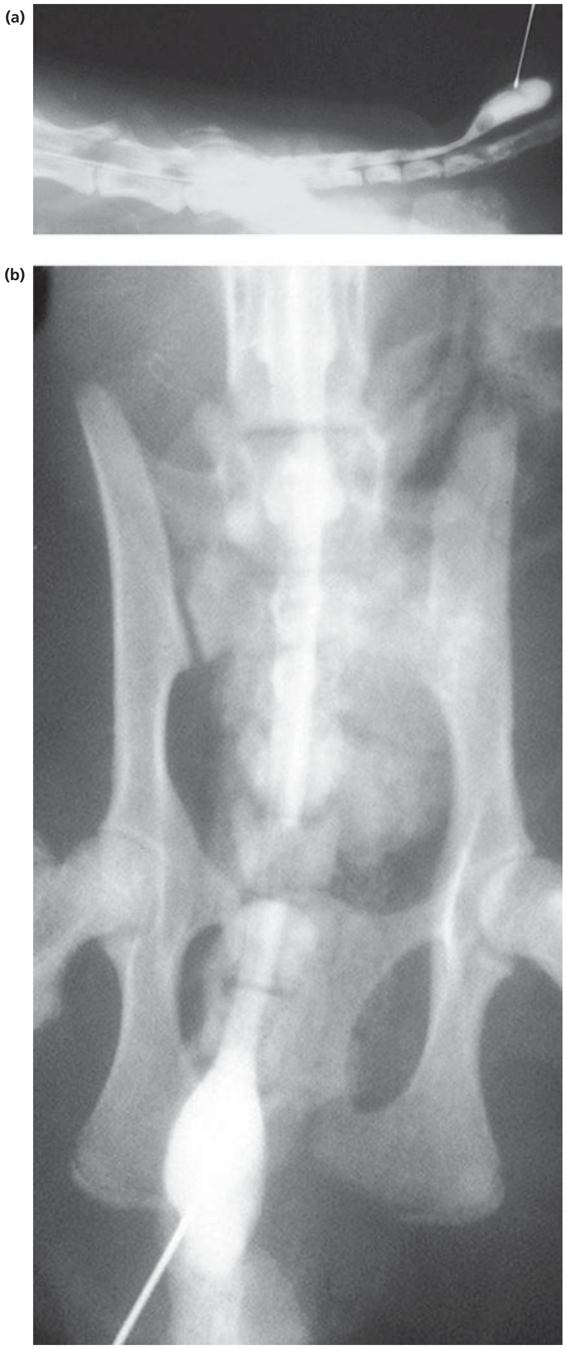

Figure 14.15 Myelogram performed via a meningocele extending into the coccygeal region in a cat, lateral (A) and ventrodorsal (B) views. (Dr. G Kort, 2014. Reproduced with permission from Dr. G Kortz.)

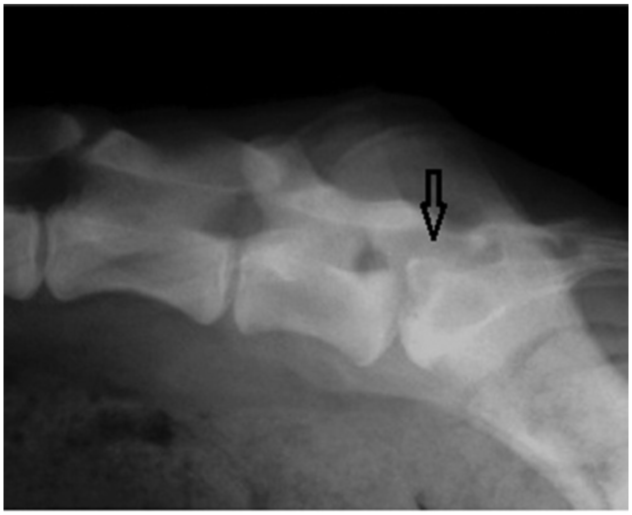

Figure 14.16 Lateral radiograph of a 1-yr-old German Shepherd showing the typical appearance of sacral osteochondrosis (arrow).

though they can be seen in any region of the vertebral column, they are commonly observed in the lumbosacral region, in association with degenerative lumbosacral stenosis. They are also occasionally seen in thoracolumbar spine of large-breed dogs, and in the cervical region of giant-breed dogs with the osseous form of cervical spondylomyelopathy. The majority of reported dogs with lumbosacral/caudal lumbar synovial cysts were large-breed, middle-aged or older dogs, although lumbar cysts have also been reported in a 2-yr-old Boxer. The pathophysiology of ESC is not well established. It is thought that degeneration of the zygapophyseal joint causes protrusion of the synovial membrane through defects of the joint capsule. Protrusion of the synovial membrane will cause the formation of a para-articular cavity filled with synovial fluid.

Clinical signs include pelvic limb lameness or weakness with caudal lumbar/lumbosacral pain on palpation. Some of the affected dogs with lumbosacral cysts had transitional vertebrae, and this may be a risk factor.

Diagnosis of synovial cysts is best done with MRI (Fig. 14.18, Fig. 14.19). In human beings, MRI is reported to have a sensitivity of 90% for the diagnosis of ESC, compared with 70% with CT. MRI in dogs reveals the cysts as well-circumscribed extradural masses on one or both sides of the vertebral canal. They are hyperintense in T2-weighted images, with variable characteristics on T1-weighted images.

Treatment of these cysts is typically surgical, many times done at the same time as the decompressive surgery for lumbosacral stenosis. In humans, however, many of these cysts are asymptomatic, and in many cases in dogs they may be incidental findings. So, attempting medical management with activity restriction and anti-inflammatories is recommended initially. The outcome with surgical management is typically excellent.

c. Stenotic vertebral canal and cartilaginous exostoses can affect the cauda equina. These disorders are discussed in Chapter 13.

3. Congenital malformations of the cauda equina[11, 23, 55, 56, 58, 76, 91, 98]

Soft-tissue malformations associated with sacrocaudal dysgenesis/agenesis of cats are described above. Congenital spinal cord malformations (discussed in Chapter 13) can affect the cord segments of the cauda equina as well. However, there are some malformations of the cauda equina that are more common, or exclusive, to this region of the spine:

a. Meningocele/myelomeningocele—a meningocele is a tube-like extension of the meninges (containing CSF)

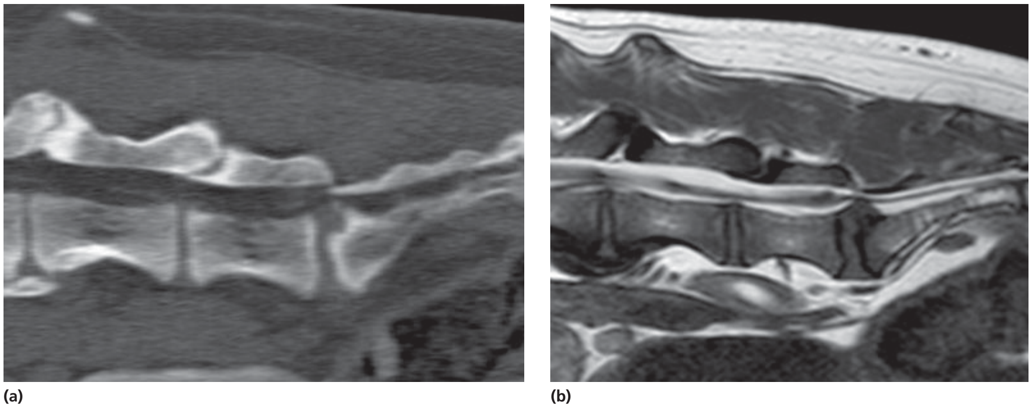
(a) (b)

Figure 14.17 Sagittal reconstructed computed tomography (A) and T1-weighted magnetic resonance imaging (B) of a dog with sacral osteochondrosis. Note that the irregular craniodorsal aspect of the sacrum and bony fragment are more easily visualized on CT compared to MRI. (Courtesy Dr. Steven De Decker, Royal Veterinary College.)

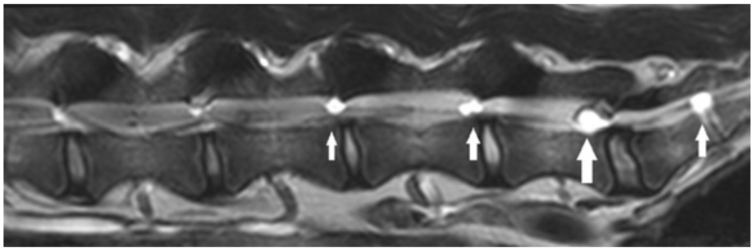

Figure 14.18 Sagittal MR image (T2-weighted) of a 1.5-yr-old German Shepherd dog, exhibiting multiple extradural synovial cysts (arrows).

through a spina bifida defect of the vertebra that attaches to the overlying skin. A meningomyelocele is a less-common variant of a meningocele that contains cord segments. Occasionally, a meningocele will contain a large piece of skin-associated fat, and is termed a lipomeningocele. These abnormalities are most common in the sacrococcygeal area of the spine. English bulldogs and Manx cats appear to be predisposed to this disorder. Clinical signs of dysfunction, when present, are primarily urinary and fecal incontinence. Clinical signs of hyperesthesia are usually absent. If tethered cord syndrome is not a large contributing factor to the clinical dysfunction, there is no effective therapy for this condition. If the defect is open to the environment, the development of life-threatening meningomyelitis is a concern.

b. Tethered cord syndrome—this refers to a disorder in which caudal traction is placed on the cauda equina due to abnormal fixation of the filum terminale (spinal cord meningeal termination) during embryonic development. Traction causes neurologic dysfunction, which can sometimes be alleviated by surgical intervention. Tethered cord syndrome can occur primarily as a defect of the filum terminale, or more commonly as a component of spina bifida and meningocele/myelomeningocele.

4. Hydromyelia and syringomyelia

Hydromyelia and syringomyelia may affect the spinal cord contributions to the cauda equina. Specifics of hydromyelia/syringomyelia are discussed in Chapter 7 and Chapter 13.

5. Dermoid sinus (pilonidal sinus)

This disorder may occur in the sacrocaudal region of the spine. Dermoid sinus is discussed in more detail in Chapter 13.

C. Neoplastic[57]

Various primary and secondary bony and soft-tissue neoplasms (discussed in Chapter 13) can affect the lumbosacral region and the cauda equina (Fig. 14.20, Fig. 14.21). Occasionally, retroperitoneal tumors will involve the nerves of the lumbosacral plexus, causing either unilateral (e.g. sciatic dysfunction) or bilateral evidence of cauda equine dysfunction.

D. Infectious/inflammatory

1. Discospondylitis[5, 16, 24, 27, 29, 30, 34, 38–41, 48–51, 65, 68, 69, 72–75, 90, 95, 96, 99]

a. Discospondylitis refers to an infection of the intervertebral disc and its contiguous vertebrae, usually by coagulase-positive *Staphylococcus* bacteria (e.g. *intermedius*, *aureus*). Other bacterial organisms have been reported (e.g. *Streptococcus*, *Brucella*), as well

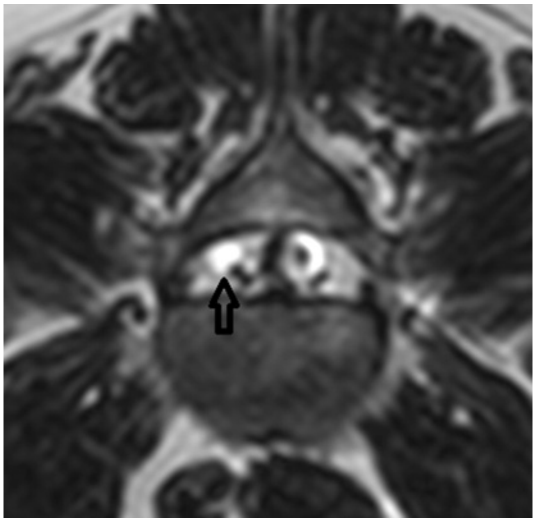

Figure 14.19 Transverse MR image (T2-weighted) of a 4-yr-old German Shepherd dog, showing an extradural synovial cyst (arrow).

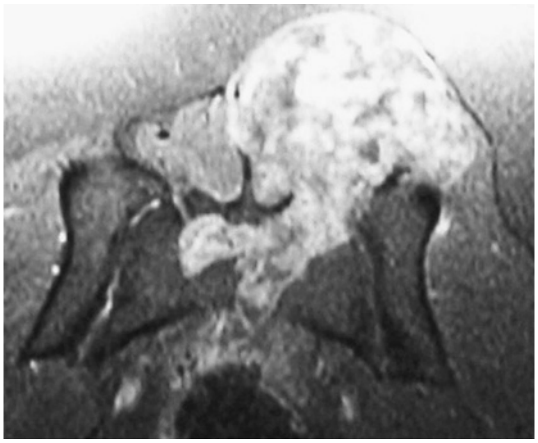

Figure 14.20 Transverse MR image (T1-weighted with contrast) of the lumbosacral region of a dog. A large mass invading the vertebral canal is evident. A chondrosarcoma was diagnosed surgically.

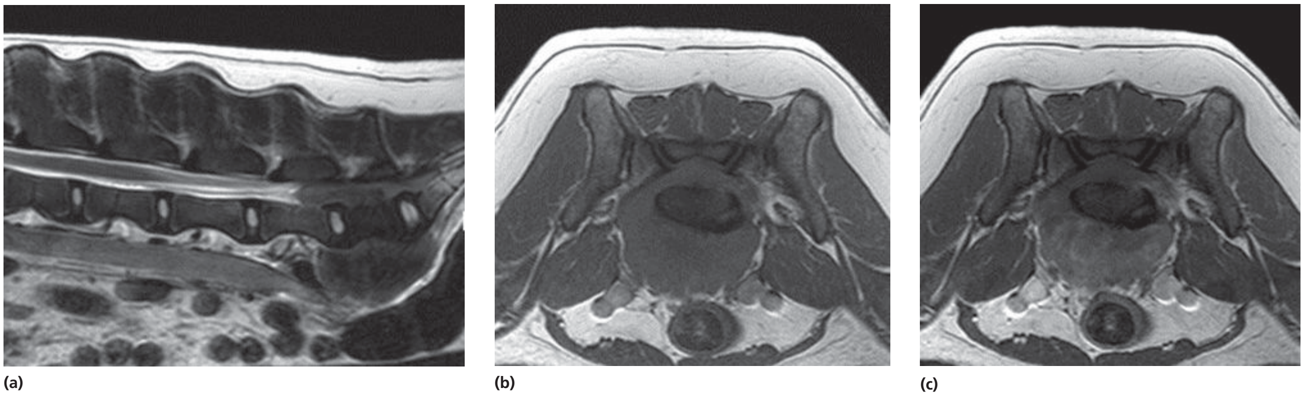

Figure 14.21 Images of a dog with a large mesenchymal tumor at the lumbosacral region. (A) Sagittal T2-weighted MR image. (B) Transverse T1-weighted image at the caudal body of L7. (C) Transverse T1-weighted image postcontrast showing the contrast enhancement of the mass invading the vertebral canal.

as fungal organisms (e.g. *Aspergillus* spp.). There is evidence to suggest that some dogs that develop discospondylitis may have defective immunocompetence as a predisposing factor. Infectious organisms may gain access to the disc space and vertebrae via a number of proposed mechanisms:

1. Hematogenous spread—believed to be the most common mechanism, even though the primary source of infection is not always found. The urinary tract is generally thought to be the most likely source of infection in most cases.
2. Foreign body migration—the best example is plant awn migration. The barbs of plant awns favor migration through tissue. These awns may carry bacteria with them to the disc space and/or serve as a nidus for bacterial localization once they arrive at the disc space.
3. Iatrogenic—infection may develop following spinal surgery or paravertebral injection. This is considered to be the least likely mechanism for bacterial localization to the disc space and vertebrae.

Discospondylitis is most commonly encountered in medium- to giant-breed male dogs of any age, but has been reported in small-breed dogs as well as in cats. In one large retrospective study of dogs with discospondylitis, older dogs were overrepresented, as were male dogs and purebred dogs (especially Great Danes). The odds of having discospondylitis in this study were highest for dogs >10 yrs of age. Any area of the spine may be affected, but the thoracolumbar spine is more commonly affected than the cervical spine. The L7–S1 disc space may be the most common site affected by discospondylitis. A large proportion of dogs in the study mentioned above (40.7%) had multiple discospondylitis lesions (Fig. 14.22).

b. Most dogs with discospondylitis display progressive clinical signs over at least several weeks, but some dogs develop signs acutely. Clinical signs are often nonspecific, but usually include hyperesthesia associated with the spinal lesion(s). Dogs with lumbosacral discospondylitis tend to walk with a stilted pelvic limb gait. Decreased appetite, weight loss, depression, fever,

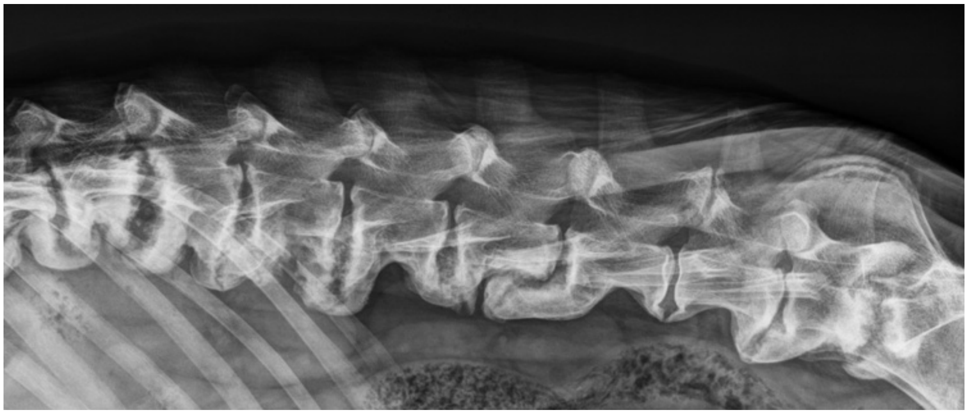

Figure 14.22 Lateral radiograph of a dog showing multiple sites of discospondylitis.

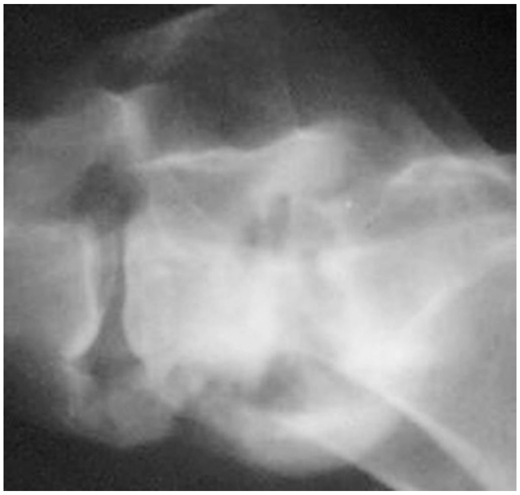

Figure 14.23 Typical radiographic appearance of severe discospondylitis at the L7–S1 intervertebral disc space (lateral view).

and reluctance to move are other common nonspecific clinical features of this disease. Many dogs have no neurologic deficits or mild evidence of neurologic dysfunction (e.g. proprioceptive deficits with or without mild paresis). Some patients may be severely paretic or plegic.

c. A diagnosis of discospondylitis is usually based on characteristic radiographic findings of the disease in a patient with supportive historical and clinical features. Radiographs usually reveal collapse of the affected disc space(s), bony lysis in the endplate regions of the affected disc space(s), and a variable component of bony proliferation and endplate sclerosis (Fig. 14.23). These latter changes are often seen in chronic cases. A separate radiographic appearance, termed "vertebral physitis," has also been reported, primarily in young dogs (< 2 yrs of age). The majority of vertebral physitis cases have involved the lumbar vertebrae. In this condition, bony lysis seems to originate in the caudal physeal region of the vertebral body, rather than the disc/endplate region. Other clinical features of vertebral physitis appear to be indistinguishable from discospondylitis, however.

Radiographic changes may lag behind clinical signs by as much as 2–4 wks. A patient with normal radiographs and clinical features suggestive of discospondylitis may still have that disease. Subtle lesions may also be missed if the radiographs are performed in the awake patient. In some cases, bone scintigraphy, CT, or MRI of suspected lesions may be valuable.

Bloodwork results are often normal, although leukocytosis is occasionally evident on a complete blood count. Urinalysis may reveal evidence of a urinary tract infection in some dogs. Bacteria may be cultured from the blood, urine, and/or affected disc spaces (fluoroscopically guided needle or surgical aspirate) of some patients. The reported success rate of such culture attempts is variable, but in general it is about 50%. There is some evidence that needle aspiration of infected disc space(s) is more sensitive than urine or blood culture. CSF examination and advanced imaging (preferably MRI) should be considered in those patients with severe neurologic deficits, especially in nonambulatory patients. The role of contrast radiography in discospondylitis is controversial. However, compressive lesions that are potentially surgically correctable (e.g. concurrent disc extrusion/protrusion, inflamed or granulomatous epidural fat) may not be appreciated without contrast studies in situations (e.g. emergencies) in which MRI is not readily available. In one study, no adverse effects were associated with myelography or epidurography in dogs with discospondylitis. Compressive lesions were identified in over half of the dogs in that study, and the vast majority (73%) were soft-tissue (versus bony) lesions. However, the median degree of compression was small (5%), and often was not severe enough to explain the degree of neurologic deficits. Other factors, such as interference to intrinsic spinal cord blood supply by inflammatory mediators and/or dynamic vertebral subluxation, are likely to be involved in causing neurologic dysfunction in cases of discospondylitis. Although most bacterial discospondylitis cases are due to Staphylococcal infections, *Brucella* needs to be ruled out (e.g. rapid slide agglutination test, card test) due to its zoonotic potential.

d. Ideally, medical treatment of discospondylitis is guided by culture and antibiotic sensitivity testing of the offending organism. Since the organism is usually a *Staphylococcus* sp., first-generation cephalosporins or beta-lactamase-resistant penicillin drugs (e.g. oxacillin) are often effective. In severely affected (e.g. paralyzed) patients, intravenous antibiotics should be administered for the first 5–7 days, after which oral antibiotics can be instituted. Concurrent treatment with antibiotics active against anaerobic bacteria should be considered, especially if there is minimal to no response to therapy within the first week of treatment. Antibiotic therapy has traditionally been recommended for at least several months. In the authors' experience, discospondylitis patients usually require treatment well beyond several months. In one large retrospective study on canine discospondylitis, the mean duration of antibiotic treatment was 53.7 wks, suggesting that traditional recommendations regarding treatment duration may be too conservative. Analgesic drugs (e.g. oral codeine) may also be necessary in some cases. One author (CWD) has had success using oral acetaminophen with codeine in very painful dogs with discospondylitis. Dosing of this drug is based on the codeine (1–2 mg/kg, every 6–8 hrs), not the acetaminophen. Each acetaminophen tablet contains 60 mg of codeine. Surgical intervention may be warranted in patients with vertebral instability or with compressive lesions identified with CT, MRI, or contrast radiography. The treatment of patients with *Brucella* infections typically entails a combination of tetracyclines and aminoglycosides. Itraconazole is recommended for *Aspergillus* infections. Prognosis is generally favorable with bacterial discospondylitis, particularly in cases with no or mild neurologic deficits. Prognosis is more guarded in dogs with resistant bacteria and in dogs with severe neurologic deficits. In general, obvious clinical improvement is to be expected within the first week of antibiotic therapy. Follow-up radiographs of affected disc spaces every 1–2 mos are recommended to monitor the progress of disease. Fungal (e.g. *Aspergillus* sp.) discospondylitis is associated with a poor prognosis, as the infection is usually disseminated at the time of diagnosis.

2. Meningitis/meningomyelitis

Both granulomatous meningoencephalomyelitis and the infectious diseases listed in Chapter 13 can affect the cauda equina.

E. Ischemic/vascular

1. Intermittent neurogenic claudication[20, 35, 56, 73]

This is a physiological phenomenon that has been proposed to explain exercise-associated pain and lameness that is observed in some patients with cauda equina lesions. Radicular blood vessels will dilate during exercise to meet metabolic demands. Since these vessels may pass through stenotic intervertebral foramina, their dilation can lead to secondary compression and ischemia of the associated nerve roots. This may be manifested clinically as hyperesthesia.

F. Traumatic[22, 35, 52, 73, 74, 88]

Trauma to the spine is discussed in Chapter 15, and principles of medical and surgical therapy are similar when considering the cauda equina and lumbosacral region. However, there are some aspects specific to the cauda equina region to be considered. In contrast to the spinal cord segments, nerve roots of the cauda equina may experience considerable stretching with displaced fractures of the lumbosacral area, yet still remain structurally and functionally intact (remember that nerves are part of the peripheral nervous system). Surgical repair of caudal lumbar and lumbosacral fracture/luxations (Fig. 14.24) is often challenging, due to the sparse amount of bone available caudal to the injury for placing implants (e.g. pins, screws).

Cats will occasionally present with fracture/luxations of the sacrococcygeal region, due to suspected traction injury. It is theorized that the tails of these cats are trapped by car tires as the cats are running to avoid being hit. The resultant traction applied to the cauda equina may result in temporary or permanent neurologic damage. These cats often display varying degrees of urinary and fecal incontinence, in addition to tail dysfunction. Some cats also exhibit pelvic limb dysfunction. It is unclear whether surgical intervention is of value for this condition. Many of these cats will make full recoveries, especially if anal tone and perineal sensation are intact and appropriate bladder management is instituted soon after injury. Failure to regain urinary continence within 1 mo of trauma is a negative prognostic indicator.

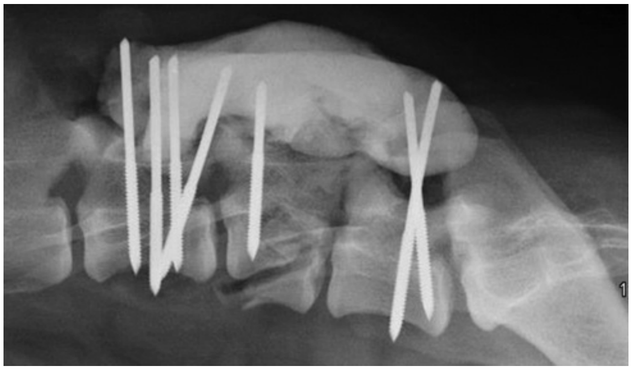

Figure 14.24 Lateral postoperative radiographic image of an L6 vertebral fracture/luxation repaired with threaded pins and polymethyl methacrylate.

Sacral fractures often accompany multiple pelvic fractures in dogs and cats. In general, the preservation of deep pain sensation (nociception) in the areas of innervation of the cauda equina nerve roots is a favorable prognostic indicator. Lateralized sacral fractures in dogs tend to have a better prognosis for neurologic recovery than those located in a more central location.

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Video Resources

Video resources are available on the companion website: www.wiley.com/go/dewey/neurology

See video 31.

CHAPTER 15

Spinal Trauma Management

Daniel J. Fletcher, Curtis W. Dewey, & Ronaldo C. da Costa

Introduction

Injuries associated with spinal trauma include spinal cord contusion, vertebral fracture or luxation, and traumatic intervertebral disc herniation (see Chapter 13). Common causes of spinal trauma in dogs and cats include motor vehicle accidents, animal–animal or human–animal interactions, falls, and projectile injuries. Patients with spinal trauma commonly have concurrent injuries to other major organ systems, necessitating rapid and thorough assessment and survey for evidence of other life-threatening injuries.

Pathophysiology of spinal trauma[2–5, 8, 19, 21, 22, 25, 27, 30–32, 38, 40, 41, 48, 50, 53, 61, 62, 65, 69, 71, 75, 78]

The pathophysiology of traumatic spinal cord injury can be divided into two main components: primary injury and secondary injury. Primary injury occurs as a direct result of the trauma, while secondary injury includes several biochemical processes that are triggered by the primary injury, and that perpetuates spinal cord damage in the hours to days after the traumatic event.

A. Primary spinal cord injury
   Spinal luxation, vertebral fracture, traumatic intervertebral disc herniation, spinal cord contusion, and extra-axial hemorrhage are examples of primary spinal cord injuries that can occur secondary to trauma.
   1. Concussion vs. compression—it is important to understand that not all injuries affect the spinal cord in the same way. Intervertebral disc extrusion is a form of spinal cord injury that is primarily compressive in nature. There is a concussive component, but this component is typically less significant. This explains the rapid recovery when the spinal cord is decompressed. Patients with external trauma, such as those hit by a car, have primarily a concussive spinal cord injury. They may also have compressive injuries caused by fractures or hematomas, but the concussive injury is the most relevant. Compression impacts spinal cord perfusion by limiting arterial supply and occluding venous drainage, and causes direct damage to myelin and axons. Concussion is a more severe form of spinal cord injury. It has been shown that the prognosis of dogs with severe spinal cord injury (plegic with absent nociception) caused by external trauma is significantly worse compared with those dogs with acute intervertebral disc extrusion.
   2. Vertebral fracture and luxation—the stability of a spinal luxation or vertebral fracture is commonly determined using a three-compartment model of the vertebra (Fig. 15.1). The dorsal compartment incorporates the articular processes, laminae, pedicles and spinous processes; the middle compartment includes the dorsal longitudinal ligament, the dorsal aspect of the vertebral body and the dorsal portion of the annulus fibrosus; the ventral compartment contains the ventral longitudinal ligament, the lateral and ventral aspects of the annulus fibrosus, the nucleus pulposus, and the remaining portions of the vertebral body. When any two of the three compartments are compromised, the injury is considered unstable. The type of fracture or luxation that occurs is dependent upon the magnitude of force applied as well as the nature of that force with respect to the spinal column. Extension of the spine commonly results in vertebral lamina, facet, or pedicle fractures. These types of fractures often occur simultaneous with rupture of the annulus fibrosus. Therefore, these types of fractures are commonly unstable with extension of the spine, but remain stable in flexion. Shearing or compressive forces most commonly result in vertebral body fractures, and these types of fractures are generally unstable. Spinal cord compression can also result if fracture fragments are located within the vertebral canal. Pure compression forces of sufficient magnitude result in vertebral compression fractures. These fractures are rarely unstable due to preservation of the dorsal ligaments. Flexion of the vertebral column (with or

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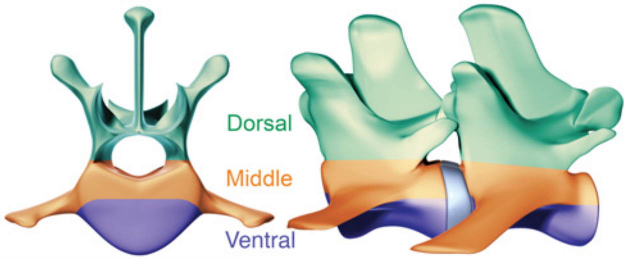


Figure 15.1 Schematic representation of the three-compartment model for evaluating stability of a vertebral fracture/luxation. (Shores, 1992.[72] Reproduced with permission from Elsevier.)

without rotation) most commonly results in vertebral luxation, but often does so without vertebral fracture. Damage to both the dorsal and ventral stabilizing ligamentous structures is the cause of the resultant instability. Rotation of the vertebral column with or without flexion is the most common cause of vertebral fracture with concurrent spinal luxation. Similar to luxation without fracture, the instability of this type of injury is due to compromise of both dorsal and ventral ligamentous structures. The form of vertebral luxation seems to differ between dogs and cats. In dogs the caudal segment is displaced ventrally in the majority of cases, whereas in cats it tends to be displaced dorsally.

3. Traumatic intervertebral disc herniation—this type of primary injury typically occurs in dogs with underlying intervertebral disc disease, most commonly chondroid degeneration of the dorsal aspect of the annulus fibrosus. This pathology predisposes the annulus to rupture with trauma, resulting in compression of the spinal cord due to herniation of the nucleus pulposus into the vertebral canal (see Chapter 13). In a recent study, less than one-third of dogs with traumatic disc extrusion had spinal cord compression. Most dogs had the so-called type III, noncompressive, high velocity/low volume, explosive disc herniations. These noncompressive traumatic herniations occur most commonly in older chondrodystrophic breeds, but can be seen in any dog. Although it is much less common, cats can also develop chondroid degeneration of the intervertebral disc, predisposing them to traumatic herniation.
4. Spinal cord contusion—reports of hemorrhage into the spinal cord parenchyma are rare in the veterinary literature; however, it is likely that contusions do occur secondary to vertebral fracture, spinal luxation, or traumatic intervertebral disc herniation. Contusions are the result of damage to blood vessels in the spinal cord parenchyma, and in addition to resulting from direct trauma to the cord, they may also develop secondary to traumatic motion of the spinal cord within the vertebral canal, resulting in coup and contrecoup lesions, similar to cerebral contusions that develop after head trauma.
5. Extra-axial hemorrhage—disruption of blood vessels serving the supportive structures surrounding the spinal cord can result in an accumulation of blood and hematoma formation. Subdural or epidural accumulations can cause neurologic dysfunction by compressing the spinal cord and compromising spinal cord blood flow. Although epidural and subdural spinal hematomas have been reported secondary to trauma in humans, they are rare. Several veterinary case reports describe the development of epidural hematomas secondary to spontaneous intervertebral disc herniation, but there are no published reports of these types of injuries secondary to trauma.

B. Secondary spinal cord injury

Many biochemical processes are set into motion by traumatic spinal cord injury and lead to continued spinal cord injury over the first 24–48 hrs after the primary injury. An understanding of these mechanisms of secondary injuries is essential when devising a therapeutic plan for a patient with spinal cord trauma.

1. Excitotoxicity—excitatory neurotransmitters such as glutamate and aspartate are present in increased concentrations in the spinal cord parenchyma due to leakage from damaged neurons as well as decreased clearance by ischemic astrocytes. Stimulation of neighboring neurons by these neurotransmitters leads to adenosine triphosphate (ATP) depletion as well as an influx of sodium and calcium. The result is cellular edema and spinal cord swelling. Compression of the swollen spinal cord contributes further to cellular ischemia.
2. Loss of autoregulation and ischemia—spinal cord blood flow remains constant despite changes in systemic blood pressure due to intrinsic autoregulatory mechanisms, causing vasoconstriction in response to increased blood pressure and vasodilation in response to decreased blood pressure. These autoregulatory mechanisms are commonly compromised after spinal cord trauma, and systemic hypotension, common in patients with trauma, leads to decreased spinal cord blood flow. If hypotension persists, spinal cord ischemia can result. The ischemia affects primarily the gray matter because its metabolic needs are higher and the blood supply to the gray matter is five times higher than the white matter.
3. Accumulation of intracellular calcium—excitotoxicity and activation of voltage-gated calcium channels result in activation of phospholipase A2, triggering the inflammatory cascade. In addition, ATP is depleted due to the binding of calcium to phosphates, mitochondrial dysfunction occurs, and cytotoxic edema develops. All of these processes triggered by increases in intracellular calcium concentration lead to continued neuronal cell death.
4. Oxidative injury—the presence of increased intracellular calcium, ischemia-reperfusion phenomena, the presence of iron and copper due to hemorrhage, and the high lipid content of spinal cord tissues all favor the production of

reactive oxygen species. Neuronal cell membranes, rich in polyunsaturated fatty acids, provide an excellent medium for chain reactions that perpetuate this injury. This cycle of oxidative damage contributes to ongoing cellular injury and necrosis.

5. Inflammation—local spinal cord and systemic inflammation secondary to traumatic injury can be severe. Inflammatory mediators contribute to secondary injury by inducing nitric oxide (NO) production via inducible nitric oxide synthetase (iNOS), providing a chemotactic stimulus for influx of inflammatory cells, and activating the arachidonic acid cascade. Several of these inflammatory mediators are potent activators of coagulation, resulting in microvascular thrombosis and further spinal cord ischemia.
6. Apoptosis—following acute spinal cord injury, neurons, glial, and endothelial cells die by necrosis or apoptosis. Oligodendrocyte death caused by apoptosis is a prominent feature of the early phase of acute spinal cord injury and continues for extended periods after injury, contributing to demyelination and loss of function. Oligodendrocyte apoptosis occurs primarily through activation of the Fas receptors by microglial cells expressing the Fas ligand, and p75 neurotrophin receptor signaling. Activation of the Fas receptor triggers the caspase cascade, resulting in apoptosis.

Initial assessment and emergency treatment[1, 23, 29, 45, 46, 65–67, 72]

Although the neurologic signs present in patients with spinal trauma can be severe, the clinician must take a global approach when initially evaluating the patient, and must take care to identify all imminently life-threatening injuries. The basic "ABC" approach—quickly evaluating the patency of the airway, the ability of the patient to breathe, and the effectiveness of circulation—will afford identification of most life-threatening injuries. Most patients with significant traumatic injuries will present in a state of hypovolemic shock due to inappropriate vasodilation, blood loss, or both. A minimum database—including packed cell volume (PCV), total solids (TS), Azostix (AZO), and blood glucose (BG)—is part of the initial patient assessment. Hypovolemia and hypoxemia can contribute to secondary spinal cord injury, and the rapid correction of perfusion deficits is of paramount importance.

A. Fluid therapy

A patient with a systolic blood pressure less than 90 mmHg or a mean arterial blood pressure less than 80 mmHg is hypotensive and at risk of secondary spinal cord injury. Aggressive fluid resuscitation is warranted in all hypovolemic trauma patients. If the patient is anemic, whole blood or packed red blood cell (pRBC) transfusion may assist in maintaining normovolemia as well as adequate tissue oxygenation by improving blood oxygen content, the major determinant of which is hemoglobin concentration. Fluid support may include one or more of the following choices:

1. Synthetic colloids: 10–20 mL/kg over 15–20 min to effect (up to 40 mL/kg in the initial hour) for hypovolemic shock. This can be given as a rapid bolus in dogs; give it in 5 mL/kg increments over 5–10 min in cats. In the euhydrated trauma patient, Hetastarch is an excellent choice for restoring normal blood pressure. Dextran-70 is an acceptable alternative. Dehydrated trauma victims should receive isotonic crystalloid resuscitation.
2. Hypertonic saline (7%): 4–5 mL/kg over 15–20 min for hypovolemic shock. Hypertonic saline is also available as a 23.4% solution, which cannot be administered undiluted, but may be mixed 1:3 with hetastarch or dextran-70 (e.g. 20 mL of 23.4% hypertonic saline + 40 mL hetastarch or dextran-70 in a 60 mL syringe) to produce a solution of synthetic colloid suspended in a 7% hypertonic saline solution. Hypertonic saline also has positive inotropic effects, immunomodulatory effects, and reduces endothelial swelling.
3. Isotonic crystalloids (e.g. Lactated Ringer's solution, 0.9% saline): 20–30 mL/kg bolus over 15–20 min for hypovolemic shock. May be repeated as necessary after reassessment. Since overhydration is a concern with crystalloid administration, the "shock dose" (90 mL/kg in the dog, 60 mL/kg in the cat) of crystalloids should be given incrementally to effect as described above. If the entire volume is not necessary to restore euvolemia and normal blood pressure, fluid administration should be tapered when these physiologic goals are met.
4. Blood products: Administration of 1 mL/kg of packed red blood cells (pRBCs) or 2 mL/kg of whole blood will increase the PCV by 1%. The severity of anemia will dictate the total dose to be administered, but 10–15 mL/kg of pRBCs is a reasonable starting dose. Blood products are typically administered over 4 hrs, but may be given faster (to effect) if the patient is unstable. Boluses of blood products are acceptable in the severely anemic trauma patient. Goals of therapy with blood products are a packed cell volume (PCV) between 25 and 30%. Patients with demonstrated coagulopathy should also be treated with fresh frozen plasma (FFP) at a dose of 10–15 mL/kg 2–3 times per day until the coagulopathy has resolved.

B. Pressors

In patients unresponsive to fluid therapy, vasopressor agents should be used to maintain adequate systemic blood pressure. Patients with inappropriate vasodilation, which is common in traumatized animals, may benefit from dopamine (5–12 μg/kg/min) or norepinephrine infusion (1–10 μg/kg/min). Patients with decreased cardiac contractility due to underlying heart disease or traumatic myocardial injury may respond to dopamine or dobutamine (1–20 μg/kg/min) infusion.

C. Oxygenation and ventilation

Hyperoxygenation (but not hyperventilation) is recommended for most trauma patients. Initial assessment is based upon respiratory rate and effort, mucous membrane and tongue color, and thoracic auscultation. Pneumothorax and pulmonary contusions are common sequelae of trauma, and must be promptly addressed. In the face of increased respiratory rate and effort, lung sounds may not consistently be decreased on auscultation in patients with pleural space disease (e.g. pneumothorax or hemothorax). A rapid, shallow breathing pattern, pale oral mucous membranes, and evidence of respiratory distress are indications of pleural space disease, and thoracocentesis should be done in any trauma patient with these signs. Thoracocentesis should be considered a diagnostic test as well as a therapeutic intervention. If negative pressure cannot be obtained via thoracocentesis, a chest tube should be placed immediately. If arterial blood gas analysis is available, the partial pressure of oxygen in arterial blood (PaO_2) should be maintained at or above 90 mmHg for dogs and 100 mmHg for cats. Pulse oximeters are extremely useful, and relatively accurate, estimators of oxygenation status. However, the reliability of pulse oximeters varies with model used, with the PaO_2 level (pulse oximeters may overestimate oxygenation status at lower PaO_2 levels), and with the patient's hemodynamic status.

Patients who are conscious and not obviously deteriorating neurologically should be administered supplemental oxygen via facemask, nasal cannulae, nasal oxygen catheter, or transtracheal oxygen catheter. Facemasks tend to stress dogs and cats, and should only be used temporarily, until another form of oxygen (O_2) delivery can be instituted (e.g. nasal O_2). The use of an O_2 cage is generally an ineffective method of administering supplemental O_2 to patients with severe spinal injury, as most require frequent or constant monitoring. Oxygen cages do not allow for concomitant close patient observation (requires opening the cage door) and maintenance of a high-oxygen environment. With nasal and transtracheal O_2 catheters, an inspired oxygen concentration of 40% is provided with flow rates of 100 mL/kg/min and 50 mL/kg/min, respectively. Oxygen concentrations as high as 95% can be delivered with proportionally higher flow rates. Nasal O_2 catheters should not be placed farther than the level of the medial canthus.

Patients with airway trauma causing obstruction or spinal cord disease causing hypoventilation should be intubated and ventilated. If intubation is not possible due to airway obstruction, emergency tracheostomy is indicated. Arterial blood gas measurement is the best way to monitor ventilation, which is reflected in $PaCO_2$ levels. End-tidal CO_2 measurement is a useful monitoring tool, but tends to underestimate the true $PaCO_2$ levels due to the likelihood of dead space ventilation. Venous CO_2 levels ($PvCO_2$) are also helpful, and are usually less than 5 mmHg greater than $PaCO_2$. However, in patients with perfusion deficits, peripheral $PvCO_2$ levels can be significantly higher than arterial values, and should be interpreted cautiously. Ventilatory rates of 10–15 breaths per minute should be sufficient to maintain $PaCO_2$ levels between 35 and 45 mmHg in the absence of significant pulmonary parenchymal disease. Hyperventilation may be deleterious to the spinal trauma patient due to potential vasoconstriction, which reduces spinal cord blood flow. The goal should be normocapnia ($PaCO_2$ of 35–45 mmHg).

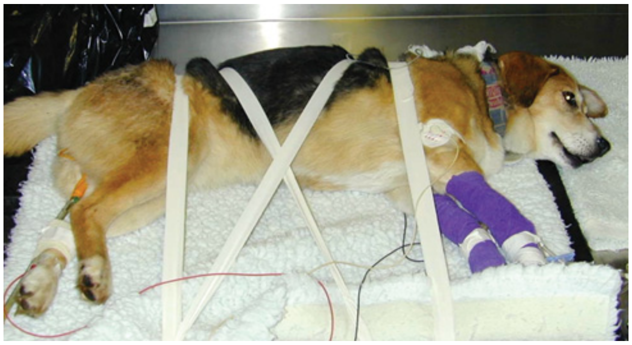


Figure 15.2 Patient with spinal trauma taped to a backboard to prevent further spinal cord injury.

D. The initial neurologic examination (Video 32)

Once immediately life-threatening extra-central nervous system problems have been identified and addressed, an initial brief neurologic exam should be done to localize any spinal cord lesions and to determine whether an unstable fracture is present. Nonambulatory animals should be minimally manipulated on presentation until the presence of an unstable injury has been ruled out. Initially, all patients should be treated as if an unstable injury is present. Taping patients to a rigid "backboard" (Fig. 15.2) can provide external coaptation sufficient to protect the spinal cord from significant additional trauma in the face of unstable spinal injuries.

The initial neurologic exam should include evaluation of mentation, complete cranial nerve examination, assessment of ambulation, and presence of voluntary motor function, segmental reflexes, and superficial pain sensation in all four limbs. If superficial pain sensation is absent, an assessment of deep pain sensation (nociception) in the affected limbs should be done. In patients with thoracolumbar trauma, the cutaneous trunci reflex should also be tested, and may provide further localizing information. In addition to the neurologic exam, an orthopedic evaluation of affected limbs should be done to determine whether musculoskeletal injury could be responsible, but only to the degree that such an evaluation can be done safely in a patient with a potentially unstable spinal injury. The vertebral column should be gently palpated to identify areas of crepitus, potential misalignment, or pain. Extensor rigidity of the thoracic limbs in combination with paraplegia (Schiff–Sherrington posture, Fig. 2.2) indicates severe thoracolumbar injury. Although this finding is useful in the context of neurolocalization, it has not been shown to be a prognostic indicator. It may be present in animals with spinal cord lesions of varying severity. Patients without evidence of mentation, cranial nerve, or orthopedic abnormalities but who are unable to ambulate should raise the clinician's index of suspicion for severe spinal trauma. Significant spinal cord injury may be present even if the animal was noted to ambulate immediately post injury. Brachial plexus injury is likely in patients with an absence of flexor reflex in one thoracic limb, Horner's syndrome (ptosis, miosis, enophthalmos) in the ipsilateral eye, and ipsilateral loss of the cutaneous trunci reflex. In paralyzed animals, nociception should be evaluated in both left- and right-sided limbs (evaluating medial and lateral digits) and tail. Absence of nociception carries a guarded prognosis for dogs with intervertebral disc extrusion and a poor prognosis for patients with external spinal cord injury.

Diagnostic imaging procedures[4, 6, 19, 23, 47, 52, 65, 72]

A. Vertebral column radiographs

Vertebral column radiographs are generally indicated in animals with suspected vertebral injury, but must be done cautiously to minimize the risk of further injuring the spinal cord. All trauma patients with evidence of myelopathy should be treated as if they have unstable fractures until definitive evidence to the contrary is available. Lateral radiographs of the vertebral column can usually be obtained safely, and can provide valuable diagnostic information in animals with spinal injuries (Fig. 15.3). Sedation for spinal radiographs can lead to increased instability of the spine due to relaxation of the paraspinal musculature, causing further spinal cord trauma; therefore, sedated patients should be handled very carefully. Patient positioning can be crucial to obtaining spinal radiographs of good diagnostic quality; therefore, radiographs with poor patient positioning should be interpreted cautiously. Taping the patient to a rigid backboard may be necessary to prevent worsening (Fig. 15.2). Lateral radiographs can be taken with the patient immobilized in this way. Ventrodorsal radiographs can also be obtained in a laterally recumbent patient immobilized with this technique with the use of a horizontal beam technique. It is important to know that a significant percentage of patients with spinal trauma have more than one fracture or luxation (Fig. 15.4). Careful evaluation of posture, spinal reflexes, and cutaneous trunci reflex should help to identify those cases. When in doubt, it is recommended to acquire radiographs from more than one spinal region.

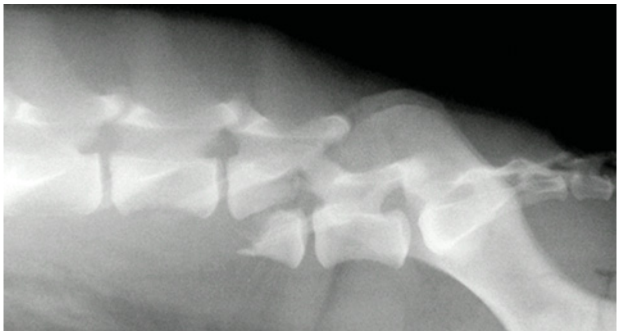


Figure 15.3 Lateral radiograph of a dog with a displaced L6 vertebral fracture.

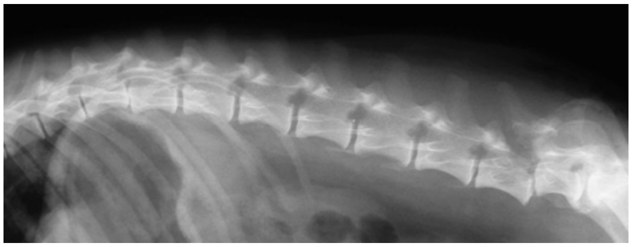


Figure 15.4 Lateral radiograph of a dog with two fractures and subluxations. The first is located at T12–T13 and the second at L6–L7.

It is also important to realize that, in canine patients with spinal trauma, plain radiography has low sensitivity for vertebral fractures (72%) and subluxations (77.5%), as well as low negative predictive values for the presence of fracture fragments within the vertebral canal (51%) compared with computed tomography (CT) (Fig. 15.5). Therefore, spinal radiographs alone should not be used to definitively rule out the presence of these types of injuries. Traumatic intervertebral disc herniations are also difficult to diagnose on spinal radiographs. Narrowing of an affected disc space has been shown to be the most useful radiographic sign of intervertebral disc herniation. However, this finding has low sensitivity (64–69%) and positive predictive value (63–71%) for diagnosis of herniation. It is important to emphasize that radiographs cannot be used as prognostic indicators. Prognosis is based on neurologic examination and the presence or absence of nociception.

B. Advanced imaging

Due to the limitations of plain radiography, advanced imaging techniques such as myelography, CT, or magnetic resonance imaging (MRI) are often required to definitively localize and evaluate the severity of spinal injury. These advanced imaging modalities require general anesthesia. Relaxation of the stabilizing paraspinal muscles results, and the risk of additional spinal cord injury is increased. Patients must be carefully manipulated and monitored during these procedures to minimize further trauma to the spinal cord due to unstable spinal injuries.

1. Myelography—contrast (iohexol, 0.25–0.45 mL/kg) is injected into the subarachnoid space via a spinal needle placed at the L4–L5 or L5–L6 junction. Radiographs are taken after contrast injection, showing a column of

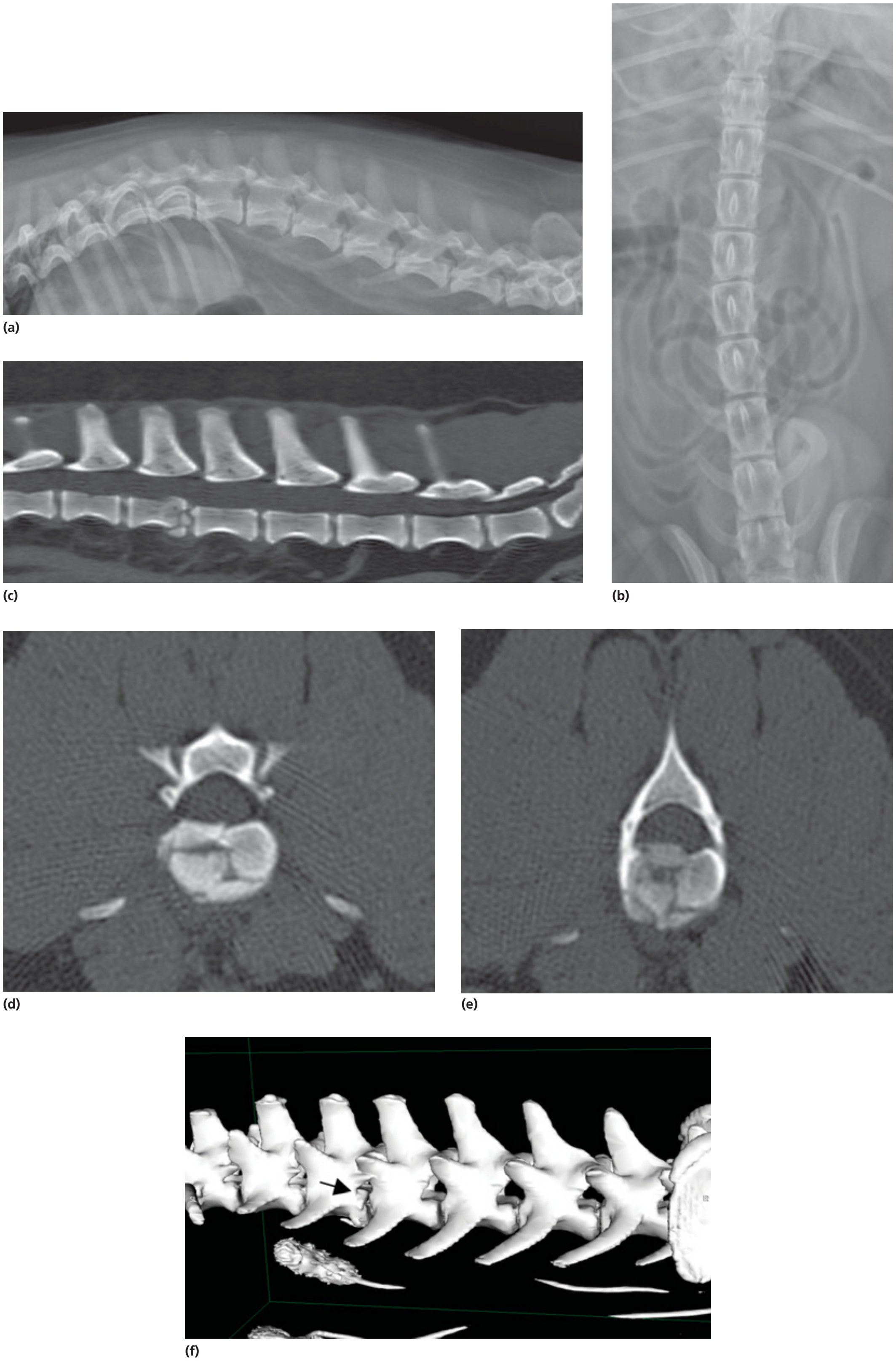


Figure 15.5 Images of a dog with vertebral fracture of the second lumbar vertebra. (A) Lateral radiograph. (B) Ventrodorsal radiograph. Note that is difficult to visualize the fracture. (C) Reconstructed CT scan. (D) and (E) Transverse CT images showing the vertebral body fracture. (F) 3D reconstruction of the CT scan (arrow pointing the fracture and small intervertebral foramen).

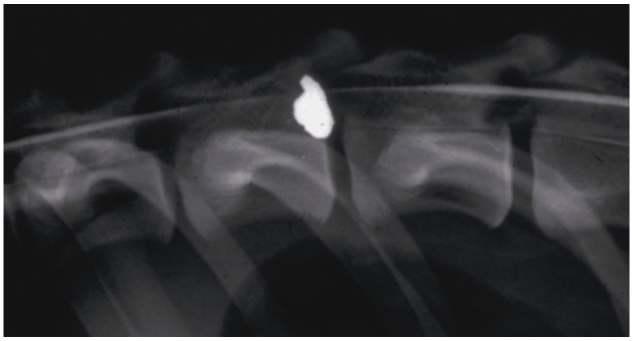


Figure 15.6 Lateral myelographic image of a dog with a gunshot injury to the spinal cord. Note the spinal cord swelling in the region of the injury.

contrast on either side of the spinal cord within the vertebral canal. Compressive lesions of the spinal cord can be identified as defects in the contrast columns. Using this technique, extradural lesions such as traumatic intervertebral disc herniation or extra-axial hematomas, as well as intraparenchymal swelling or hemorrhage, can be readily diagnosed (Fig. 15.6). However, the positioning of patients for contrast injection during myelography can cause an increased risk of spinal cord trauma if unstable spinal injuries are present. In addition, although compressive lesions are readily diagnosed with myelography, little additional information about spinal cord injuries such as edema or vertebral fractures is obtained.

2. Magnetic resonance imaging (MRI)—MRI uses a combination of a strong magnetic field and intermittent radio frequency pulses to obtain high-resolution images of soft-tissue structures (Fig. 15.7). MRI is superior for the evaluation of intramedullary changes such as spinal cord hemorrhage and edema, as well as damage to supporting soft-tissue structures such as the epaxial musculature and ligaments. It is also an excellent modality for diagnosis of traumatic intervertebral disc herniation or extra-axial hemorrhage. However, the technique provides poor detail of bony structures, and several studies in human medicine have shown that significant spinal fractures can be overlooked on MR images. It is important to be careful with MRI settings. Due to the long acquisition time, MR images are typically much thicker than CT images. Thicker MR images can average the signal and lead to erroneous interpretation (Fig. 15.8). Ideally, both MRI and CT should be performed whenever possible, since these modalities are complementary.

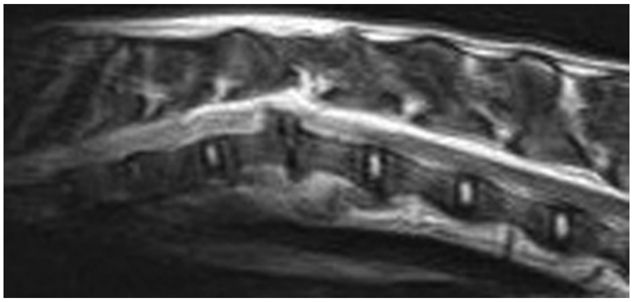
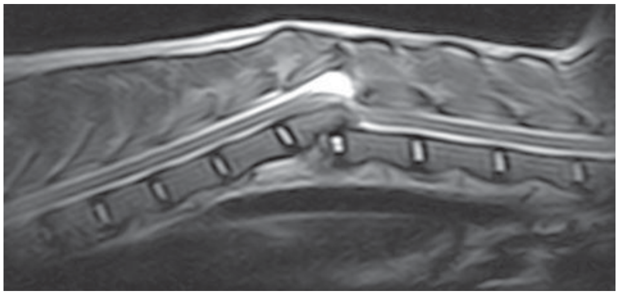
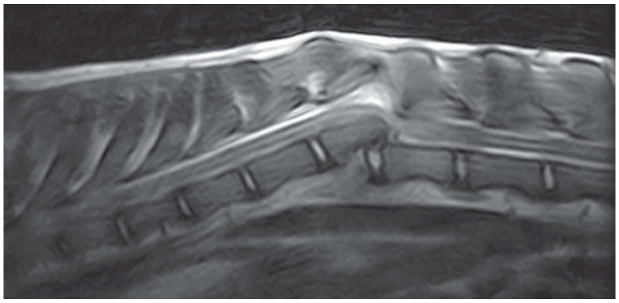


Figure 15.7 Sagittal T2-weighted MR image of a dog with a vertebral fracture and spinal cord compression.



(a)



(b)

Figure 15.8 Sagittal MRI of a dog with fracture and luxation. (A) Sagittal T2-weighted image showing what appears to be a complete luxation and spinal cord transection. Slice thickness was 3.5 mm. (B) Sagittal gradient echo image (FISP, Hyce) of 1.6 mm showing the spinal cord being compressed but still intact. (Courtesy of Drs. Célio Jardim Júnior and Pamela Sayuri Hato, Hospital Veterinário Cães e Gatos 24h, Osasco, Brazil, 2014. Reproduced with permission.)

3. Computed tomography (CT)—CT scanners utilize a rotating pair of X-ray tubes and detectors to obtain high-resolution images of soft tissue and bony structures. The resulting images consist of a set of slices of a prescribed thickness (ideally not more than 2 mm thick; thinner slices are always advantageous) of the area of interest (Fig. 15.9). Computer algorithms can be used to create three-dimensional representations of various structures, including the spinal cord, supporting structures such as ligaments and the vertebrae (Fig 15.3). This technique has been shown to be an extremely sensitive diagnostic test for acute bony lesions in human polytrauma, with sensitivity of up to 100% in several studies. With injection of intravenous contrast agents, the presence of spinal cord edema and hemorrhage can be diagnosed due to compromise of the blood–spinal cord barrier. This combination of characteristics makes it the preferred imaging modality for screening of human patients with polytrauma, including the vertebral column. CT myelography can also be performed in cases of traumatic disc herniation (Fig. 15.10).

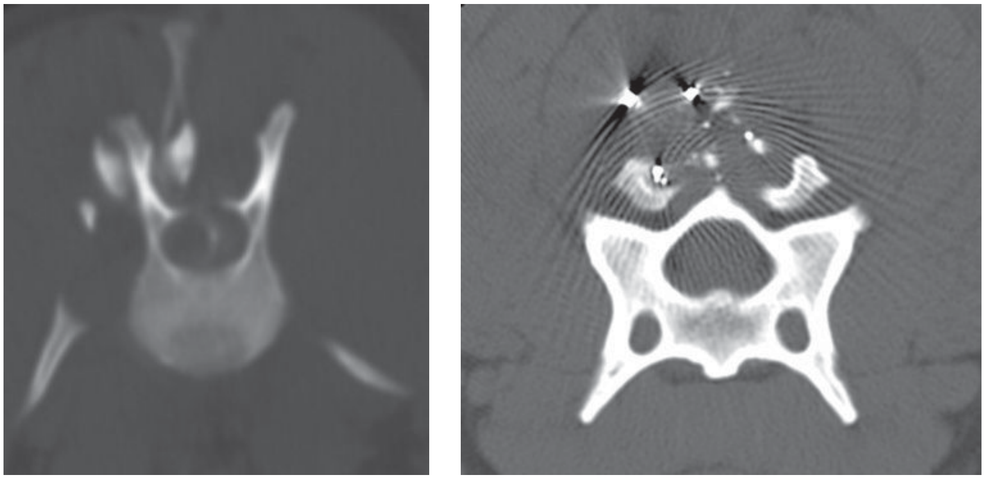


Figure 15.9 (A) Transverse CT image of a dog with a horizontally displaced L2 vertebra. (Dr. P Scrivani, Cornell University, 2014. Reproduced with permission from Dr. P Scrivani.) (B) Transverse CT image of a dog with a gunshot wound with fracture of the spinous and transverse processes.

Specific therapy for spinal trauma[9–18, 20, 23, 24, 26, 28, 33–36, 39, 42, 43, 47–49, 51, 54–62, 64, 65, 70, 72–74, 76, 77]

A. Primary injury

Treatment of primary traumatic spinal injury may include surgical and/or medical intervention. The severity and nature of the underlying primary injury will dictate the most appropriate treatment, and the protocol must be tailored to the individual patient

1. Vertebral fractures and luxations—these types of injuries may be treated nonsurgically, or with surgical decompression, reduction, and/or fixation. There is considerable debate in the veterinary literature regarding indications for surgical vs. nonsurgical management of vertebral fractures and spinal luxations. The personal opinion of the surgeon and the choice of the owner ultimately determine which patients are surgical candidates. However, several general indications are widely agreed upon to be indications for surgical management:
   a. minimal voluntary motor function or complete paralysis
   b. clinical or radiographic evidence of highly unstable fractures
   c. progression of neurologic signs despite appropriate nonsurgical management.

   There are various surgical options for stabilization and internal fixation, including the use of bone plates, screws, Steinmann pins, and polymethyl methacrylate (PMMA) cement. These procedures require advanced training, and referral to a board certified surgeon or neurosurgeon should be recommended. Surgical management results in an immediate stabilization of the vertebral column and more rapid return to function. However, these procedures are expensive, and complications such as worsening of spinal cord injury due to instability of the extraspinal muscles during anesthesia and surgical manipulation, implant failure, and infection are possible.
2. External coaptation and strict cage rest for 6–8 wks to allow healing are the main components of nonsurgical therapy for these types of injuries—many materials are available for splint construction, including fiberglass, thermoplastics, plaster, metal rods, or other materials that can be fashioned to conform to the patient's body shape. The splint will not successfully aid healing unless the entire vertebral region is immobilized. When bandaging the splint in place, it is imperative that the patient's ventilation not be compromised. Daily bandage checks are essential to ensure that no soiling or other complications have developed. Nonsurgical management is generally less expensive in the short-term, does not require specialized equipment, and allows owners to provide care at home. However, nursing care is of paramount importance and can be quite labor intensive. In addition, patients treated nonsurgically generally have longer

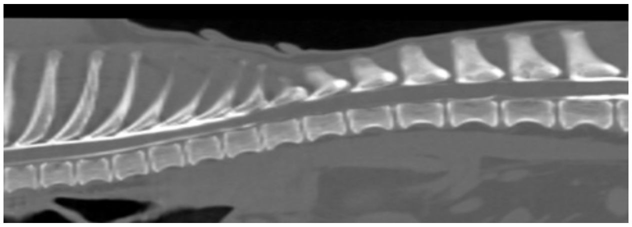


Figure 15.10 Reconstructed sagittal CT image showing severe intramedullary edema in a dog suspected of having a "type III", non-compressive intervertebral disc herniation. The myelographic column is lost over five intervertebral disc spaces.

recovery periods and a greater likelihood of persistent neurologic deficits.

3. Traumatic intervertebral disc herniation—both surgical and nonsurgical treatment can be used and the decision should be guided by imaging findings. It appears that most traumatic disc herniations ("type III" discs) are noncompressive in nature, thus no benefit will be gained by surgical decompression. If compression is seen, depending upon the site and severity of the herniation, dorsal laminectomy, hemilaminectomy, or a ventral slot procedure may be indicated. Stable patients with intact voluntary motor function are candidates for medical management, consisting of strict cage rest for 3–4 wks to allow resolution of spinal cord edema and inflammation. Anti-inflammatory medications, such as steroids at anti-inflammatory doses (e.g. 0.5 mg/kg prednisone PO q 12 hrs, tapered over 1 wk) or nonsteroidal anti-inflammatories (e.g. carprofen, deracoxib), can be used initially for pain relief, but it should be stressed that these medications do not have any significant protective effect on the spinal cord. The subject of intervertebral disc extrusions is covered in detail in Chapter 14.
4. Spinal cord contusion—contusion rarely occurs as a sole entity, and is usually the result of a compressive lesion or spinal instability. Treatment involves addressing the concurrent primary injury via surgical or nonsurgical management and medical therapy to reduce secondary injury.
5. Extra-axial hematoma—aggressive surgical evacuation to relieve spinal cord compression is recommended in people with traumatic extra-axial hemorrhage. Because of more limited access to advanced imaging modalities, these types of injuries are rarely diagnosed in veterinary medicine secondary to trauma. If diagnosed, surgical decompression is recommended in these cases.

B. Secondary injury

Secondary injury, as described above, develops immediately after the traumatic event and continues in the hours to days post injury. It is responsible for much of the progression of neurologic dysfunction noted after a traumatic event. Many therapies to ameliorate secondary injury have been proposed in the clinical and experimental literature.

1. Maintenance of perfusion—as discussed previously, maintaining systemic blood pressure and blood oxygen content is of paramount importance in reducing secondary spinal cord injury. Spinal cord blood flow autoregulatory mechanisms are commonly compromised by trauma, and patients sustaining spinal trauma frequently have respiratory, cardiovascular, or head trauma as well as significant hemorrhage, all of which can lead to decreased systemic blood pressure and oxygen delivery. In the face of impaired autoregulation, the damaged spinal cord is at high risk of ischemic injury. As outlined above, aggressive fluid resuscitation should be implemented to maintain adequate perfusion. Patients unresponsive to fluid therapy alone may benefit from vasopressors. Oxygenation and ventilation should also be closely monitored, and deficits addressed.
2. Corticosteroids—the use of corticosteroids to ameliorate secondary injury after spinal cord trauma is highly controversial in both human and veterinary medicine. There is evidence from the experimental and clinical literature of both the benefit and the harm from the use of these drugs in patients with spinal cord injury. A thorough understanding of the evidence for both benefit and harm is essential for the clinician considering administration of these drugs. Methylprednisolone sodium succinate (MPSS) has been extensively investigated in both experimental studies and clinical trials as a therapy for secondary spinal cord injury. Proposed neuroprotective mechanisms include improvement of spinal cord blood flow, antioxidant (i.e. free-radical scavenging) effects, and anti-inflammatory activity. Free-radical scavenging has been shown experimentally to be the most important protective effect in patients with spinal cord injury. Other common corticosteroids (e.g. dexamethasone, prednisone) have minimal antioxidant effects, and are unlikely to have any significant neuroprotective effect, although they may reduce the discomfort associated with the injury. A series of three human clinical trials (the National Acute Spinal Cord Injury Study, or NASCIS) provide the primary evidence of a beneficial effect of MPSS in patients with spinal cord injury. The only placebo-controlled trial (NASCIS 2) showed a mild improvement in motor scores at 6 wks for patients treated with MPSS (30 mg/kg bolus, followed by a constant rate infusion of 5.4 mg/kg/hr for 48 hrs) compared to the placebo group, but this effect was not present at 6 mos or 1 yr post injury. Only in a post hoc, subgroup analysis were the authors able to show an improvement in motor scores at 6 wks, 6 mos, and 1 yr in the group of patients treated with MPSS for 48 hrs beginning 3–8 hrs post injury. No difference in outcome between the treatment groups was noted at any of the time points for patients treated less than 3 hrs or greater than 8 hrs post injury. There were no differences in mortality between the groups, but there was an increased incidence of severe pneumonia and a trend for an increased risk of sepsis in the groups treated with MPSS for 48 hrs at the 6-wk time point.

There has been much debate in the human literature over the results of the NASCIS 2 trial. Although the use of high-dose MPSS for patients with spinal cord injury still appears to be considered standard of care, several surveys have shown a lack of confidence in this therapy among human neurosurgeons. In veterinary medicine, a recent prospective placebo-controlled clinical trial compared MPSS and placebo as adjunctive therapies for the surgical decompression of dogs with paraplegia with absent nociception secondary to intervertebral disc extrusion. In order to be enrolled, the dogs had to be paralyzed for less than 24 hrs and did not received corticosteroids or nonsteroidal anti-inflammatory drugs. No benefit was seen with the use of MPSS. Interestingly, although multiple experimental studies in veterinary medicine have reported several gastrointestinal side effects of the high-dose MPSS protocol, no side effects were reported. Even though this study did not evaluate MPSS in external spinal cord injury, considering the mild beneficial effect seen in people and the lack of benefit in dogs with severe intervertebral disc disease, there is no evidence to support the use of MPSS in dogs with acute spinal cord injury.

3. Polyethylene glycol (PEG)—PEG is a hydrophilic polymer that exerts a neuroprotective effect on nerve fibers by sealing damaged membranes, allowing the fibers to more rapidly restore normal sensory and motor conduction. PEG also reduces the effects of excitotoxicity by sealing defects in neuronal cell membranes, reducing leakage of excitatory neurotransmitters. A preliminary study showed that dogs treated with PEG (2 mL/kg of a 30% solution) within 72 hrs of acute, spontaneous intervertebral disc had improved outcomes compared to historical controls. In the prospective placebo-controlled trial of MPSS previously mentioned, PEG was also evaluated as an adjunctive therapy in dogs with acute intervertebral disc herniation and absent nociception. No benefits were seen in the dogs that received PEG compared to placebo; therefore, the use of PEG is not recommended in dogs with spinal cord injury.
4. Cell based therapies—there is significant interest in cell-based therapies for spinal cord injury. Cell-based approaches for spinal cord functional repair center on two fundamental directions that are not mutually exclusive: restitution of white matter long tracts (“regenerative” approach) and cell (i.e. neuronal or oligodendrocyte) replacement. While there is a wealth of experimental studies, primarily in rodents, clinical data of patients showing benefit are still limited. A recent meta-analysis of 12 studies in people using bone marrow mesenchymal and hematopoietic stem cells, olfactory ensheathing cells, Schwann cells, and fetal neurogenic tissue indicated that the quality of the evidence of benefit of stem cells is very low. A recent comprehensive review of the topic in rodents also indicated that the quality of the evidence is weak for all cell therapies, a little more robust for olfactory ensheathing cells. In veterinary medicine, autologous olfactory glial cell transplantation has been evaluated in two studies in dogs. Olfactory glial cell transplantation was shown to be safe, with no significant short- or long-term complications. In a clinical trial with chronic paraplegic dogs with absent nociception, olfactory-derived cells improved communication across the lesion, allowing recovery of “automatic” coordination between thoracic and pelvic limbs. However, no improvement in long tract function was seen (i.e. communication between brain centers and spinal cord tracts distal to the injury). The effects were thought to be primarily local, improving plastic changes in propriospinal connectivity. The authors conclude that the olfactory mucosal transplant was unlikely to provide significant clinical benefit to human spinal cord injury patients by itself. Another clinical trial is underway with stem cells in dogs with acute spinal cord injury and the preliminary results indicate no observable benefits, compared to the control group.
5. Rehabilitation—although there are no studies showing any specific benefits of physical therapy and rehabilitation in dogs with spinal cord injury, this therapy plays a very important role in the recovery of patients with spinal cord injury. Physical therapy minimizes muscle atrophy, maintains proper range of motion, ameliorates patient discomfort, and can possibly hasten the recovery if the injury is reversible. It has been shown experimentally that locomotor training can promote plastic changes in the sensorimotor circuits below the level of injury that can lead to improvement in gait pattern, even in animals with spinal cord transection.

Prognosis and complications[4, 7, 23, 37, 44, 50, 63, 68]

Neurologic recovery after spinal trauma is difficult to predict, and is likely affected by the type and severity of primary injury as well as the effectiveness and timeliness of the treatment of secondary injury. Presence of nociception has consistently been correlated with prognosis in patients with spinal cord disease. Because it is transmitted by small diameter tracts located within the deepest areas of white matter immediately adjacent to spinal cord gray matter, the loss of nociception is evidence of functional spinal cord transection. However, some patients with a loss of nociception can recover neurologic function with treatment.

Vertebral fracture and luxation carry a poorer prognosis than traumatic disc herniation. In one study, two of 17 (12%) dogs with vertebral fractures or spinal luxation and absence of nociception regained the ability to walk, while 69% of dogs with intervertebral disc herniation and loss of nociception did so. In dogs with cervical vertebral fractures, nonambulatory status and delay of greater than 5 days to referral for surgical stabilization have been independently associated with worse outcome. Cervical vertebral fracture stabilization is associated with a high perioperative mortality (36%), but dogs that survive this period have a good prognosis for neurologic recovery. Cervical injuries also carry the risk of short-term, postoperative hypoventilation, potentially necessitating mechanical ventilation. Although costly, one retrospective study of dogs with cervical spinal cord injury showed that 10 of 14 dogs treated with mechanical ventilation survived, and nine of the 10 surviving dogs regained good neurologic function. Prognosis in cats with spinal injury is likely similar to dogs, although the literature is sparse. One retrospective study demonstrated a high incidence of myelomalacia at surgery and/or necropsy in cats with a loss of nociception after spinal trauma, suggesting that the loss of deep pain may carry a poorer prognosis in cats than dogs. Prognosis is also dependent upon the extent of other, concurrent injuries. Spinal trauma rarely occurs in a vacuum, and trauma to other organ systems is common. The cumulative effects of each individual injury on prognosis must be considered.

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Video Resources

Video resources are available on the companion website: www.wiley.com/go/dewey/neurology

See video 32.

CHAPTER 16

Neurology and Neuropharmacology of Normal and Abnormal Urination

Curtis W. Dewey & Ronaldo C. da Costa

Introduction[20, 27]

Disorders of urination are commonly encountered in patients with neurologic disease. If not properly managed, they can become more of a health concern than the underlying neurologic disorder. Serious urinary tract problems (e.g. atonic bladder, pyelonephritis) that are secondary to neurologic disease are usually preventable. The key to prevention is a combination of having a sound knowledge base and being a careful examiner. It should never be assumed that a paralyzed dog or cat is urinating adequately because someone saw a pool of urine in that patient's cage. This should always be verified (e.g. palpate the bladder, observe for voluntary urination). It is essential that the clinician understands how to deal with what is commonly referred to as the "neurologic bladder." The techniques of bladder expression and urethral catheterization are discussed in Chapter 20. This chapter focuses on the functional neuroanatomy and neuropharmacology of urination. The basic principles outlined in this chapter are necessary for the clinician to understand what type of bladder dysfunction is present (e.g. upper motor neuron [UMN] or lower motor neuron [LMN] bladder) and what drugs are likely to help in managing the dysfunction.

Functional neuroanatomy of the urinary bladder and urethra (Fig. 16.1 and Fig. 16.2)[1, 8, 9, 11–13, 16, 20, 22, 26, 27, 29, 33, 36]

A. The urinary bladder
   1. The urinary bladder is a hollow organ primarily composed of three layers of smooth muscle, collectively termed the detrusor muscle. There are also mucosal, submucosal, and serosal layers. The detrusor muscle contains both adrenergic and cholinergic (muscarinic) receptors that are important in bladder filling and contraction, respectively. The important receptors for efferent autonomic innervation of the body of the bladder are summarized below:
      a. Beta-adrenergic receptors—these sympathetic receptors are innervated by the hypogastric nerve, which in turn originates from the L1–L4 spinal cord segments in the dog (L2–L5 segments in the cat). Stimulation of these receptors causes detrusor muscle relaxation, which allows bladder filling.
      b. Muscarinic cholinergic receptors—these parasympathetic receptors are innervated by the pelvic nerve, which originates from the sacral (S1–S3) spinal cord segments. Stimulation of these receptors causes detrusor muscle contraction, which leads to bladder emptying.
   2. There are also sensory receptors (stretch and pain) in the wall of the bladder. Stretch receptors are innervated by afferent axons that travel through the pelvic nerve toward the sacral spinal cord segments. Pain receptors are innervated by afferent axons that travel in both the pelvic and hypogastric nerves, but primarily in the hypogastric nerves.

B. The urethra
   1. For practical purposes, the neck of the bladder can be thought of as the proximal aspect of the urethra. The smooth muscle of the urethra is primarily innervated by the hypogastric nerve and is often considered to represent an internal sphincter, although it is not a true sphincter. The external urethral sphincter is composed of striated muscle that encircles the distal urethra. The external urethral sphincter is innervated by the pudendal nerve. This is a somatic motor nerve whose cell bodies are in the sacral spinal cord segments (primarily S1 and S2). The important receptors for efferent urethral innervation are as follows:

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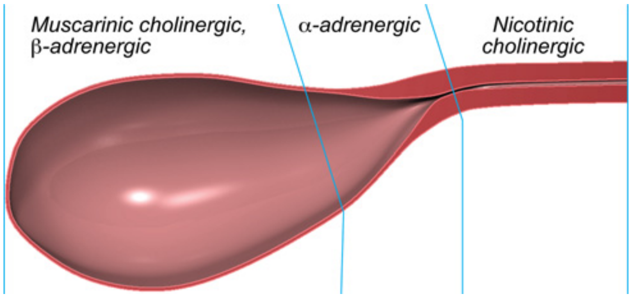

Figure 16.1 Schematic illustration depicting the location of receptor types on the bladder wall and urethra. (The Ohio State University. Reproduced with permission.)

   a. Alpha-adrenergic receptors—these sympathetic receptors are innervated by the hypogastric nerve. Stimulation of these receptors causes contraction of smooth muscle in the neck of the bladder and urethra. This muscle contraction opposes urine flow through the urethra, and therefore facilitates bladder filling.
   b. Nicotinic cholinergic receptors—these somatic motor receptors are located on the external urethral sphincter and are innervated by the pudendal nerve. The pudendal nerve is under voluntary control, but the neuronal cell bodies of this nerve within the sacral spinal cord also receive involuntary afferent input. Stimulation of these receptors causes sphincter contraction, which opposes urine flow through the urethra, thus facilitating bladder filling.

2. Similar to the bladder, there are sensory receptors in the wall of the urethra for conveying information concerning distention (stretch), pain, and urine flow. These receptors are innervated by afferent axons that travel in the pudendal nerve toward the sacral spinal cord segments.

Local reflex arcs[8, 9, 11, 13, 16, 20, 22, 25–27, 29, 33, 36]

A. Somewhat analogous to innervation of the limbs, there are inherent spinal reflex arcs involved in bladder filling and emptying. Although there is some level of spinal reflex control of urination in adult dogs and cats, these reflex arcs cease to function autonomously after infancy (3–4 wks in puppies, 7–12 wks in kittens). Thereafter, these reflex centers require descending influences from the brain stem for coordinated urination to occur. The reflex arcs depend on a number of anatomic structures:
   1. The pelvic plexus—this refers to the meshwork of autonomic nerves and ganglia located in the pelvic canal. Within this plexus are afferent and efferent processes of the pelvic and hypogastric nerves.
   2. The pudendal nerve—technically part of the lumbosacral plexus, this nerve is also located in the pelvic canal.
   3. The sacral spinal cord—neuronal cell bodies for the pelvic nerve are located in the intermediolateral gray matter, and neuronal cell bodies for the pudendal nerve are located in the ventral horn gray matter.
   4. The lumbar spinal cord—neuronal cell bodies for the hypogastric nerve are located in the intermediolateral gray matter from L1–L4 spinal cord segments in the dog and L2–L5 segments in the cat.

B. As the bladder fills, stretch receptors are stimulated and this afferent information is carried via the pelvic nerve to the parasympathetic nuclei in the sacral spinal cord. Efferent impulses from these nuclei through the pelvic nerve initiate detrusor contraction. As the detrusor muscle contracts, another volley of afferent impulses enters the sacral spinal cord. Some of these afferent axons inhibit the sacral neuronal cell bodies of the pudendal nerve, whereas some ascend to the lumbar spinal cord to inhibit the sympathetic cell bodies of the hypogastric nerve. The net result is bladder

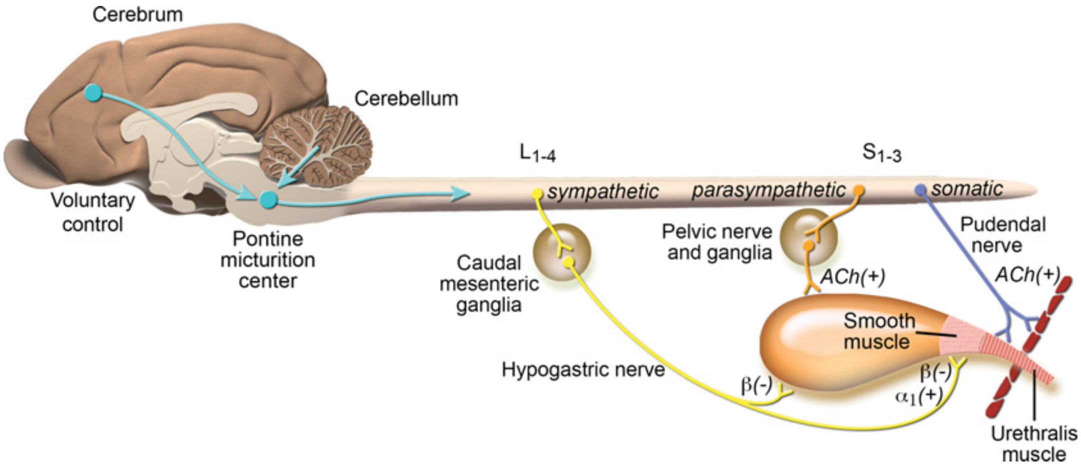

Figure 16.2 Schematic illustration depicting the neuroanatomy and neurophysiology of urination. L1–L4 = lumbar spinal cord segments. S1–S3 = sacral spinal cord segments. (The Ohio State University. Reproduced with permission.)

contraction with nearly simultaneous urethral relaxation and coordinated urination.

The brain-stem micturition center and the detrusor reflex[4, 5, 8, 9, 11, 13, 14, 18, 22, 23, 26, 27, 29, 31, 33, 36]

A. The brain-stem micturition center

Neuronal populations in the brain stem normally coordinate the spinal reflex arcs involved in bladder filling and emptying. These neurons are principally located in the reticular formation of the pons, and to a lesser degree in the midbrain and medulla. Two distinct regions of the pons have been demonstrated to be involved in the filling and evacuation phases of the detrusor reflex, respectively. The dorsolateral region of the pons contains two groups of neurons involved in the micturition reflex: a medial cell group (M region) and a lateral cell group (L region). Neurons of the M region (Barrington's nucleus) project excitatory axons to the parasympathetic (muscarinic cholinergic) motor neurons in the sacral spinal cord that give rise to the pelvic nerves. Axonal processes from M region neurons also innervate inhibitory interneurons (GABA-ergic) that synapse on nicotinic cholinergic motor neurons in the sacral spinal cord that give rise to the pudendal nerves. Activation of neurons of the M region facilitates urinary bladder evacuation.

Axons projecting from the L region neurons have excitatory synaptic connections with nicotinic cholinergic sacral motor neurons that give rise to the pudendal nerves. Activation of L region neurons facilitates urinary bladder filling. The brain-stem micturition center can be considered the UMN for normal urination.

B. The detrusor reflex

Some of the afferent impulses (from stretch receptors) from the bladder and urethra are conveyed rostrally up the spinal cord (via spinothalamic pathways) to the brain-stem micturition center, rather than terminating on spinal cord neuronal pools. Neurons of the brain-stem micturition center subsequently convey descending efferent information through the spinal cord (reticulospinal tracts, tectospinal tracts) to the various spinal cord neuronal pools involved in urination. The coordinated act of urination that results from completing this brain-stem/spinal cord reflex arc is referred to as the detrusor reflex. It should be kept in mind that this is a brain-stem reflex that does not require conscious input (cerebral cortical influence) to operate.

Forebrain and cerebellar influence on the detrusor reflex[4, 5, 8, 9, 11, 13, 14, 17, 20–22, 26, 27, 29, 35]

A. Forebrain influence

Afferent impulses from the bladder reach the cerebral cortex via the pelvic (cat) and hypogastric (dog and cat) nerves and ascending spinal cord tracts. The sensations of stretch and pain are conveyed to the cerebral cortex via these afferent pathways. The detrusor reflex can be consciously inhibited via the cerebral cortex; this is the basis of house-training. The detrusor reflex can also be voluntarily initiated (e.g. territorial marking behavior). Patients with cerebral cortical dysfunction typically urinate normally, but will do so in inappropriate locations (loss of learned urination habits). The basal nuclei and preoptic area of the hypothalamus may play a role in the initiation of bladder evacuation. The ventromedial region of the hypothalamus has an inhibitory influence on urination.

B. Cerebellar influence

The influence of the cerebellum on urination appears to be minor. The cerebellum normally exerts an inhibitory influence over the detrusor reflex. Cerebellar lesions may result in increased frequency of urination.

Normal bladder filling and evacuation[1, 4, 5, 8, 9, 11, 13, 14, 16, 20, 22, 23, 25–27, 29, 31, 33, 36]

A. Bladder filling (primarily controlled by L region of the pons; Fig. 16.3)

1. As the bladder gradually fills with urine, afferent information is conveyed to neurons in the brain-stem micturition center. As the bladder is not stretched appreciably during this phase, the signal to brain-stem neurons involved in the micturition reflex promotes further bladder filling. Brain-stem neurons involved in facilitating urine storage have the following efferent influences on spinal cord neuronal pools:
    - a. Facilitation of the somatic efferent neuronal cell bodies comprising the pudendal nerve.
    - b. Facilitation of the adrenergic efferent neuronal cell bodies comprising the hypogastric nerve.
    - c. Inhibition of the cholinergic efferent neuronal cell bodies comprising the pelvic nerve.
2. The brain-stem micturition center neurons involved in urine storage will remain active until bladder capacity is reached. Until then, the net effects of the above influences are bladder relaxation and urethral constriction.

B. Bladder evacuation (primarily controlled by M region of the pons; Fig. 16.4)

1. When bladder capacity is reached, the resultant stretching of the detrusor muscle produces an afferent "threshold" stimulus. The threshold phenomenon can be compared to an on/off switch; once a critical level of stretch or distention is produced in the detrusor muscle, the signal to the micturition center changes to promote bladder emptying. Neurons involved in urinary bladder evacuation have the following efferent influences on the spinal cord neuronal pools involved in urination:

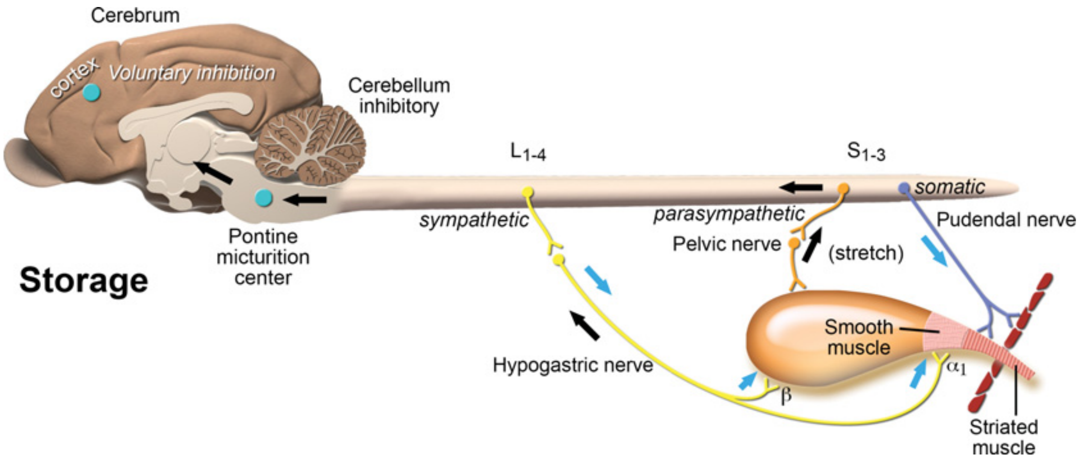
Cerebrum
cortex
Voluntary inhibition
Cerebellum
inhibitory
L1-4
S1-3
somatic
Pudendal nerve
parasympathetic
Pelvic nerve
(stretch)
sympathetic
Pontine
micturition
center
Storage
Smooth
muscle
Hypogastric nerve
β
α1
Striated
muscle

Figure 16.3 Illustration depicting the neural control of urine storage. The predominant input is sympathetic with the hypogastric nerve transmitting input to the adrenergic receptor in the bladder body (β) and bladder neck/urethra (α). (The Ohio State University. Reproduced with permission.)

   a. Inhibition of the somatic efferent neuronal cell bodies comprising the pudendal nerve.
   b. Inhibition of the adrenergic efferent neuronal cell bodies comprising the hypogastric nerve.
   c. Facilitation of the cholinergic efferent neuronal cell bodies comprising the pelvic nerve.
2. The net effects of the above influences are bladder contraction and urethral relaxation, resulting in coordinated evacuation of the bladder.

Diagnostic evaluation[6]

A complete history of the problem should be obtained to determine whether the patient has urinary retention or urinary incontinence. The physical examination should include observation of voiding, noting stream size, dysuria, duration, and urine color. Bladder palpation and, if possible, measurement of the residual volume should be performed. Normal residual volumes for dogs are less than 10 mL (0.2–0.4 mL/kg) and for cats less than 2 mL. Manual expression of the bladder is also useful to evaluate the urethral sphincter tone. The neurologic examination should include careful evaluation of gait, posture, and tail tone, perineal and pelvic limb reflexes, and spinal palpation. The goal is to establish whether we are dealing with an upper or LMN lesion. It is important to remember that the L4–S3 spinal cord segments are located within the L4 and L5 vertebral bodies in the majority of dogs, so lesions at this region and caudally will cause LMN signs. Ancillary diagnostic tests such as complete blood count, biochemistry profile, urinalysis, radiographs, abdominal ultrasonography, CT, and/or MRI may be necessary. Urodynamic tests, such as cystometry or urethral pressure profile, can also be performed, but these are rarely used.

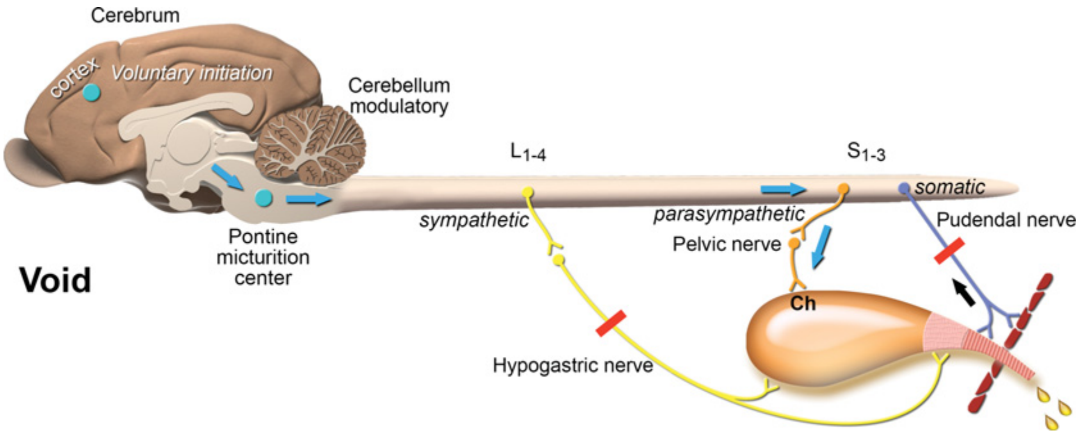
Cerebrum
cortex
Voluntary initiation
Cerebellum
modulatory
L1-4
S1-3
somatic
Pudendal nerve
parasympathetic
Pelvic nerve
sympathetic
Pontine
micturition
center
Void
Ch
Hypogastric nerve

Figure 16.4 Illustration depicting the neural control of urine voiding. The predominant input is parasympathetic, with the pelvic nerve transmitting input to cholinergic receptors in the urinary bladder. (The Ohio State University. Reproduced with permission.)

Upper motor neuron (UMN) and lower motor neuron (LMN) bladder dysfunction[3, 7, 10, 11, 18, 20, 22, 27, 30, 33, 34]

A. Upper motor neuron (UMN) bladder dysfunction
   1. This type of bladder dysfunction is encountered with lesions between the pons and the L7 segment of the spinal cord. Such lesions interfere with or abolish the detrusor reflex. Patients are either completely unable to urinate or cannot effectively accomplish bladder emptying. This is encountered most commonly in patients with severe T3–L3 myelopathies.
   2. The hallmark of UMN bladder dysfunction is increased tone. This phenomenon may be thought of as a disinhibition of the spinal cord neuronal pools involved in urination. The urethral musculature typically becomes hyperactive and the bladder fills with urine. Upon palpation, the bladder often feels turgid (especially when enlarged) and is difficult or impossible to express manually.

B. Lower motor neuron (LMN) bladder dysfunction
   1. This type of bladder dysfunction occurs with lesions of the sacral spinal cord or sacral nerves within the vertebral canal (cauda equina area), or with lesions of the pelvic/lumbosacral plexus area within the pelvic canal. These lesions also attenuate or abolish the detrusor reflex. This type of bladder dysfunction is seen most commonly with traumatic injuries to the caudal lumbar and sacral spine.
   2. The hallmark of LMN bladder dysfunction is decreased tone. Both the detrusor and urethral musculature typically become flaccid, and the patient constantly dribbles urine. The bladder is often difficult to discern as an isolated structure (due to the flaccidity), in contrast with the UMN bladder. Slight abdominal pressure usually causes urine to be easily expressed. It is very difficult to tell by palpation, however, if the bladder has been adequately emptied. In some patients, the unattenuated efferent hypogastric nerve activity provides enough internal urethral sphincter tone to make bladder expression difficult.
   3. Patients with lesions causing LMN bladder dysfunction often exhibit decreased or absent perineal reflexes and sensation.

Pharmacologic manipulation of bladder function[2, 3, 11, 15, 18–20, 22, 24, 27, 28, 32, 33]

A. Although there exists a multitude of pharmacologic agents that can be employed to manipulate bladder and urethral function, only a few of these drugs are commonly used. The following discussion will focus on those drugs most frequently used in clinical practice (Table 16.1 and Fig. 16.5).
   1. Bethanechol chloride
      a. This is a parasympathomimetic (cholinergic drug) used to facilitate detrusor muscle contraction in both UMN and LMN bladder dysfunction. Bethanechol directly stimulates cholinergic receptors.
      b. The dosage is empiric. The oral dose for dogs is 2.5–25 mg (depending on the size of the dog) per dog, q 8 hrs. For cats, the dosage is 1.5–5 mg per cat, q 8 hrs.
      c. The half-life of elimination is unknown for dogs and cats. However, most patients seem to have some benefit from the drug within 24 hrs, suggesting a relatively short half-life.
      d. Side effects may occur with this drug and reflect cholinergic overstimulation. Most commonly, gastrointestinal side effects are exhibited. These include anorexia, salivation, vomiting, diarrhea, and abdominal pain. Excessive lacrimation is also a possibility. A cholinergic crisis (e.g. increased bronchial secretions, hypotension) can occur, but it is very unlikely with standard doses of this drug.
      e. Because bethanechol does not cause urethral relaxation, and may even enhance urethral sphincter tone, it is recommended that it not be administered as a sole urinary drug to a patient with the typical UMN bladder (i.e. increased urethral sphincter tone). Bethanechol is contraindicated in patients with suspected or confirmed gastrointestinal or urinary tract obstruction.
   2. Diazepam
      a. This drug is discussed in Chapter 9 as an anticonvulsant agent. Diazepam also has a relaxing effect on striated muscle, and is therefore used to relax the external urethral sphincter in patients with UMN bladder dysfunction. Diazepam may also promote relaxation of the external urethral sphincter by stimulating GABA-ergic inhibitory interneurons in the sacral spinal cord.
      b. The dosage for both dogs and cats is 0.2 mg/kg per os, q 8 hrs.
      c. Side effects are usually limited to excessive sedation. It should be kept in mind that cats have been reported to develop fatal hepatic necrosis in association with oral diazepam administration. This idiosyncratic reaction to diazepam in cats is probably not common, but clients should be informed of its existence.
   3. Phenoxybenzamine hydrochloride
      a. This is an alpha-adrenergic antagonist that is used to decrease tone in the internal urethral sphincter. It is used most commonly in UMN bladder dysfunction, but may also be indicated in some cases of LMN bladder dysfunction (i.e. increased sympathetic tone from the hypogastric nerve can cause a clinical problem even with decreased external urethral sphincter tone).

Table 16.1 Pharmacologic agents used in the treatment of disorders of micturition.

Action	Agents	Mechanism of action	Recommended dosage	Possible adverse effects	Contraindications
Increase detrusor contractility	**Bethanechol***	Parasympathomimetic	Dog: 5–25 mg PO q8h Cat: 1.25–5 mg/cat PO q8–12 hrs	Cholinergic: GI hypermotility, ptyalism, vomiting, diarrhea	Urethral obstruction, GI obstruction
	Cisapride	Prokinetic agent	Dog: 0.5 mg/kg PO q8h Cat: 1.25 mg/cat PO q8–12 hrs	Diarrhea, possible abdominal pain	GI obstruction Reduce dose with hepatic insufficiency
	Metoclopramide	Dopamine antagonist	Dog: 0.2–0.5 mg/kg PO q8h Cat: 0.2–0.5 mg/kg PO q8h	May lower seizure threshold Hyperactivity	GI obstruction
Decrease detrusor contractility	Propantheline	Anticholinergic	Dog: 0.25–0.5 mg/kg PO q8–12 hrs	Tachycardia, vomiting, abdominal distension, ileus	Constipation
Increase urethral resistance	Phenylpropanolamine	β-sympathomimetic	1.5 mg/kg PO q8–12 hrs	Urinary retention Hypertension	Hypertension
Decrease urethral resistance	**Phenoxybenzamine**	Smooth muscle relaxation, α-antagonism	Dog: 0.25 mg/kg PO q8–12 hrs or 2.5–20 mg/dog PO q8–12 hrs Cat: 1.25–7.5 mg/cat PO q8–12 hrs	Hypotension, tachycardia, GI upset	Cardiac disease, hypovolemia Glaucoma, Renal failure, Diabetes mellitus
	Prazosin	Smooth muscle relaxation, α-1 antagonism	Dog: 1 mg/15 kg PO q 12–24 hrs Cat: 0.25–0.5 mg/cat PO q 12–24 hrs	Hypotension Mild sedation Ptyalism	Cardiac disease Renal failure
	Tamsulosin	Smooth muscle relaxation, α-1 antagonism with high uroselectivity	Dog: 10–30 μg/kg q 12–24 hrs	Hypotension Rarely due to high affinity to α-1A receptors More frequent ejaculation	Fertility problems
	Diazepam	Skeletal muscle relaxation via central effect	Dog: 0.25–1 mg/kg PO q8–12 hrs Cat: 1–2.5 mg/cat PO q8–12 hrs	Sedation Paradoxic excitation Hepatic necrosis with PO in cats only	Pregnancy Hepatic disease
	Baclofen	Skeletal muscle relaxation via direct effects	Dog: 1–2 mg/kg PO q8h Cat: not recommended	Weakness GI upset Pruritus	

Source: Adapted from Lane and Westropp, 2009[19] and Lorenz *et al.*, 2011[22].
**Common agents in bold.
GI = gastrointestinal; PO = orally, q8h = every 8 hrs.

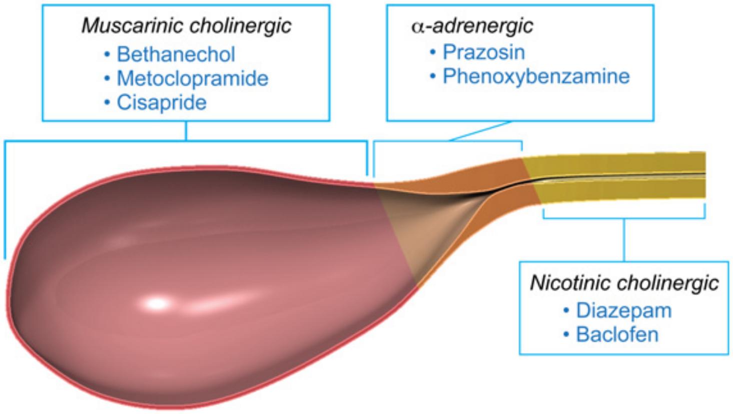

Figure 16.5 Schematic illustration depicting the mechanism of action of pharmacologic agents in the bladder and urethra. (The Ohio State University. Reproduced with permission.)

Phenoxybenzamine has been shown to have carcinogenic potential and may be discontinued in the near future. An alternative alpha-adrenergic antagonist, prazosin (see the “Miscellaneous drugs” section below), can be used if phenoxybenzamine is not available.

 b. The dosage for dogs and cats is 0.25–0.5 mg/kg per os, q 12 hrs.
 c. The most common side effect is hypotension, due to inhibition of vascular adrenergic receptors. Patients who have been given too much phenoxybenzamine generally appear lethargic and may be tachycardic. They typically respond to drug discontinuation and fluid therapy. Gastrointestinal upset may also occur with phenoxybenzamine administration.
 d. The half-life of elimination of phenoxybenzamine is unknown in dogs and cats. Since it often takes several days for the clinical effects of this drug to be appreciated, the half-life is thought to be relatively long.

4. Phenylpropanolamine hydrochloride
 a. This is a mixed adrenergic agonist that increases the tone of the internal urethral sphincter. Since the goal in most of the neurologic causes of bladder dysfunction is to keep the bladder empty, this drug is not commonly used in neurologic patients. It is most commonly used in cases of hormone-related incontinence. However, it may be useful in some cases of LMN bladder dysfunction in which detrusor function has improved to a greater degree than urethral continence.
 b. The dosage for dogs and cats is 1.5 mg/kg per os, q 8–12 hrs.
 c. The elimination half-life of this drug is unknown for dogs and cats, but it appears to have a relatively quick onset of action.
 d. Potential side effects of this drug include hypertension, anorexia, and restlessness/irritability.

5. Miscellaneous drugs

Drugs that may be helpful in improving bladder contractility include metoclopramide, cisapride, and propranolol. These drugs should be considered when bethanechol is ineffective. Metoclopramide and cisapride are gastrointestinal prokinetic agents with cholinergic activity. Propranolol is a beta-adrenergic antagonist. The oral dose of metoclopramide for dogs and cats is 0.2–0.5 mg/kg body weight, q 8 hrs. Possible side effects of metoclopramide include behavioral abnormalities and constipation. Oral cisapride is administered at a dosage of 0.5 mg/kg body weight, q 8 hrs. in dogs. The recommended oral dose of cisapride in cats is 1.25–5.0 mg per cat, q 8–12 hrs. Adverse side effects that may occur with cisapride administration include diarrhea and abdominal pain. Propranolol is dosed orally at 0.2–1.0 mg/kg body weight, q 8 hrs in dogs; the oral dose for cats is 2.5–5.0 mg per cat, q 8–12 hrs. Hypotension, syncope, bronchoconstriction, bradycardia, hypoglycemia, and diarrhea are all potential side effects of propranolol administration.

Several drugs may be helpful in effecting urethral relaxation, in addition to phenoxybenzamine and diazepam. Prazosin, an alpha-adrenergic antagonist, was mentioned earlier. The oral dose of prazosin for dogs is 0.067 mg/kg body weight, q 8–12 hrs. The oral dose for cats is 0.25 mg per cat, q 12–24 hrs. Prazosin can produce marked hypotension. It is recommended that one-half of the calculated dose be administered for the first several days of treatment and the patient observed for clinical signs of hypotension. A newer alpha-adrenergic antagonist drug called tamsulosin has a much higher uroselectivity, and it is a very good alternative to prazosin. Tamsulosin has been shown to have a 12- to 20-fold higher affinity for the alpha-1A receptors that are located in the urethra. Because it has minimal effects on alpha-1B and 1D adrenoceptors it causes minimal changes in blood pressure, thus it should be the drug of choice for any patient with cardiac disease. Tamsulosin therefore has a wide margin of safety. The recommended dose is 10–30 μg/kg q 12–24 hrs. Baclofen is a spinal-reflex-inhibiting drug that acts by decreasing activity of spinal cord motor neurons and interneurons. The drug has been used in people to cause relaxation of the external urethral sphincter. There is little clinical information concerning the use of baclofen in dogs, and none in cats. The recommended dose for baclofen in dogs is 5–10 mg/kg body weight, q 8 hrs. Potential side effects of baclofen include weakness, dizziness, and ptyalism. Baclofen use is not recommended in cats. Dantrolene is a muscle relaxant that antagonizes calcium release from skeletal muscle sarcoplasmic reticulum; it has been used to produce relaxation of the external urethral sphincter musculature. The oral dose of dantrolene in dogs is 1–5 mg/kg body weight, q 8 hrs. The oral dose in cats is 0.5–2.0 mg/kg body weight, q 8 hrs. Potential side effects of dantrolene administration include sedation, gastrointestinal upset, dizziness, generalized muscle weakness, hypotension, and hepatotoxicity. Long-term dantrolene administration is not recommended due primarily to the chance of severe hepatotoxicity.

A neuroprosthetic device has been recently proposed to treat urinary retention in chronic paraplegic dogs with UMN lesions characterized by retention and overflow. The implant and receiver were placed via dorsal laminectomy, stimulating the sacral nerves, and urination was controlled via an external stimulator device. The device provided excellent bladder emptying in eight out of nine dogs. This is an alternative to dogs that cannot be medically managed and that have recurrent urinary tract infections.

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CHAPTER 17

Disorders of the Peripheral Nervous System: Mononeuropathies and Polyneuropathies

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Introduction[249, 314]

The peripheral nerves are made up of myelinated and unmyelinated motor and sensory axons, and are essential for the normal functioning of both the voluntary and autonomic nervous systems. Some neuropathies are characterized by exclusively or primarily motor dysfunction, others by sensory dysfunction, and some by a combination of motor and sensory dysfunction. Some of the salient features of autonomic neuropathies in dogs and cats have only recently been described. Technically speaking, a mononeuropathy refers to a dysfunction of one cranial nerve (e.g. facial nerve) or one named peripheral nerve (e.g. radial nerve). A polyneuropathy refers to multiple (i.e. more than one) nerve dysfunction. In this text, multiple cranial nerve dysfunction (without dysfunction of peripheral nerves to the limbs) and multiple peripheral nerve dysfunction in the same limb (e.g. brachial plexus neuropathy/neuritis) will be referred to as multiple mononeuropathies. This distinguishes these relatively focal disorders from more generalized polyneuropathies (e.g. idiopathic polyradiculoneuritis).

In general, neuropathies reflect a failure of the lower motor neuron (LMN). Although some of the diseases discussed in this chapter have abnormal axons and/or myelin in both the central (CNS) and peripheral (PNS) nervous systems, clinical signs of peripheral disease usually predominate. In those neuropathies in which motor nerves are affected, typical clinical signs include decreased to absent reflex activity, poor muscle tone, and neurogenic muscle atrophy (Videos 13 and 33). A recurring theme with canine and feline neuropathies is that tentative diagnoses are often based upon a combination of clinical features that are characteristic of specific diseases. Electrodiagnostic and nerve/muscle biopsy evidence may confirm the presence of a neuropathy, but rarely provides a specific diagnosis by itself. Even when a specific disease entity is confirmed histopathologically (e.g. dysautonomia), the underlying etiology often remains undetermined. Indeed, the underlying cause(s) of the majority of canine and feline neuropathies is (are) unknown. For many of these disorders, therefore, there are no effective treatments. However, some of these disorders resolve spontaneously, and others may not necessarily adversely affect the quality of the patient's life. For some of the breed-associated neuropathies, specific genetic mutations have been identified as being responsible for the neuropathy; this trend is likely to continue over time.

It is important that the clinician be able to localize disorders to the PNS. In human studies, both acquired and inherited neuropathies are categorized as primarily demyelinating, axonal degradation and secondary loss of myelin, or a combination of both based on electrodiagnostic testing. In primarily demyelinating neuropathies, there is a significantly decreased nerve conduction velocity (NCV) versus a normal or mildly decreased NCV seen in axonal degradation and secondary demyelinating neuropathies. Moderately decreased NCVs are a feature of combination neuropathies. In human studies, these classifications lead to DNA test developments based on the specific mutation present in the myelin, axons, or both. Classification of canine and feline neuropathies is not common practice currently; however, it may lead to important treatment options in the future.

The multitude of reported neuropathies may seem intimidating, but a working knowledge of all these disorders is unnecessary. Once the neuroanatomic diagnosis is made (PNS), appropriate reference sources should be consulted in an attempt to arrive at a specific diagnosis. Knowing that there is a wide spectrum of neuropathies—with different causes, severities, and prognoses—is important both to patient management and client communication. Disorders of cranial nerve (CN) VIII (hearing and balance) are discussed in Chapter 11 and are not discussed in this chapter.

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Disorders of peripheral nerves in dogs and cats (Table 17.1)

A. Degenerative/Inherited[66, 314]

1. Hereditary polyneuropathy of Alaskan malamutes (HPAM)/idiopathic polyneuropathy of Alaskan malamutes (IPAM) and hereditary polyneuropathy of Greyhounds[36, 45, 66, 101, 231, 314]
   a. Hereditary polyneuropathy of Alaskan malamutes refers to dogs from Norway, while idiopathic polyneuropathy of Alaskan malamutes refers to dogs from the United States. Although there are some differences between the two groups of dogs, they are considered together in this text because of their many clinical similarities. Greyhound dogs are afflicted with a comparable disorder to the Malamute dogs. This disorder is inherited in an autosomal recessive manner, and the specific gene mutation (*NDRG1*) responsible for this neuropathy has recently been identified. This disease is characterized by the degeneration of both motor and sensory axons and myelin throughout the PNS. In general, the Alaskan Malamute, Greyhound, and several other breed-related polyneuropathies have been likened to Charcot–Marie–Tooth (CMT) disease

Table 17.1 Neuropathies of dogs and cats.

Degenerative/ Inherited	Anomalous/ Developmental	Metabolic	Neoplastic	Inflammatory/ Infectious, Autoimmune	Traumatic	Toxic
Alaskan Malamute/ Greyhound polyneuropathy Dancing Doberman disease Distal sensorimotor neuropathy Birman cat polyneuropathy Boxer dog axonopathy Giant axonal neuropathy Laryngeal paralysis/ polyneuropathy complex Inherited polyneuropathy of Leonberger dogs Laryngeal paralysis Distal denervating disease Golden Retriever hypomyelinating polyneuropathy Miniature Schnauzer demyelinating polyneuropathy Hypertrophic neuropathy Megaesophagus Idiopathic facial paralysis Sensory neuropathy Idiopathic self-mutilation Spinal muscular atrophy Dysautonomia Lysosomal storage disease	Optic nerve hypoplasia	Diabetic neuropathy Hyperadrenocorticoid neuropathy Hyperchylomicronemia (cats) Hyperoxaluria (cats) Hypothyroid neuropathy	Paraneoplastic neuropathies Malignant nerve sheath tumors Mononuclear cell neoplasia (myelomonocytic neoplasia, lymphosarcoma)	Brachial plexus neuritis/ neuropathy Optic neuritis Polyradiculoneuritis Chronic inflammatory demyelinating polyneuropathy/ chronic relapsing polyneuropathy Protozoal polyradiculoneuritis Sensory ganglioradiculoneuritis Trigeminal neuritis Hemifacial spasm Ischemic neuromyopathy	Isolated nerve injury Compartment syndrome Brachial plexus injury	Thallium poisoning Pyridoxine poisoning Vincristine neuropathy Delayed organophosphate toxicity (cats) Walker hound mononeuropathy Salinomycin toxicity (cats)

of humans. CMT represents a group of phenotypically heterogeneous peripheral nerve disorders of a suspected or known genetic basis.

b. Clinical signs typically begin at 10–18 mos of age in Malamutes and 3–9 mos of age in Greyhounds and consist initially of pelvic limb paresis and ataxia and reduced exercise tolerance. Dogs with IPAM generally present with more severe clinical signs. Progression of the disease in Malamutes is variable, but worsening paraparesis or tetraparesis—as well as regurgitation, coughing, and/or dyspnea (due to megaesophagus, laryngeal paresis/paralysis, and aspiration pneumonia)—may develop. Spinal reflexes are usually depressed or absent, particularly in the pelvic limbs. Moderate to severe muscle atrophy may be appreciated in all muscles with both forms of the disease. Atrophy may be especially prominent in the shoulder and thigh areas in cases of HPAM, while dogs with IPAM primarily demonstrate distal muscle atrophy. Additionally, dogs affected with the latter form may demonstrate appendicular and paraspinal hyperesthesia. The Greyhound polyneuropathy is very similar in clinical features and progression. Greyhounds progress from having exercise intolerance, a high-stepping gait, and "bunny-hopping" in the pelvic limbs to severe muscle atrophy, tetraparesis, ataxia, and dysphonia. As the disease progresses further, proprioceptive deficits, laryngeal paresis, and loss of spinal reflexes develop.

c. A tentative diagnosis is based upon history, signalment, and typical clinical features, as well as abnormal results of electrodiagnostic tests, nerve and muscle biopsies, and/or upon histopathologic findings postmortem. As mentioned, a definitive diagnosis can be achieved via identification of a point mutation at the *NDRG1* gene locus.

d. The disease is typically progressive and there is no known treatment. The prognosis for short-term survival for HPAM varies from favorable to poor, as some dogs will improve, whereas others will continue to worsen. In general, dogs that improve tend to do so transiently and often die or are euthanized due to residual deficits and/or complications secondary to these deficits (e.g. paresis, respiratory problems, regurgitation). The prognosis for IPAM is poor, as only continued progression is typically seen. Though some Alaskan Malamutes have been reported to stabilize, these dogs often die or are euthanized within 6 mos. None of the reported Greyhounds has survived longer than 10 mos from the onset of clinical signs.

2. Dancing Doberman disease[27, 60, 66, 314]

   a. This is an enigmatic peripheral neuromyopathy, principally affecting the gastrocnemius muscles, seen only in Doberman Pinschers. Although clinical and pathological features suggestive of both nerve and muscle disease have been described, it is unclear whether this syndrome is primarily a myopathy, a neuropathy, or a combination of the two.

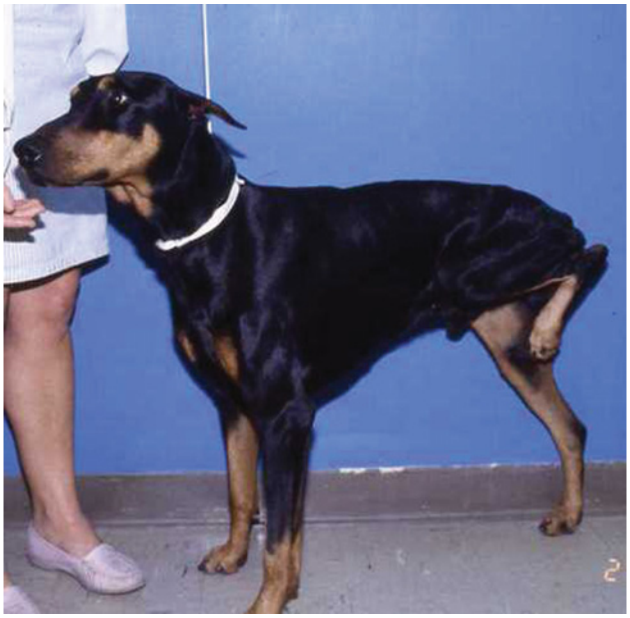

Figure 17.1 Typical posture of a dog with Dancing Doberman disease. (Courtesy of Dr. Gregg Kortz.)

   b. Age at onset of clinical signs of dysfunction has ranged from 6 mos to 7 yrs. The first observable abnormality is flexing of one pelvic limb while standing (Fig. 17.1). Within several months, these dogs typically begin alternately flexing and extending both pelvic limbs when standing, giving the appearance of dancing. Affected dogs often prefer to sit, rather than stand, are not lame while walking, and do not appear to be in any discomfort. Over time, Dobermans with this disease can develop conscious proprioceptive deficits and paraparesis. Gastrocnemius muscle atrophy may also develop. The disease is very slowly progressive (over years) and generally does not adversely affect the life of affected dogs.

   c. Diagnosis is primarily based upon the unusual and characteristic clinical findings and ruling out other causes for the unusual pelvic limb carriage (e.g. orthopedic diseases, myelopathies, cauda equina lesions). Electrodiagnostic testing (especially electromyography [EMG] examination of the gastrocnemius muscles) and muscle/nerve biopsy results may help support the diagnosis.

   d. Despite the fact that there is no treatment for the disease, the long-term prognosis for an acceptable quality of life is good.

3. Great Dane distal sensorimotor polyneuropathy[4,25,28,66,154,353]
   a. A distal, symmetric, polyneuropathy with a suspected inherited basis has been reported in Great Danes. This disease is characterized by the distal degeneration of motor axons, with less frequent involvement of sensory or autonomic nerve fibers.
   b. The reported age of onset has ranged from 1 to 5 yrs. Clinical signs may present acutely, and initially include decreased hock flexion and a "skipping" gait. These reportedly progress over the following weeks, and may progress to include distal hyporeflexia and, eventually, recumbency.
   c. Diagnosis is based upon history, signalment, and typical clinical features, as well as abnormal results of electrodiagnostic tests, and nerve and muscle biopsies.
   d. A definitive treatment is not currently available for this disorder. The prognosis for affected animals is considered poor due to the progressive nature of this disease.
4. Birman cat distal polyneuropathy[25,28,59,66,234,314]
   a. This is a disease of Birman kittens with suspected autosomal recessive inheritance. Loss of myelin and axons of the PNS and CNS results in clinical signs of disease. The lesions are most severe in the distal portions of axons, suggesting a dying-back process. Axonal integrity depends upon anterograde transport of substances (e.g. proteins) from the neuronal cell body throughout the length of the axon, and retrograde conveyance of cellular waste products from the axon back to the cell body to be degraded. Disease processes that adversely affect either the neuronal cell body or axonal transport mechanisms will likely have most serious consequences on the distal-most aspect of the axon. As the disease process continues, axonal degeneration will proceed proximally, "dying back" toward the neuronal cell body. The pathogenesis of Birman cat distal polyneuropathy is unknown.
   b. Affected kittens exhibit clinical signs of neurologic dysfunction at approximately 8–10 wks of age. Slow progression is typically seen. Pelvic limb ataxia and paresis (with frequent falling episodes), subtle hypermetria of all four limbs, and plantigrade stance in the pelvic limbs are characteristic clinical features of the disorder. Kittens with this disorder also tend to adduct their hocks.
   c. Tentative diagnosis is based upon signalment, historical and clinical findings, and results of diagnostic tests (e.g. EMG, nerve/muscle biopsy). Definitive diagnosis is based upon a histopathology of the CNS and PNS lesions.
   d. There is no known treatment for this progressive disease and the prognosis is poor.
5. Boxer dog progressive axonopathy[25,28,66,103,130,131,135,314]
   a. This is an autosomal recessively inherited trait characterized by widespread degeneration of myelin and multiple axonal swellings (spheroids) in both motor and sensory axons of the CNS and PNS. Central lesions predominate within both the spinal cord and the caudal brain stem (predominantly the spinal tract of the trigeminal nerve, the rostral olivary, cuneate and accessory cuneate nuclei, and cerebellar white matter and nuclei). The pathogenesis is unknown, but is suspected to involve defective slow axonal transport, with resultant accumulations of neurofilaments and membranous organelles (constituents of the spheroids) along the axon. It is thought that this disease is primarily an axonopathy, with secondary demyelination.
   b. Age of onset of clinical signs is typically 2–6 mos of age (usually 2–3 mos). Pelvic limb ataxia and hypermetria are initially exhibited and this abnormal gait remains the salient clinical feature throughout the course of disease progression. Myotatic reflexes are decreased or absent and decreased muscle tone is apparent. Muscle atrophy is typically minimal to nonexistent with this disease.

      Ataxia and paresis slowly progress and may also involve the thoracic limbs. Conscious proprioception (e.g. proprioceptive positioning/placing) is often normal initially, but deteriorates over time. Pain sensation (nociception) remains intact. Mild signs of cerebellar dysfunction (ocular tremors, head-bobbing) have been described in a few dogs, late in the course of the disease.
   c. A tentative diagnosis can be made based upon signalment, historical and clinical findings, as well as abnormal results of nerve conduction studies and nerve/muscle biopsies. Spontaneous activity is not typically seen with EMG. Definitive diagnosis requires demonstration of characteristic histopathologic abnormalities (e.g. spheroids) in both the PNS and the CNS.
   d. The prognosis is variable. There is no treatment for this disorder, but some dogs will stabilize by 12–18 mos of age and the clinical signs will remain relatively static for months or even years. Most of these dogs are eventually euthanized due to inability to ambulate.
6. Giant axonal neuropathy of German Shepherds[25,28,66,103,106,107,314]
   a. This is a rare condition characterized by distal axonal swellings in both sensory and motor axons of the PNS and CNS. There is a loss of both axons and myelin. The pathogenesis is unknown, but impaired axonal transport mechanisms are suspected. This is inherited as an autosomal recessive trait.

b. Onset of clinical signs is typically around 15 mos of age. Pelvic limb ataxia and paresis are noted initially, along with a plantigrade stance. Signs progress to a loss of patellar reflexes and proprioceptive placing reactions, and hypotonia of pelvic limb musculature with distal (below the stifle) muscle atrophy. Tetraparesis is typically evident by 18–24 mos of age. Voice change, megaesophagus (with subsequent regurgitation and occasional aspiration pneumonia), and fecal incontinence also commonly develop within several months of disease onset. A curly hair coat is also a frequent finding in these dogs.

c. A tentative diagnosis is based upon signalment, historical and clinical findings, and abnormal results of electrodiagnostic tests and nerve/muscle biopsies. Lesions are reportedly seen in diffusion-weighted magnetic resonance images of human patients with giant axonal neuropathies. Definitive diagnosis hinges upon finding characteristic histopathologic changes in the PNS and CNS.

d. There is no treatment for this progressive disease and the prognosis is poor.

7. Laryngeal paralysis-polyneuropathy complex[25, 27, 28, 35, 37, 66, 118, 217, 242, 255, 299, 314]

a. This sensorimotor neuropathy is characterized by widespread loss of peripheral axons (axonal necrosis), especially in distal segments, in young Dalmatian and Rottweiler dogs. The pathogenesis is unknown, although an autosomal recessive mode of inheritance is suspected in Dalmatians. This disease is thought to involve a dying-back process of axons, affecting distal segments of axons most severely. Sixteen Dalmatians and five Rottweilers have been reported with this disorder. Six Pyrenean mountain dogs have been reported with a similar, inherited, laryngeal paralysis-polyneuropathy complex as well. The authors have encountered a similar condition in a litter of young Argentinean dogs.

b. Onset of clinical signs is typically from 2 to 6 mos of age in Dalmatians and between 2 and 3 mos of age in Rottweilers. Clinical signs relating to laryngeal paralysis, including respiratory distress (e.g. inspiratory stridor, coughing, cyanosis, dyspnea) with associated exercise intolerance, and voice change (dysphonia) are commonly seen. Limb paresis (worse in the pelvic limbs in Rottweilers) with hyporeflexia is also a consistent clinical feature. Gagging, regurgitation (due to a megaesophagus), facial and lingual paralysis, hypermetric gait, and muscle atrophy are additional clinical signs associated with the Dalmatian disease. One of five Rottweiler puppies displayed regurgitation associated with megaesophagus. A peculiar finding in the affected Rottweilers was bilateral cataracts, seen in four of the five dogs; the cause of these cataracts was undetermined.

c. A tentative diagnosis of this disorder is based upon signalment, history, characteristic clinical findings, and abnormal results of diagnostic tests (e.g. electrodiagnostics, nerve/muscle biopsies). Definitive diagnosis of this disorder is based upon the character and distribution of axonal lesions identified post mortem.

d. There is no treatment for this disorder. The prognosis is poor, as most dogs die or are euthanized shortly after presentation due to respiratory dysfunction, often involving severe aspiration pneumonia.

8. Inherited polyneuropathy of Leonberger dogs[66, 109, 280, 298]

a. A distal polyneuropathy has been reported in Leonberger dogs, which shares many pathologic and genetic characteristics with the CMT axonal neuropathy seen in humans. Two genetically distinct (gene mutations identified) forms of this disorder, Leonberger polyneuropathy 1 (LPN1) and Leonberger polyneuropathy 2 (LPN2), have been identified. The genetic mutation found for LPN1 (*ARHGEF10* deletion) is the same mutation responsible for a similar juvenile polyneuropathy of Saint Bernard dogs (one of the breeds from which the Leonberger was derived). LPN1 is inherited as an autosomal recessive trait, whereas LPN2 is inherited as an autosomal dominant trait. This disorder is characterized by chronic, progressive, distal axonal loss and demyelination. Italian Spinone dogs have reportedly presented with a similar distal polyneuropathy, and an autosomal recessive mode of inheritance is suspected in this breed.

b. The age of onset of clinical signs in Leonberger dogs has reportedly ranged from 1 to 9 yrs of age, although the majority have been 1 to 3 yrs of age at presentation. Dogs with LPN1 tend to have particularly severe disease with onset less than 4 yrs of age (mean of 2 yrs), whereas dogs with LPN2 have a broader range of onset of clinical signs (1 to 10 yrs; mean of 6 yrs). Italian Spinone dogs typically present between 8 and 10 yrs of age. Affected dogs show exercise intolerance, distal muscle atrophy, decreased spinal and cranial nerve reflexes, and laryngeal paralysis/paresis. Hip and stifle hyperflexion while ambulating is also classically seen, along with a tendency to “throw” the foot forward during the pelvic limb’s swing phase. Facial nerve paralysis and/or a decreased gag reflex have been infrequently reported.

c. A presumptive diagnosis can be made based upon signalment, historical and clinical findings, as well as abnormal results of electrodiagnostic testing and corroborating muscle/nerve biopsy results. Definitive diagnosis for the Leonberger disorder is achieved by identifying the causative gene mutation. The LPN1 mutation accounts for 20% of all Leonbergers with polyneuropathy and the LPN2 mutation accounts for 25% of these dogs. Therefore, there is a group of Leonberger dogs with polyneuropathy that will not be identified by testing for LPN1 or LPN2.

Symptomatic treatments, such as surgical lateralization of the arytenoid cartilage to improve respiratory function, may improve quality of life. However, definitive treatments are not yet available.

d. Although disease severity appears to vary among affected dogs, long-term prognosis is considered guarded. A subset of dogs will continuously deteriorate, becoming tetraplegic or developing complications from laryngeal dysfunction, such as aspiration pneumonia.

9. Laryngeal paralysis[17, 20, 25, 26, 28, 46, 56, 77, 99, 117, 118, 129, 143, 144, 152, 172, 179, 184, 201, 203, 206, 207, 214–216, 229, 242, 262, 265, 273, 279, 284, 296, 314, 320, 332–334, 354, 358]

    a. This refers to a motor neuropathy of the recurrent laryngeal nerve that appears to occur in two major forms. The first form is a hereditary disease of immature animals (less than 12 mos of age) and the second form is an acquired (also referred to as idiopathic laryngeal paralysis) disorder of middle-aged to older dogs and cats. It is now accepted that acquired laryngeal paralysis is a manifestation of a generalized neuromuscular disease, rather than an isolated neuropathy. Many patients affected by acquired laryngeal paralysis have concurrent esophageal dysfunction and eventually develop a generalized polyneuropathy within 1 yr. Electrodiagnostic testing abnormalities and histopathologic findings support a generalized polyneuropathy in many dogs with acquired laryngeal paralysis.

    Both forms appear to be much more common in dogs than cats. In both disorders, denervation atrophy of the cricoarytenoideus dorsalis muscle and axonal and myelin loss in the recurrent laryngeal nerve(s) are characteristic features. The pathogenesis is unknown for both forms of laryngeal paralysis. Specific information pertaining to the two forms of this neuropathy is as follows:

    1. Hereditary laryngeal paralysis—this is best described for the Bouvier des Flandres breed, in which the disease is inherited as an autosomal dominant trait. An autosomal dominant pattern of inheritance is seen in the Bouvier des Flandres and Wallerian degeneration of the recurrent laryngeal nerve and concurrent histopathologic changes in the nucleus ambiguus have been documented. An inherited basis for this disorder has also been proposed in Siberian Huskies, and in a litter of Siberian Husky/Alaskan Malamute crossbreed dogs. Recurrent laryngeal nerve degeneration is due to neuronal degeneration in the nucleus ambiguous of the brain stem. Onset of clinical signs is typically between 4 and 6 mos of age. However, age of onset of clinical signs has been reported up to 7 yrs of age in this breed. A similar disease has been described in young Siberian Husky and Husky crossbred dogs, Bull Terriers, Rottweilers, and white-coated German Shepherd dogs.
    2. Acquired (idiopathic) laryngeal paralysis—this is encountered most commonly in older large- and giant-breed dogs, such as Labrador Retrievers, Saint Bernards, Newfoundlands, Irish Setters, and Afghan hounds. Labrador Retrievers represent between 69 and 73% of late-onset laryngeal paralysis cases, suggesting a familial or genetic predisposition in this breed. A high likelihood of older dogs presenting with laryngeal paralysis having underlying generalized neuromuscular disease has been reported. There appears to be no breed or sex predilection for cats with laryngeal paralysis. The median age of cats with laryngeal paralysis was reported as 11 yrs in one study. A focal pharyngeal laryngeal blastomycosis infection has been reported in one dog, with a clinical presentation indistinguishable from idiopathic laryngeal paralysis cases. Laryngeal paralysis secondary to a pulmonary squamous cell carcinoma has also been reported in a cat. In the majority of acquired cases, the underlying cause is undetermined.

    b. Clinical signs reflect dysfunction of the arytenoid cartilages and vocal folds and include dysphonia, inspiratory noise (stridor), and respiratory distress (especially when exercising). Retching, gagging, and coughing associated with eating and drinking may also be appreciated. These clinical signs are directly related to the arytenoid cartilages and vocal folds remaining in a paramedian position during inspiration. Essentially, this creates an upper airway obstruction. Concurrent megaesophagus has been reported with laryngeal paralysis in a small percentage of both canine and feline cases. Clinical signs tend to progress in severity over several months. Clinical signs related to generalized neuromuscular disease—such as exercise intolerance, muscle atrophy, and absent patellar reflexes—have been reported. High-impact exercises, excitement, increased environmental humidity, and ambient temperature all exacerbate clinical signs.

    c. Both forms of this neuropathy are diagnosed by historical and clinical features and by ruling out other causes of laryngeal paresis/paralysis (e.g. neuromuscular junction disorders, hypothyroidism). Assessment of vocal fold movement during standard laryngoscopy may be used to confirm laryngeal paralysis. A light plane of anesthesia is recommended for this procedure, as anesthetic agents may impair vocal fold movement. Thiopental, given intravenously to effect, has been shown to least influence laryngoscopy results. The CNS stimulant doxapram reportedly improves visualization of laryngeal paralysis but may also temporarily worsen airway obstruction, necessitating the intubation of affected dogs. Effective vocal fold evaluation in sedated dogs has also been reported using transnasal laryngoscopy. Abnormal EMG activity in the cricoarytenoideus dorsalis muscle and neurogenic atrophy appreciated in biopsy samples of this muscle support the diagnosis. A full electrodiagnostic evaluation should be performed to rule out generalized neuromuscular disease, particularly if corresponding neurologic signs are present. Lastly, sound spectrogram analysis may provide a noninvasive method of detecting laryngeal paralysis.

d. Clinical signs tend to progress in both forms of this disease. Absent patellar reflexes have been associated with a worse prognosis in affected dogs, likely due to their association with generalized neuromuscular disease. Other than exercise restriction and avoiding stressful situations, there is no effective medical treatment to halt or impede disease progression. However, many patients will do well with corrective surgery (e.g. arytenoid lateralization). Corrective surgery for canine laryngeal paralysis has been associated with variable complication rates, ranging from 34 to 74% in various reports. Complications were most likely to occur in dogs requiring bilateral arytenoid lateralization. Bilateral surgery has also been associated with a higher risk of recurrence of clinical signs in affected dogs. The most common postoperative complication was aspiration pneumonia. The placement of low-tension sutures during unilateral cricoarytenoid lateralization may be associated with a lower incidence of aspiration pneumonia, while still achieving sufficient vocal fold abduction. A technique using video assistance for unilateral cricoarytenoid laryngoplasty surgery has been reported. In an effort to assess real-time arytenoid abduction during suture tensioning, the cricoarytenoid suture was tightened under video observation of the rima glottidis with a rigid endoscope. The short-term surgical outcome in 13/14 of these dogs was good and this technique is a useful way to assess the final arytenoid position intra-operatively

Minor complications of arytenoid lateralization surgery include continued coughing, gagging, or exercise intolerance. Seroma formation at the surgery site has also been reported. Minor complications did not affect owner-determined quality-of-life scores in one survey. Successful surgical treatment of this disorder with either an endoscopically inserted cricoid implant or a calcium hydroxyapatite vocal fold injection have also been reported. Similarly, preliminary evidence has shown that surgical re-innervation of the laryngeal muscles, or functional electrical stimulation of laryngeal adductor muscles, may be effective treatments for this disorder, although full clinical evaluations of these procedures are not yet available.

10. Rottweiler distal sensorimotor polyneuropathy[25, 28, 31, 40, 66, 91, 116, 154, 275, 294]

a. This polyneuropathy of young adult Rottweilers is characterized by a widespread loss of axons (axonal necrosis) and myelin in both motor and sensory nerves of the PNS, especially in the terminal axonal segments. This appears to be a dying-back neuropathy, but the specific pathogenesis is unknown. The disease appears to be reminiscent of a human neuropathy termed hereditary motor and sensory neuropathy (HMSN) type II. Rottweiler distal sensorimotor polyneuropathy is similar in many respects to a syndrome reported sporadically in large dogs of various breeds (e.g. Irish Setter crossbred dogs, Great Danes, German Shepherds) referred to as distal symmetric polyneuropathy.

b. The dogs reported with this disease ranged in age from 1.5 to 4 yrs at the time of clinical disease onset. The clinical course consists of paraparesis initially, which slowly progresses to tetraparesis, with hyporeflexia and hypotonia, and atrophy of distal limb muscles. The disease is typically slowly progressive (sometimes over a year) and may even wax and wane, although acute presentations have been reported. Dogs with distal symmetric polyneuropathy may exhibit decreased nociception and masticatory muscle atrophy.

c. Diagnosis is based upon signalment, historical and clinical findings, and abnormalities noted on electrodiagnostic testing (especially EMG of distal limb muscles) and nerve/muscle biopsies.

d. Some dogs seem to transiently respond to glucocorticoid therapy, but this is a progressive disease with no known treatment. The long-term prognosis is guarded to poor.

11. Distal denervating disease[26, 28, 103, 134, 314]

a. A motor polyneuropathy of unknown pathogenesis has been reported in dogs in the United Kingdom. Lesions are restricted to the degeneration of distal axons and myelin of motor nerves.

b. There is no age, sex, or breed predisposition. Clinical signs of a LMN tetraparesis (hypotonia, decreased to absent spinal reflexes) develop over a period of 1 wk to 1 mo. Signs of cranial nerve dysfunction may also occur, including dysphonia, facial weakness, and atrophy of masticatory muscles. There is no evidence of sensory dysfunction. Atrophy of proximal limb muscles is characteristic. Respiration, swallowing, and bladder control remain unaffected. Most dogs recover fully with supportive care within 4–6 wks.

c. Diagnosis is based upon clinical findings and abnormal results of electrodiagnostic tests and nerve/muscle biopsies. Treatment is supportive.

d. The prognosis is favorable, as most dogs recover fully within 4–6 wks.

12. Golden Retriever hypomyelinating polyneuropathy[25, 28, 34, 66, 103, 222, 314]

a. A peripheral hypomyelination disorder has been reported in Golden Retriever littermates. Nerve biopsies from affected dogs revealed normal axons with deficient myelination. The pathogenesis is unknown, but abnormal Schwann cell function is suspected.

b. The affected puppies exhibited an ataxic, mildly paretic pelvic limb gait at 7 wks of age. Mild pelvic limb muscle atrophy, a crouched pelvic limb stance, and bunny-hopping while running were also observed. The puppies improved clinically over time.

c. Diagnosis is based upon signalment, historical and clinical findings, and results of electrodiagnostic testing (e.g. decreased motor conduction velocity) and nerve/muscle biopsy.

d. The prognosis appears to be favorable, as the puppies either improved clinically or remained unchanged as they grew older.

13. Miniature Schnauzer demyelinating polyneuropathy[330]

a. An unusual demyelinating polyneuropathy has been identified in three related (two littermates, all shared the same dam) black Miniature Schnauzers. This disorder is characterized by the histopathologic finding of focal thickenings of the myelin sheath of peripheral nerves. These thickenings, called *tomacula*, are a result of excessive folding and compaction of myelin. This disorder appears to be similar to demyelinating forms of CMT disease of humans. A genetic basis is suspected.

b. Two (intact males) of the three reported dogs developed clinical signs at about 6 mos of age and were presented for evaluation at 14 and 31 mos, respectively. The third dog (intact female) presented at 31 mos of age and the onset of clinical signs was described as from an "early age." All dogs, despite having electrodiagnostic (decreased motor and sensory conduction velocity) and biopsy evidence (demyelination) of appendicular nerve dysfunction, were presented primarily for respiratory dysfunction, rather than generalized limb muscle weakness. Two dogs presented for repeated regurgitation episodes (one had evidence of megaesophagus) and aspiration pneumonia, and one dog for inspiratory stridor (due to bilateral laryngeal paralysis) and subtle exercise intolerance. This latter dog had evidence of megaesophagus on thoracic radiographs on a recheck examination.

c. Diagnosis of this disorder in the three reported dogs was based upon clinical features, electrodiagnostic testing, and results of nerve (abnormal myelination) and muscle biopsy (normal).

d. Although the prognosis for this disorder cannot be determined from the three reported cases, all three dogs were alive and stable at the time of submission of the manuscript, for a considerable period after the onset of clinical disease. This suggests that this is not a rapidly progressive neuropathy.

14. Hypertrophic neuropathy[25, 28, 59, 66, 67, 79, 103, 304, 314]

a. This is a demyelinating peripheral polyneuropathy that is inherited as an autosomal recessive trait in Tibetan Mastiffs. This disorder has also been described in cats. There is widespread demyelination and remyelination with minimal axonal degeneration, leading to gross hypertrophy of the affected nerves. The pathogenesis is thought to involve a defect in Schwann cell ability to produce and maintain a stable myelin sheath.

b. Onset of clinical signs of dysfunction is typically at 7–10 wks of age in Tibetan Mastiff dogs, and between 7 and 12 mos of age in cats. Affected puppies usually exhibit pelvic limb weakness that rapidly progresses to the thoracic limbs. A shuffling, plantigrade gait is characteristic. Decreased spinal reflexes, muscle hypotonia, and dysphonia are also common features of the disease. Most afflicted dogs are nonambulatory tetraparetic within a few weeks of the onset of clinical signs. Pain perception (nociception) is unaffected. Cats with hypertrophic neuropathy display generalized tremors that worsen with activity, hypermetric gait, plantigrade stance, depressed spinal reflexes, and decreased sensation in the facial region and extremities. Mild limb paresis and muscle atrophy may also be appreciated.

c. Diagnosis of this condition is based upon signalment, historical and clinical findings, and abnormal results of electrodiagnostic tests and nerve/muscle biopsies.

d. There is no treatment for this progressive disease and the prognosis is poor. A subset of dogs may improve in their signs, but residual weakness is frequently seen in these cases.

15. Megaesophagus (congenital and idiopathic acquired)[15, 25, 28, 64, 74, 139, 148, 159, 160, 205, 235, 300, 310, 312, 314, 328, 350]

a. Megaesophagus can result from a number of diseases of nerve, muscle, neuromuscular junctions, or gastrointestinal tract. Additionally, megaesophagus may be seen secondary to vascular ring anomalies or a persistent left cranial vena cava. A predisposition to esophageal dysmotility without megaesophagus, likely representing delayed esophageal maturation, has been reported in young Terrier dogs. However, this discussion focuses on the congenital disorder of immature animals and the acquired (idiopathic) disorder of adult animals. Congenital and acquired megaesophagus are more common in dogs than cats. Both forms of megaesophagus may represent a neuropathy (motor and/or sensory) affecting the vagus nerves, but there is no compelling evidence to support this. In short, both forms of megaesophagus are idiopathic.

b. Clinical signs of megaesophagus usually include regurgitation, and secondary respiratory problems due to aspiration pneumonia. Congenital megaesophagus has been reported primarily in Great Danes, German Shepherd dogs, Irish Setters, Newfoundlands, Greyhounds, Shar Peis, Miniature Schnauzers, and Wire-haired Fox Terriers. In the latter two dog breeds, this has been shown to be an inherited disease. Congenital megaesophagus has also been reported in Siamese cats. Idiopathic acquired megaesophagus can occur in dogs and cats at any age. In a recent report of cats with disorders of esophageal motility, 30% were congenital and 43% were idiopathic acquired.

c. Diagnosis of both congenital and acquired idiopathic megaesophagus is based mainly upon signalment and historical and clinical findings (particularly radiographic evidence of megaesophagus; Fig. 17.2), and ruling out other causes of megaesophagus. Especially in adult animals, there is a multitude of potential causes of megaesophagus. These causes should be ruled out before assigning a diagnosis of idiopathic acquired megaesophagus.

d. There is no specific treatment for these idiopathic conditions. Patients should either be fed with their heads elevated or preferably via a gastrostomy tube. Antacids (e.g. cimetidine) and motility modifiers (e.g. metoclopramide, cisapride) may be helpful in decreasing gastric acidity (decreased lung damage with aspiration) and increasing gastroesophageal sphincter tone, respectively. These motility-modifying agents have not been shown to improve esophageal function in dogs. In dogs with megaesophagus, increasing gastroesophageal sphincter tone may be counterproductive if the patient is being fed by mouth, but may decrease gastroesophageal reflux in a patient fed with a gastrostomy tube. In contrast to dogs, there is recent evidence that the majority (78%) of cats with esophageal motility disorders exhibit clinical improvement when treated with motility modifiers. The difference between dogs and cats in regard to clinical response to motility modifiers is likely due to the large proportion of smooth muscle in the feline esophagus. Metoclopramide and cisapride are smooth muscle stimulants. The majority of the canine esophageal musculature is skeletal (striated), whereas the majority of the esophageal musculature in cats is smooth.

Prognosis is guarded for congenital megaesophagus. In some patients, the megaesophagus resolves as the animal matures, while in others there is either no change or worsening of the megaesophagus. In these latter dogs, the combination of severe malnutrition and recurrent aspiration pneumonia is often fatal. The prognosis for acquired idiopathic megaesophagus is often guarded to poor, especially in dogs. The megaesophagus rarely spontaneously resolves in these patients, and the potential for severe, recurrent aspiration pneumonia is high.

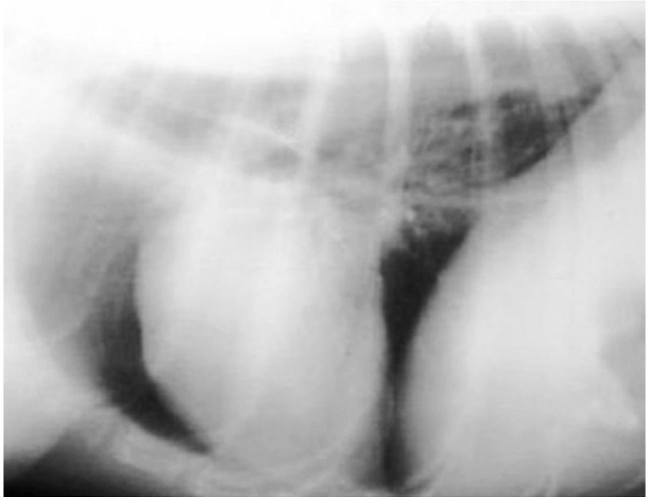

Figure 17.2 Lateral thoracic radiograph of a dog with megaesophagus.

16. Idiopathic facial paralysis[9, 10, 18, 21, 26, 28, 32, 150, 171, 173, 177, 191, 213, 225, 263, 268, 289, 313, 314, 318, 331]

a. This is an acute mononeuropathy of one (usually) or both facial nerves that has been reported in dogs and cats. The pathogenesis is unknown but a similar condition occurs in humans (Bell's palsy). There is some evidence in the human medical literature that Bell's palsy is due to an immune-mediated response triggered by herpes simplex viral infection. Histopathologic evidence of axonal and myelin loss, without evidence of inflammation, has been described with this disorder.

b. Affected animals are usually middle-aged to older (e.g. over 5 yrs of age). Although this problem has been reported in a number of breeds, Cocker Spaniels appear to be consistently overrepresented. Clinical signs reflect acute dysfunction of one or both (uncommonly) facial nerves. Drooping of the ears and lips, deviation of the nasal philtrum toward the normal side (if unilateral paralysis), decreased to absent palpebral reflex and menace response, and excessive salivation on the affected side are all typical clinical findings (Fig. 17.3). Some patients will have trouble

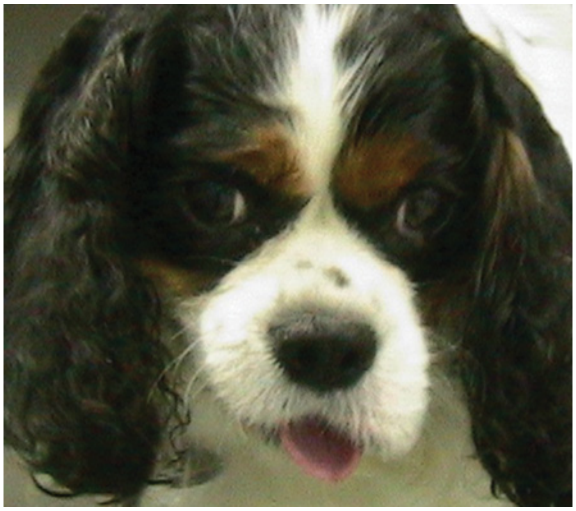

Figure 17.3 Dog with unilateral (left-sided) facial nerve paralysis.

keeping food from dropping out of the lips on the affected side. Corneal ulceration may occur, both to inadequate blinking ability and interruption of the parasympathetic input to the lacrimal gland (in the facial nerve). Though uncommon, some patients may also exhibit signs of vestibular dysfunction (CN VIII; see Chapter 11).

c. Diagnosis is based on characteristic historical and clinical findings and ruling out other causes of acute facial nerve dysfunction (e.g. otitis media/interna, hypothyroidism). The clinician should bear in mind that Cocker Spaniels are predisposed also both to otitis and hypothyroidism.

d. The prognosis is guarded for the complete return to function of the facial nerve. Full recovery may occur in weeks to months, but in many cases some degree of facial nerve paresis appears to be permanent. Treatment is symptomatic (e.g. artificial tears to prevent corneal drying). The use of corticosteroids for this disease is controversial, especially considering the apparent lack of inflammation. There is some evidence of efficacy for corticosteroid treatment of Bell's palsy in people.

17. Sensory neuropathy of long-haired Dachshunds[25,28,66,98,103–105,108,146,314,335]

a. Believed to be inherited as an autosomal recessive trait, this disorder is characterized by degeneration of principally distal sensory axons in both the PNS and the CNS. The pathogenesis of this disorder is unknown. A similar disorder has been reported in a Jack Russell Terrier and four Border Collies. An experimentally induced sensory neuropathy with distal axonal degeneration, secondary to chronic dietary deficiencies of phenylalanine and tyrosine, has also been reported in cats.

b. Clinical signs of dysfunction may be evident by 8–12 wks of age and include mild ataxia, loss of proprioception (especially in the pelvic limbs), and widespread reduction or loss of superficial and deep pain perception. Some patients may exhibit vomiting and/or urinary incontinence, presumably due to degenerative changes in the autonomic nervous system. Self-mutilation may also be exhibited. There is no evidence of muscular atrophy in these dogs, and spinal reflexes may be normal or slightly reduced.

c. Diagnosis is made via history, signalment, and clinical findings, along with results of electrodiagnostic testing (decreased to absent sensory nerve potentials) and muscle/nerve biopsy.

d. The prognosis for this disorder is poor, due to the progressive nature of the disorder and/or the severity of clinical signs.

18. Sensory neuropathy of Pointer dogs[25,28,66,82,84,86,103,104,314]

a. An autosomal recessively inherited sensory polyneuropathy has been reported in English Pointer dogs as well as Czechoslovakian Short-haired Pointer dogs. This condition has also been reported in 13 French Spaniels, with presumed autosomal recessive inheritance. The pathogenesis is unknown, but the disease is characterized by a loss of sensory neurons (as well as their axonal processes and myelin) and an associated lack of an important nociceptive neurotransmitter called substance P.

b. Clinical signs typically become apparent between 2 and 12 mos of age. There is loss of pain perception to the distal aspect of the paws (e.g. the toes) and a decreased pain sensation proximal to the carpus and tarsus. There is the possibility that paresthesia/dysesthesia may contribute to the clinical picture. The dogs begin to lick and then chew their digits, ultimately leading to autoamputations (Fig. 17.4). Apparently painless fractures and osteomyelitis of the paw may occur. There are no other neurologic deficits, other than altered pain perception to the distal limbs.

c. A tentative diagnosis is usually based upon history, signalment, clinical findings, and, potentially, nerve biopsy results. Results of electrodiagnostic tests are normal in this disease. Definitive diagnosis is based upon histopathologic evaluation of spinal ganglia, axonal processes of the sensory nuclei of those ganglia (both in the PNS and CNS), and a lack of staining for substance P in the spinal cord.

d. There is no effective treatment for this disorder and the prognosis is poor.

19. Idiopathic self-mutilation[26,28,95,125,246,264,329]

a. Also known as acral lick dermatitis, this self-mutilatory behavior of "high-strung" breeds of dogs and cats (e.g. Doberman Pinschers, German Shepherd

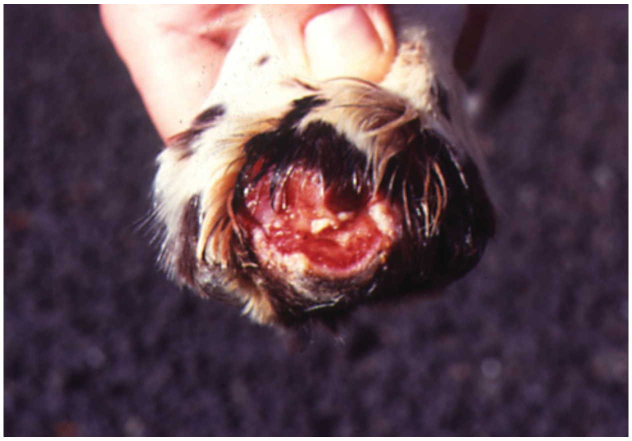

Figure 17.4 Automutilation of the digits in a Pointer dog with sensory neuropathy. (Courtesy of Dr. Jacques Penderis.)

dogs, Siamese and Abyssinian cats) may be due to a mild sensory polyneuropathy. There is electrophysiologic and histopathologic evidence to support this theory. The pathogenesis of this suspected sensory polyneuropathy is unknown.

- **b.** Clinical signs of this disorder are usually limited to licking, biting, or scratching an area of skin around the tarsal or carpal areas.
- **c.** Diagnosis of this syndrome is typically based on typical historical and clinical findings in a “nervous” or “high-strung” pet. Other dermatologic conditions should be ruled out. Some patients will respond (decreased self-mutilatory behavior) to the tricyclic antidepressant drug clomipramine, at a dose of 1–3 mg/kg per os, per day. Secondary skin infections should be treated with appropriate antibiotic regimens.
- **d.** The prognosis for control of this condition is good.

20. Spinal muscular atrophy (SMA)[25, 28, 52, 69–73, 80, 87, 99, 151, 168, 189, 212, 219, 236, 244, 252–254, 271, 272, 276, 295, 297, 314, 325]

- **a.** Spinal muscular atrophy represents a spectrum of uncommon disease syndromes characterized by a premature degeneration of motor neurons primarily in the spinal cord and, to a variable degree, the brain stem. There are multiple forms of SMA, described in a number of dog breeds, with various clinical presentations and levels of severity. In some forms of the disease, there may also be cerebellar neuronal degeneration. It is currently not clear as to whether all of these disorders belong in the same category (e.g. SMA) or if some should be classified as multisystem neuronal degeneration.

  Most of these disorders appear to be analogous to infantile spinal muscular atrophy of humans, with onsets of dysfunction occurring during the first several weeks to months of life. Adult-onset SMA, similar to amyotrophic lateral sclerosis (ALS, or Lou Gehrig’s disease) of people and equine motor neuron disease, is rarely reported in dogs and cats. The pathogenesis of this disease is unknown, but SMA is believed to represent an abiotrophy, or premature cell death. These disorders are suspected or proven, depending upon the specific disorder, to be autosomally inherited traits. In the most completely studied form of this disease syndrome, hereditary SMA of Brittany Spaniels (autosomal dominant inheritance), there is evidence that both abnormal cytoskeletal neuronal protein production (e.g. neurofilaments) and imbalances of excitatory CNS neurotransmitters (e.g. aspartate, glutamate) are linked to premature neuronal cell death.
- **b.** Spinal muscular atrophy has been reported in numerous breeds, including Brittany Spaniels, English Pointer dogs, German Shepherd dogs, Rottweilers, Swedish Lapland dogs, Great Dane crossbred dogs (Stockard’s paralysis), Cairn Terriers, Briquet Griffon Vendéen dogs, a Saluki, and several cats. The typical clinical picture is that of a rapidly progressing polyneuropathy (LMN paresis) in the first 1–6 mos of life, mainly or exclusively affecting the limbs. Paresis with decreased to absent spinal reflexes and neurogenic muscle atrophy usually progresses to paralysis within weeks. Pelvic limb paresis typically occurs prior to thoracic limb paresis. Limb joints may become malpositioned and immovable, subsequent to pronounced muscle atrophy. Some dogs have a more protracted disease course, with less severe signs. For example, the German Shepherd dog disease appears to be an asymmetric, focal loss of motor neurons in the cervical intumescence, with relatively static unilateral or bilateral thoracic limb dysfunction. The accelerated (homozygous) form of the Brittany Spaniel SMA follows the typical pattern of early onset and rapid disease progression. However, the intermediate form has an onset at 6–12 mos of age and progresses slowly to tetraparesis by 2–3 yrs of age, and the chronic form has the same age at onset as the intermediate form but is nearly subclinical.

  Some breeds will exhibit signs of brain-stem (e.g. dysphonia, megaesophagus, tongue fasciculations) or cerebellar (e.g. head tremor) dysfunction, in addition to the LMN signs to the limbs. Apparent cataplectic episodes have been observed in the Cairn Terrier disease. This disorder may belong in the category of multisystem neuronal degeneration (see Chapter 7) rather than SMA.
- **c.** A tentative diagnosis of spinal muscular atrophy is based upon signalment, historical and clinical findings, and abnormal results of electrodiagnostic testing and nerve/muscle biopsies. A definitive diagnosis

depends upon brain-stem and spinal cord histopathologic findings.

   d. There is currently no effective treatment for this group of diseases, and the prognosis for the majority of them is poor. There is recent evidence that 4-aminopyridine, a drug that can both improve axonal conduction and increase acetylcholine release at the neuromuscular junction, may hold some promise as a potential therapy for SMA patients. Despite the poor prognosis overall, Brittany Spaniels with intermediate and chronic forms of the disease may do well for years. The German Shepherd dog disease also appears to be self-limiting.

21. Canine and feline dysautonomia[2, 13, 19, 26, 28, 48, 54, 59, 99, 103, 126, 140, 183, 193, 210, 211, 240, 247, 256, 258, 283, 286, 291, 292, 314, 315, 346, 347]
   a. This is a degenerative polyneuropathy of the autonomic nervous system in dogs and cats of unknown pathogenesis. Degeneration and loss of neuronal cell bodies occurs to various degrees in parasympathetic and sympathetic ganglia, intermediolateral columns of the spinal cord, and parasympathetic nuclei of the brain stem. The tendency for cases of dysautonomia to cluster in certain geographic regions (e.g. Missouri, Kansas) suggests either a toxic or an infectious etiology. A genetic influence on susceptibility to dysautonomia has also been proposed. Risk factors for the development of dysautonomia in dogs have been identified. Living in rural areas, consumption of wildlife (e.g. birds, rabbits), spending the majority of time outdoors, and access to cattle, pastureland, and farm ponds are all associated with the development of canine dysautonomia. Most cases of canine dysautonomia are identified between the months of February and April.
   b. Although a wide age range has been reported, most dogs and cats afflicted with this disease are young adults. In one report of canine dysautonomia, the median age at onset of clinical signs was 14 mos and in another it was 18 mos. Clinical signs develop relatively quickly (usually within 48 hrs in cats, within 2 wks in dogs) and primarily reflect parasympathetic dysfunction. However, chronic progressive autonomic dysfunction has been reported in a dog, whose clinical signs progressed over a 4-yr period. Consistently reported abnormalities include mydriasis with absent pupillary light reflex (PLR), dry mucous membranes (often with associated nasal congestion), retching, vomiting/regurgitation (megaesophagus is often present), dysphagia, prolapse of the third eyelid, urinary incontinence/dysuria (often with a distended bladder), fecal incontinence with decreased anal tone, constipation (more common in cats), diarrhea (more common in dogs), and bradycardia. Some patients will also have deficient tear production (abnormal Schirmer tear test) and abdominal pain (presumably due to intestinal ileus). Nonspecific clinical signs of lethargy, weight loss, and dehydration are also commonly observed.
   c. A tentative diagnosis is based primarily on clinical signs of autonomic dysfunction. Orthostatic hypotension has also been reported in affected dogs. Pharmacologic testing (e.g. pilocarpine ocular drops, bethanechol challenge) can also be performed to confirm abnormal autonomic receptor function (i.e. denervation hypersensitivity). Dysautonomic patients tend to demonstrate miosis shortly after ocular installation of 1–2 drops of dilute (0.05–0.1%) pilocarpine. These patients also tend to exhibit improved ability to urinate after subcutaneous administration of a low dose (0.04 mg/kg) of bethanechol. Definitive diagnosis requires demonstrating neuronal cell loss in the parasympathetic nervous system postmortem.
   d. There is no specific treatment for this disease, and spontaneous clinical recoveries are uncommon. Recovery has been reported in cats. However, this recovery may not begin to be apparent for several months and may take a prolonged period. During this convalescent time, intensive nursing care, including tube-feeding, bladder expression, enemas, correction/prevention of electrolyte abnormalities and dehydration, and anti-emetic administration (e.g. metoclopramide) may be required of the owner. The survival of severely affected cats has been estimated to be between 25 and 50% with such supportive treatment. Bradycardia may be a negative prognostic indicator. Most patients with dysautonomia either die or are euthanized due to complications of the disease.

22. Lysosomal storage diseases[21, 25, 28, 59, 66, 103, 137, 274, 314, 339]
   a. Some of the lysosomal storage diseases discussed in Chapter 7 can have peripheral polyneuropathy as part of the clinical syndrome. In some cases, a peripheral polyneuropathy can be the only clinical abnormality (e.g. Niemann–Pick disease in Siamese cats). The lysosomal storage diseases that may include signs of polyneuropathy as part of the clinical picture include the following:
      1. Fucosidosis—a glycoproteinosis of English Springer Spaniels.
      2. Globoid cell leukodystrophy (Krabbe's disease)—a sphingolipidosis most common in West Highland White and Cairn Terriers.
      3. Glycogen storage disease type IV—a glycogenosis reported in Norwegian Forest cats.
      4. Niemann–Pick disease—a sphingolipidosis reported in Siamese and Balinese cats.
   b. Clinical signs for most of these disorders reflect multifocal disease of the nervous system. Tentative diagnosis is based upon historical and clinical findings, abnormal electrodiagnostic test results, and lesions supportive of the suspected disorder in muscle/nerve

biopsies. Diminished enzyme activity (of the suspected enzyme of interest) in leukocytes, skin biopsies, or cultured cells (e.g. skin fibroblasts, hepatocytes) may be used as a confirmatory diagnostic test in some of these disorders.

    c. There is no treatment for these progressive diseases, and the prognosis is poor.

B. Anomalous/developmental: Optic nerve hypoplasia[23,28,110,121,192,326]

  1. This idiopathic congenital condition is uncommonly reported in dogs and rare in cats. There is a lack of neurons in the ganglion layer of the retina and atrophy of the optic nerve. Other concurrent ocular abnormalities (retinal dysplasia, retinal detachment) have been reported. Optic nerve hypoplasia can occur either unilaterally or bilaterally.
  2. This condition is believed to be a heritable trait in Miniature Poodles. It has been reported in a number of different breeds, however. Diagnosis is based upon a history of visual problems since opening of the eyelids in infancy, clinical signs of blindness, mydriasis, and absent direct PLR on the affected side(s), and ophthalmoscopic findings of a small optic disc on the affected side(s).
  3. The visual deficits are permanent and there is no treatment for this congenital condition. These patients will, however, make acceptable pets.

C. Metabolic

  1. Diabetic neuropathy[23,28,38,59,99,123,138,161,166,185,188,196,199,229,230,237,308,314,321,323,337,340,359] (Video 34)
     a. A polyneuropathy associated with diabetes mellitus has been described in both dogs and cats. The prevailing thought has historically been that this neuropathy primarily reflects a distal (dying back) axonopathy with secondary demyelination/remyelination. However, more recent evidence suggests that abnormal Schwann cell/myelin function may play a pivotal role in the development of diabetic neuropathy, with axonal damage being comparatively less important. The pathogenesis of axonal and Schwann cell/myelin dysfunction is unknown, but several hypotheses exist. It is likely that certain aspects of all these hypotheses act in concert to effect peripheral nerve dysfunction. The three hypotheses include the following:
        1. Vascular hypothesis—microvascular disease is known to occur with diabetes mellitus. The mechanisms responsible for microvascular compromise are not clearly defined, but may include: decreased vasodilatory molecules (e.g. prostacyclin, prostaglandin E_1) and increased vasoconstrictive molecules (e.g. thromboxane A_2, endothelin) in vascular endothelium, due to altered lipid metabolism; abnormally functioning hemoglobin and 2,3-diphosphoglycerate, due to protein glycosylation; and thrombosis subsequent to altered vessel compliance (accumulation of glycosylated molecules in and around endothelial cells) and increased red blood cell and platelet aggregation (altered blood flow dynamics and imbalance of vasodilatative/vasoconstrictive substances). Abnormal thickening of the perineurium (the sheath surrounding fascicles of myelinated axons in the peripheral nerve) of diabetic dogs has been reported. This thickened perineurium may also lead to vascular compromise of the axons and Schwann cell/myelin. Interference with the microcirculation to the peripheral nerves may result in ischemia and axonal/myelin degeneration.
        2. Metabolic hypothesis—several cellular metabolic aberrations occur in the diabetic state, which may interfere with axonal conduction and Schwann cell/myelin function. Most of these metabolic alterations are linked to the polyol pathway, which is dependent on the enzyme aldose reductase. There is increased activity of the polyol pathway due to excess glucose substrate, with subsequent accumulation of sorbitol. Sorbitol accumulation leads to depletion of myoinositol, a molecule necessary for normal function of cellular Na^1/K^1 ATPase. Myoinositol is also an integral component of several membrane phospholipids. In addition, sorbitol is slowly metabolized to fructose. During this oxidative process, membrane-damaging free-radical species (e.g. superoxide, nitric oxide) may be produced. Finally, excessive intracellular glucose may lead to the nonenzymatic glycosylation of proteins necessary for normal cell metabolism and axonal transport mechanisms, altering the functional capabilities of those proteins. Any one or a combination of these metabolic alterations may adversely affect axonal and Schwann cell/myelin function.
        3. Immune-mediated hypothesis—in addition to vascular and metabolic disturbances that secondarily affect axonal integrity, there may be more direct, autoimmune-related axonal/myelin disease concurrent with the diabetic condition. There are data to support immunologic mechanisms as being involved in diabetic neuropathy. There is some evidence that an immunologic attack of myelin may be subsequent to the glycosylation of myelin proteins. Some autoantibodies (e.g. against phospholipids) also tend to cause vascular thrombosis, providing another possible mechanism for microvascular nerve injury.
     b. Clinical signs in dogs are quite variable and range from a subclinical disorder (diagnosed via electrodiagnostics and nerve/muscle biopsy) to severe LMN tetraparesis/tetraplegia with profound neurogenic muscle atrophy. The typical clinical scenario in both dogs and cats is symmetric pelvic limb LMN paresis with

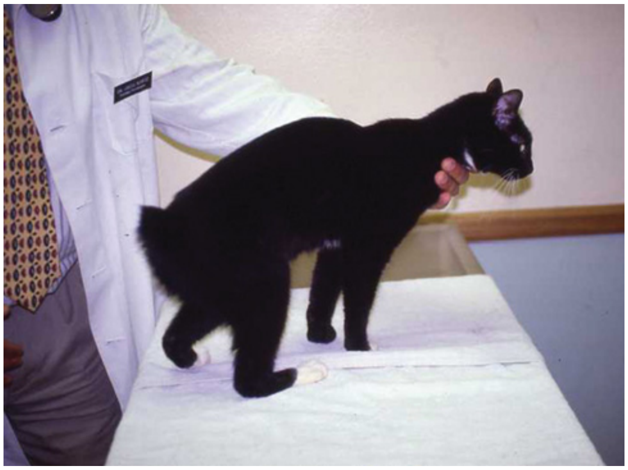

Figure 17.5 Characteristic pelvic limb posture of a cat with diabetic neuropathy. (Courtesy of Dr. Gregg Kortz.)

proprioceptive deficits, decreased reflexes, and muscle atrophy. Bilateral Horner's syndrome has also been reported with concurrent diabetes mellitus. In this case, resolution of clinical signs was seen once glycemic control was attained. The clinical picture of cats with diabetic neuropathy is more consistent than dogs. These cats usually exhibit a plantigrade posture in the pelvic limbs with their hocks touching the ground (Fig. 17.5). Decreased patellar reflexes, proprioceptive deficits, and muscle atrophy are also characteristic findings. Cats appear less likely than dogs to develop clinical signs of weakness in the thoracic limbs, although a palmigrade stance has been reported in cats with a diabetic neuropathy.

   c. Diagnosis depends upon confirming the presence of a polyneuropathy in a patient with diabetes mellitus, and ruling out other likely causes of polyneuropathy. Abnormalities are typically found with electrodiagnostic test results and muscle/nerve biopsies, supporting the diagnosis. These have been reported in motor, sensory, and mixed nerves. An autonomic neuropathy has also been reported in dogs with diabetes mellitus.
   d. Currently, there is no specific therapy proven effective for improving the polyneuropathy, but spontaneous resolution may occur after control of the diabetic condition is achieved. The prognosis remains guarded, however, since patients may not recover function, even with adequate diabetic control.

2. Hyperadrenocorticoid (Cushing's) neuropathy[23, 28, 187]
   a. There is evidence of an association between hyperadrenocorticism and polyneuropathy in dogs. Some, not all, of these dogs, have had a concurrent hyperadrenocorticoid myopathy (see Chapter 18). The pathogenesis is unknown.
   b. There is currently little knowledge available concerning the typical clinical features and prognosis for recovery for this suspected endocrine neuropathy.
3. Hyperchylomicronemia in cats[23, 28, 59, 66, 103, 181, 182, 314, 341]
   a. This is a deficiency of the hormone lipoprotein lipase that is believed to be inherited as an autosomal recessive trait. Granulomatous masses of lipid and coagulated blood (xanthomas) accumulate in various tissues. The xanthomas in the nerve roots and peripheral nerves cause a compressive neuropathy, with a loss of axons and myelin.
   b. Affected cats may have fasting hyperlipemia, giving their blood a "cream of tomato soup" coloration. Lipemia retinalis, a pallid appearance to the retinal vasculature apparent on funduscopic examination, is a consistent clinical feature of this disease. Signs of polyneuropathy are initially seen from 1 to 8 mos of age. A wide variety of neurologic abnormalities may be identified, including Horner's syndrome, paresis/paralysis of the trigeminal, facial, and recurrent laryngeal nerves, as well as motor and proprioceptive loss to radial, femoral, peroneal, and tibial nerves. Unilateral deficits are common.
   c. Diagnosis is based upon historical and clinical findings, demonstration of reduced serum lipoprotein lipase activity, and elevated serum triglyceride and cholesterol levels, as well as results of electrodiagnostic tests and nerve/muscle biopsies.
   d. Treatment for this disorder is placing the patient on a low-fat diet. Prognosis is favorable, as the clinical deficits may be reversible after a few months on the low-fat diet.
4. Hyperoxaluria in cats[28, 59, 66, 93, 103, 226, 290, 314]
   a. This autosomal recessively inherited disease is due to a deficiency of the enzyme D-glycerate dehydrogenase. Affected cats deposit oxalate crystals in renal tubules, leading to renal failure. Both oxalate and L-glyceric acid may be found in the urine. The pathogenesis of the associated polyneuropathy is unknown.
   b. Clinical signs of the disease occur acutely typically between 5 and 9 mos of age. In addition to signs of acute renal failure, these patients exhibit generalized weakness, a crouched gait, proprioceptive deficits, decreased patellar and withdrawal reflexes, and decreased nociception.
   c. Diagnosis is based upon historical and clinical findings, abnormal results of electrodiagnostic tests and muscle/nerve biopsies, and identification of L-glyceric acid and/or oxalate in the urine.
   d. There is no treatment for this condition and the prognosis is poor, both because of the renal failure and the polyneuropathy.
5. Hypothyroid neuropathy[16, 23, 28, 65, 97, 174, 176, 187, 288, 294, 314]
   a. Various neuropathies in dogs, involving both cranial nerves and peripheral motor nerves to the limbs, have been attributed to hypothyroidism. While a cause-and-effect relationship is often difficult to prove in these cases, there is abundant evidence to support

the association between hypothyroidism and neuropathies in dogs. The pathogenesis by which the hypothyroid state may lead to nerve dysfunction is unknown, but two prominent hypotheses are as follows:

1. Decreased mitochondrial ATPase activity—normal mitochondrial ATPase activity is believed to depend upon normal circulating thyroid hormone levels. This ATPase activity is required for normal axonal transport. Impaired axonal transport from hypothyroidism may lead to axonal degeneration.
2. Accumulation of acid mucopolysaccharides—hypothyroidism may lead to the accumulation of acid mucopolysaccharides in the endoneurium and perineurium of peripheral nerves, impairing their function.

b. Hypothyroid neuropathy tends to affect principally middle-aged to older dogs of the larger breeds. The clinical manifestations of hypothyroid neuropathy are diverse and include paresis or paralysis of CN V, VII, and VIII (alone or in combination), laryngeal paresis/paralysis, megaesophagus, and LMN paresis/paralysis of the limbs. An association between hypothyroidism and acquired myasthenia gravis (see Chapter 19) may exist in dogs. Since many of the clinical signs for these two disorders are similar, both disorders should be ruled out in suspect cases.

c. Diagnosis is based upon confirming the existence of hypothyroidism in a dog with a neuropathy. The presence of a neuropathy can be confirmed in many cases, based upon abnormal results of electrodiagnostic tests and muscle/nerve biopsies. Proving a dog to be truly hypothyroid may be more problematic. The standard method is demonstrating a subnormal response to exogenously administered thyroid-stimulating hormone (TSH response test). TSH may be expensive and/or difficult to obtain. Also, some test results fall into a "gray zone" that may or may not be supportive of hypothyroidism. Measuring free thyroxine (free T_4) levels by equilibrium dialysis is believed to be a relatively accurate assessment of thyroid functional status. Concurrently measuring serum TSH levels has been suggested, with elevated TSH levels expected in cases of primary hypothyroidism. A clinically acceptable method of tentatively diagnosing hypothyroid neuropathy is response to thyroid supplementation therapy in a suspect patient (neuropathy with a low resting T_4 level).

d. Treatment of hypothyroid neuropathy involves supplementation with oral thyroxine (20 mg/kg, q 12 hrs) and supportive care specific to the neuropathy exhibited by the patient (e.g. gastrostomy tube feeding in the megaesophagus patient). Prognosis is generally good for clinical recovery, with most dogs showing resolution of their clinical signs in 1–2 mos of treatment.

D. Neoplastic

1. Paraneoplastic neuropathies[14, 23, 28, 29, 33, 39, 62, 103, 170, 221, 233, 239, 314, 336, 342]

a. Both subclinical and clinical mononeuropathies and polyneuropathies have been associated with various neoplasms. These neuropathies are believed to develop as an indirect rather than a primary effect of the underlying neoplasia. The pathogenesis of this phenomenon is unknown, but several hypotheses exist. Potential explanations include elaboration of some neurotoxic factor by the tumor, disruption of axonal and/or Schwann cell metabolism by the tumor, and an immunologic reaction to antigens shared by the neoplasm and peripheral nerve elements (i.e. innocent bystander reaction). A paraneoplastic polyneuropathy has been reported occasionally with pancreatic insulinomas, and the potential exists for the associated hypoglycemia to be responsible for the neuropathy. However, peripheral nerves are particularly resistant to the effects of hypoglycemia, and peripheral neuropathy has not been associated with any other disease that results in hypoglycemia. Consequently, the hypoglycemia may not be a major contributing factor to this paraneoplastic neuropathy; a secondary effect of the insulinoma may make the peripheral nerves more sensitive to the hypoglycemic state.

b. Clinical signs are variable and may range from a subclinical neuropathy to severe LMN tetraplegia. Diagnosis of a neuropathy depends upon clinical findings and the results of electrodiagnostic testing and muscle/nerve biopsies. The existence of this phenomenon makes it imperative to rule out the existence of neoplasia in animals presenting with neuropathies, especially older patients. Diagnosis of an insulinoma is usually based upon an abnormal amended serum insulin/glucose ratio, and sometimes identifying the pancreatic tumor via ultrasound or exploratory laparotomy.

c. Treatment is directed toward the underlying neoplasia. There is no specific treatment for the associated neuropathy. The clinician should bear in mind that some antineoplastic drugs (e.g. vincristine) can lead to neuropathies.

d. Although full neurologic recovery following tumor resection has been reported, the overall prognosis for recovery from paraneoplastic neuropathies (assuming adequate control of the primary tumor) in dogs and cats is presently unknown. In people with paraneoplastic neuropathies, the prognosis is often poor for recovery. Prognosis for control of the underlying neoplasia depends largely upon the type and location of the tumor(s).

2. Malignant nerve sheath tumors (MNST)[1,6,23,28,42,44,58,63,90,99,103,119,155,158,194,197,198,223,228,243,259,261,269,270,277,278,314,317,324,352] (Video 35)
    a. These tumors arise in the cranial and peripheral nerve roots and nerves primarily in dogs, rarely in cats. The traditional nomenclature for these neoplasms is confusing and of limited clinical use. Schwannomas, neurofibromas, neurofibrosarcomas, and others all refer to malignant nerve sheath tumors with identical clinical features. Lymphosarcoma, malignant sarcoma, and hamartoma can occasionally involve peripheral nerves as well.
    b. MNSTs typically affect older dogs. Clinical signs of dysfunction depend upon the location of the tumor. MNSTs can involve spinal nerves and nerve roots at any location throughout the spine and can lead to secondary spinal cord compression. Approximately 55% of these tumors are located in the plexus area or distally and 45% are in the nerve roots, close to the spinal cord. These tumors can also involve nerve roots of the cauda equina or peripheral nerves. An intraocular MNST, arising from the ciliary nerve, has also been reported in a dog. The most common site for MNST is the nerve roots or nerves of the brachial plexus. Affected dogs typically exhibit a progressive (over weeks to months) thoracic limb lameness, for which no musculoskeletal explanation can be found. This lameness can progress to monoparesis in advanced cases (Fig. 17.6). Generalized soft tissue swelling of the affected limb has also been reported secondary to an MNST. Depending upon which nerve(s) is/are involved, there may or may not be evidence of proprioceptive loss or neurogenic muscle atrophy in the affected limb. Gentle palpation of the axillary space of the affected limb, and caudal retraction of the affected limb, may both elicit a painful response from the patient. The axillary and cranial aspects of the shoulder should be palpated. The cutaneous trunci (panniculus) reflex may also be deficient on the affected side. Ipsilateral Horner's syndrome, proprioceptive and/or motor deficits in other limbs, and neck pain all suggest extension of the tumor into the vertebral canal.

       The cranial nerve most commonly afflicted with MNST is the trigeminal nerve. Clinical signs of dysfunction in these dogs include ipsilateral neurogenic atrophy of the muscles of mastication, ipsilateral loss of facial sensation, and Horner's syndrome. If the intracranial portion of CN V is involved, other signs of brain-stem dysfunction may develop over time (due to compression).

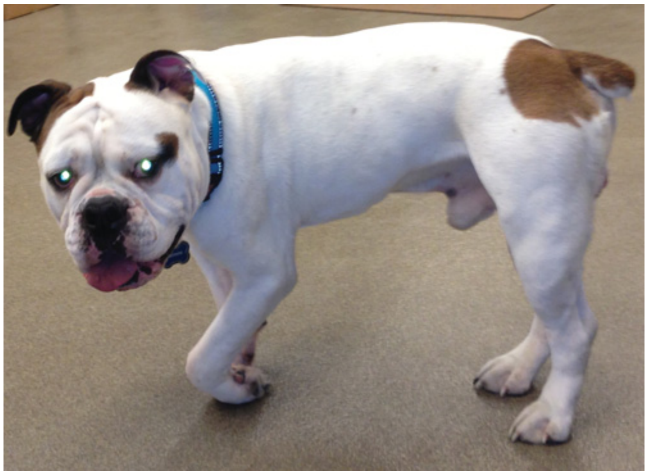

Figure 17.6 Posture of a dog with monoparesis of the left thoracic limb secondary to malignant peripheral nerve sheath tumor.

    c. A tentative diagnosis is based upon signalment, historical and clinical findings, and abnormal results of electrodiagnostic testing, imaging, and possible CSF analysis (usually if imaging is performed). Erythrocytosis secondary to an MNST may also be seen. MNSTs of the brachial plexus can sometimes be difficult or impossible to diagnose with these various tests. Identification of brachial plexus tumors with ultrasonography as tubular hypoechoic masses with no demonstrable blood flow has also been described, along with ultrasound-guided fine needle biopsy of the identified lesion (Fig. 17.7). The cytologic appearance of samples acquired from a fine needle aspiration biopsy of nerve sheath tumors has been reported. However, due to the potential for false negative results with this test, additional imaging is recommended if an MNST is suspected but not identified with ultrasonography. Based on the reported location of nerve sheath tumors, ultrasound would detect approximately 55% of tumors, thus almost half would not be identifiable. CT and MRI offer the potential of imaging both the axillary portion and the spinal portion of a brachial plexus MNST, as compared with myelography (Fig. 17.8). A CT/myelography combination may also be a valuable imaging option for this disease. MRI is the imaging modality of choice for evaluating MNSTs of cranial nerves (e.g. CN V). It is important to always use a large field of view to allow visualization of the plexus area as well as the spinal cord. The most common MRI pattern of primary nerve sheath tumors is hyperintensity on T2-weighted images (Fig. 17.9). The typical appearance of an MNST that involves the spinal cord is that of an intradural/extramedullary mass, although they may also appear as intramedullary or extradural lesions. Contrast enhancement is frequently seen. Extension of MNSTs arising from within the spinal canal through the destruction of surrounding vertebral bone, with extension into the overlying epaxial muscles, may also be seen on MRI. A definitive

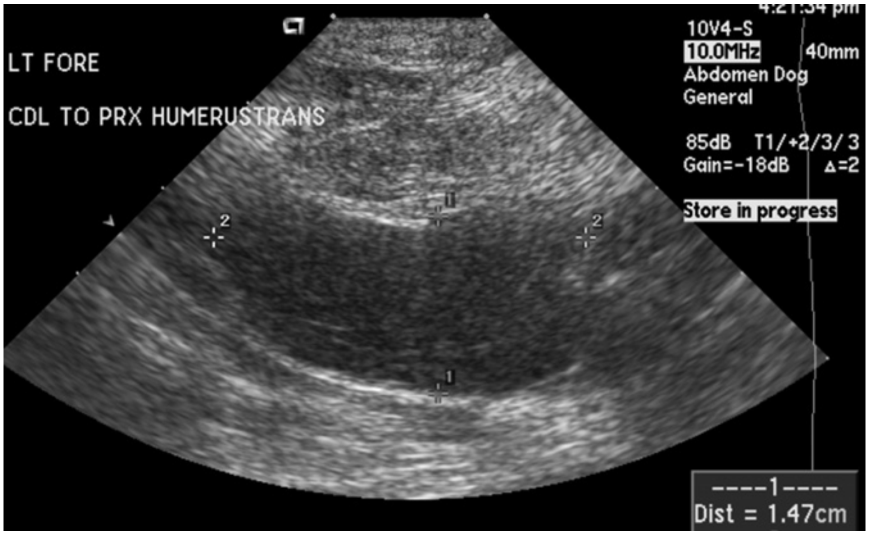

Figure 17.7 Ultrasonographic image of a dog with confirmed primary nerve sheath tumor.

diagnosis can be obtained with histopathologic analysis of biopsied tissue or at the time of tumor excision. The immunohistochemical characteristics of MNSTs in dogs have been described, and may be helpful in differentiating MNST from other sarcomas.

d. Definitive treatment for MNST, regardless of location, involves surgical removal of the neoplasm (Fig. 17.10). The responsiveness of these sarcomatous tumors to radiation therapy is unknown. Although there are sporadic reports of long-term survival following surgical removal of these tumors, the overall prognosis is poor. MNSTs tend to recur after surgical removal. Surgical removal of brachial plexus MNSTs usually involves amputation of the affected limb with or without a laminectomy procedure (depending upon whether there is tumor invasion into the vertebral canal). However, the median disease-free interval after surgery for these dogs is extremely short, especially when there is spinal cord involvement (approximately 1 mo).

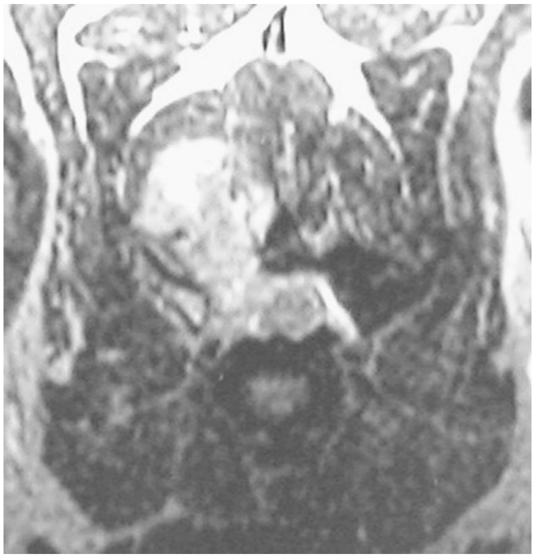

Figure 17.8 Transverse MRI (T2-weighted) of a large mass invading the cervical spinal cord. The mass was suspected to be a malignant nerve sheath tumor.

3. Mononuclear cell neoplasia (myelomonocytic neoplasia/lymphosarcoma)[63,158,250,259]

a. Multiple mononeuropathies of cranial nerves, most commonly involving the mandibular branch of CN V bilaterally, have been associated with mononuclear cell neoplasia in dogs. Myelomonocytic neoplasia is a rare malignant form of cancer that has been reported to involve cranial and peripheral nerves, as well as the CNS in a limited number of dogs. Infiltrative nodules of neoplastic myelomonocytic cells are found in cranial nerves, peripheral nerves, and ganglia, as well as multiple organ systems. Multicentric lymphosarcoma is a common form of cancer that has been reported to cause a similar clinical picture in dogs, either via direct neoplastic infiltration of cranial nerves or as a paraneoplastic phenomenon.

b. The hallmark of the few reported cases has been multiple cranial nerve dysfunction, especially bilateral dysfunction of the trigeminal nerve. Other cranial nerves have also been affected. Clinical signs of cranial nerve dysfunction have included masticatory muscle atrophy, inability to close the jaw, decreased facial sensation, decreased swallowing reflex, and unilateral or bilateral Horner's syndrome. The author has encountered several cases of cranial nerve dysfunction in dogs with multicentric lymphosarcoma. Bilateral dysfunction of CN V with a dropped jaw has been the most consistent clinical abnormality. However, one dog exhibited unilateral facial nerve (CN VII) dysfunction, in addition to bilateral CN V dysfunction.

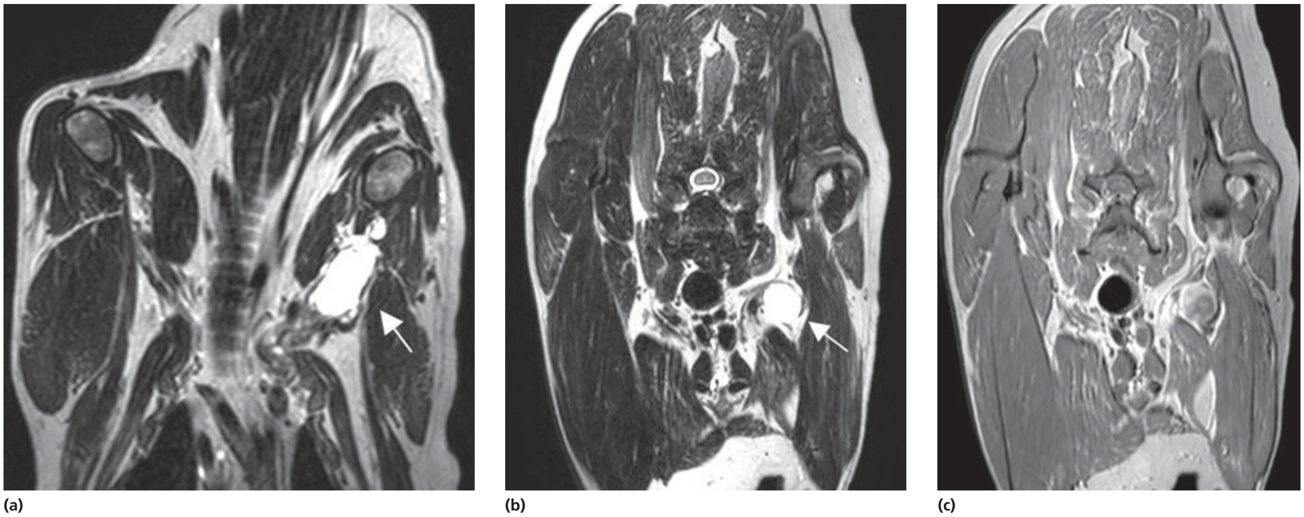

Figure 17.9 Dorsal (A), transverse T2-weighted (B), and T1-weighted (C) images post contrast administration of a dog with confirmed primary nerve sheath tumor. Note the well-defined area of hyperintensity on images A and B, and the heterogeneous contrast enhancement on C.

Another dog exhibited unilateral CN VII dysfunction as the only neurologic deficit.

c. Antemortem diagnosis is based upon signalment, historical and clinical findings, and the results of diagnostic tests that suggest or confirm the presence of neoplasia. These dogs may have bloodwork evidence suggesting malignancy elsewhere, such as leukopenia, anemia, and thrombocytopenia. Thoracic radiographs and abdominal ultrasound may reveal solid masses in cases of lymphosarcoma. Needle aspirates of such solid masses may yield a diagnosis in such cases. Neoplastic cells may also be identified in lymph node and bone marrow aspirates. Electrodiagnostic evaluation (e.g. EMG) and muscle biopsy may confirm neurogenic atrophy of masticatory muscles. CSF evaluation may be abnormal (e.g. lymphocytic pleocytosis in lymphosarcoma patients).

d. Therapy for these neuropathies is targeted toward the underlying neoplasia. Although various chemotherapy protocols are available, the prognosis for long-term survival is guarded to poor.

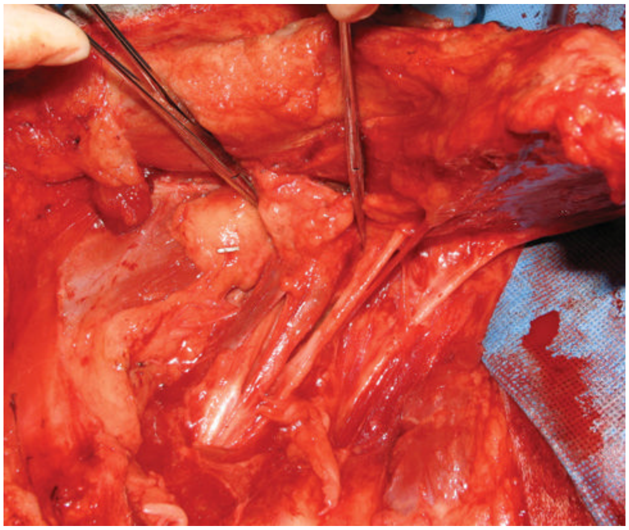

Figure 17.10 Intraoperative view of the primary nerve sheath tumor seen on Figure 17.9.

E. Inflammatory/infectious, autoimmune

1. Brachial plexus neuritis/neuropathy[3, 23, 28, 43, 89, 120, 228, 306, 314, 344]

a. This is a rare multiple mononeuropathy reported in dogs and one cat. The pathogenesis is unknown, but there is evidence to support this disease as being an allergic reaction to some immunogen, similar to the analogous disorder in people. Associations between such potential precipitating immunogens as dietary horsemeat and modified-live rabies vaccines have been made in the few reported veterinary cases. Axonal and myelin loss are mainly confined to ventral branches of the spinal nerves comprising the brachial plexus. Bilateral brachial plexus neuritis, with diffuse enlargement of the spinal nerves in this area seen on MRI, has been reported in a cat. An immune-mediated etiology was suspected in this case as well.

b. The typical clinical scenario is a patient with acute onset of bilateral LMN paresis or plegia involving the thoracic limbs. Neurogenic atrophy of thoracic limb muscle is also characteristic. One reported dog also had evidence of unilateral facial paresis.

c. A tentative diagnosis is based upon historical (e.g. history of exposure to a possible immunogen) and clinical findings. Electrodiagnostic testing and muscle/nerve biopsies should also support the diagnosis. CT or MRI may confirm nerve pathology.

d. Due to its rarity, little is known about the prognosis of this disorder. In the few cases reported, recovery appears to be prolonged. A prolonged recovery time is typical in the human form of this disease, probably due to the proximal nature of the axonal injury. There is no known specific treatment for this disorder, but glucocorticoid therapy and diets devoid of beef and horsemeat (e.g. poultry based) have been suggested.

2. Optic neuritis[26,28,111,208,238,248,305]
   a. Optic neuritis refers to inflammation of the optic nerves, optic chiasm, and/or optic tracts and exists either alone as an idiopathic (presumably immune-mediated) form or as one manifestation of a more widespread inflammatory/infectious (e.g. granulomatous meningoencephalomyelitis, canine distemper, tick-borne encephalitis virus infection, ehrlichiosis, fungal disease, protozoal disease, feline coronavirus) or neoplastic (e.g. lymphosarcoma, meningioma) disorder. The pathogenesis of idiopathic optic neuritis is unknown.
   b. Optic neuritis can occur in both dogs and cats (less common) of both sexes at any age (usually adults). The characteristic clinical findings are acute blindness (usually bilateral) with dilated pupils that are unresponsive to light. Ophthalmoscopic abnormalities (e.g. swollen optic disc) may or may not be evident, depending upon the location of the lesion with respect to the fundus. A normal electroretinogram (ERG) is supportive of optic neuritis, rather than retinal disease. The presence of neurologic deficits other than optic nerve dysfunction suggests that the optic neuritis is not a primary idiopathic condition.
   c. Diagnosis is based upon historical and clinical findings, ERG results, and tests for possible underlying disorders (e.g. CSF analysis, fungal titers).
   d. Treatment depends upon the underlying disorder. If infectious and neoplastic processes are ruled out, treatment usually consists of immunosuppressive prednisone therapy (1 mg/kg per os, q 12 hrs) for 2 wks (longer if GME is suspected), with subsequent gradual tapering of the dose. Early institution of immunosuppressive therapy is important for a favorable prognosis in idiopathic optic neuritis. Prognosis for a return of vision is guarded.
3. Acute idiopathic polyradiculoneuritis (APN) (coonhound paralysis, idiopathic polyradiculoneuritis)[5,22,23,28,49,59,76,78,88,103,115,122,124,127,147,149,156,157,162,163,165,169,190,204,224,227,241,251,282,311,314,316,348,351,355–357] (Video 36)
   a. An idiopathic inflammatory disorder primarily involving both axons and myelin of ventral nerve roots occurs in dogs, and is probably the most common polyneuropathy in this species. Although much less common, an analogous polyneuropathy has been described in cats. This disease is very similar to Guillain–Barré syndrome (GBS) in human beings. Varying degrees of axonal and myelin loss in motor nerves explain the characteristic clinical signs. Although most cases of GBS of people are associated with widespread demyelination, there is evidence that axonal loss is more prominent than demyelination in most dogs with polyradiculoneuritis. Demyelination is thought to be most severe in the ventral nerve roots in dogs, with minimal myelin loss in the major nerve trunks.

      Although the pathogenesis is uncertain, an autoimmune process is suspected. It is possible that an infectious process and secondary molecular mimicry is the underlying cause for this disease. The term “coonhound paralysis” refers to those dogs with a history of being bitten or scratched by a raccoon shortly before developing clinical signs of disease. The term “idiopathic polyradiculoneuritis” refers to patients with an identical clinical disorder, but with no possible exposure to raccoons. These two subcategories probably reflect the same disease syndrome, with the trigger for the inflammatory process being as yet unidentified in the latter subcategory. In humans, GBS is most commonly temporally associated with gastrointestinal *Campylobacter jejuni* infections. Other antecedent factors in humans with GBS include *Mycoplasma pneumonia*, *Toxoplasma gondii*, *Borrelia burgdorferi*, vaccinations, HIV, cytomegalovirus, Epstein–Barr virus, and surgical procedures. The proposed etiology involves molecular mimicry, or the production of autoantibodies against axolemmal components, which, in turn, stimulate immune axonal attack. Epitopes located on the myelin of peripheral nerves or the nodes of Ranvier can also be targeted autoantibody sites. Antibody production is known to be stimulated by molecular mimicry between *C. jejuni* lipo-oligosaccharide and human peripheral nerve gangliosides (located on human peripheral nerve surface membranes).

      A recent study showed that dogs with acute idiopathic polyradiculoneuritis were more likely to have serum IgG antibody titers to *T. gondii* compared to control dogs. IgM titers were not detected, therefore the likelihood of dogs with APN becoming infected with *T. gondii* within 7–10 days of neurologic signs was unlikely. It takes an average of 4–6 wks for IgG titers to develop with natural *T. gondii* infections. The presence of elevated IgG titers in dogs with APN suggests they were infected several weeks before the development of clinical signs. This does not necessarily support an immune-mediated peripheral neuropathy.

      Due to the complexity of the *Toxoplasma* organism, several antigen recognition patterns were found. The only antigen pattern seen in dogs with APN and not control dogs was the 36kDa. The 36kDa antigen was reported to be the IgG target antigen in cats experimentally infected with *T. gondii*, pregnant women with clinical signs of infection in addition to sheep, goats, and cattle with clinical *T. gondii* infections.

b. The typical clinical scenario for APN describes a rapidly developing LMN paresis/plegia, usually beginning in the pelvic limbs, and eventually involving the thoracic limbs. Most affected animals will progress to being either nonambulatory tetraparetic or tetraplegic within 10 days of the initial onset of clinical signs. It is not uncommon for this stage of dysfunction to be reached within a 72-hr period. The development of life-threatening respiratory paralysis is a concern, especially in the more rapidly developing cases. Loss or change of voice (aphonia and dysphonia, respectively) is common, and some patients will also exhibit facial weakness. Spinal reflexes are typically absent (with the exception of the perineal reflex, which is normal), muscles are hypotonic, and neurogenic atrophy develops quickly in recumbent patients. Proprioceptive placing reactions will be normal in those animals that still have enough motor ability to perform the efferent limb of these tests. These patients retain the ability to urinate and defecate, and will readily eat and drink if the head is supported. Pain sensation also remains intact. In fact, these animals often seem hyperesthetic upon limb manipulation, which may reflect the inflammatory nature of the disease.

In dogs with coonhound paralysis, there is a history of an encounter with a raccoon approximately 1–2 wks prior to the onset of clinical signs. In patients with idiopathic polyradiculoneuritis, identical clinical features are present as described, with no possibility of a raccoon scratch or bite.

c. Diagnosis is typically based upon the signalment (usually a mature hunting-breed dog in coonhound paralysis), history (e.g. exposure to a raccoon), and characteristic clinical signs of a rapidly progressive polyneuropathy. Other potential causes of polyneuropathy should be ruled out. Electrodiagnostic tests and muscle/nerve biopsies will also support the diagnosis of a polyneuropathy. It is important to realize that many, if not most, of these dogs will exhibit abnormal EMG activity with normal motor nerve conduction velocities (MNCV). Considering that MNCV primarily reflects myelin integrity, rather than the number of functional axons in a peripheral nerve, this phenomenon should not be confusing. The patients often do not have enough functional axons to ambulate, but the remaining axons have essentially normal myelination. A specific type of nerve conduction velocity test (F wave) that evaluates the ventral nerve roots is often abnormal in dogs with polyradiculoneuritis. CSF examination may demonstrate increased protein levels.

d. There is no specific therapy for this disease, but IV immunoglobulin seems promising. A recent study showed that dogs treated with intravenous (IV) immunoglobulin recovered faster compared with dogs without IV immunoglobulin. The median time for ambulation without assistance was 27.5 days for dogs treated with immunoglobulin versus 75.5 days for the control group. Humans with GBS recover more rapidly when treated with plasma exchange or human immunoglobulins IV within 4 wks of disease onset. Glucocorticoids have been suggested, but there is no evidence of efficacy. Nursing care, physical therapy, and proper nutrition are essential for recovery. The inflammatory phase of this disorder is believed to be transitory, but the damaged axons need to remyelinate and, to some degree, regrow. The prognosis for full recovery is often favorable, but it is typically prolonged, usually taking several weeks to several months. Some patients develop life-threatening respiratory paresis/paralysis in the acute phase of the disease (usually those dogs whose signs progress rapidly over 72 hrs) and may need to be mechanically ventilated. A recent study showed that dogs that required mechanical ventilation had a high rate of iatrogenic complications and euthanasia. Re-exposure to raccoons is to be avoided in dogs having recovered from coonhound paralysis, as this may trigger a relapse of the disease.

4. Miscellaneous forms of polyradiculoneuritis[23, 28, 59, 314]

a. Rarely reported forms of polyradiculoneuritis in dogs and cats include chronic polyradiculoneuritis, chronic relapsing polyradiculoneuritis, and cauda equina polyradiculoneuritis. The etiology and pathogenesis of these rare disorders are unknown, but the presence of inflammatory infiltrates in the nerve roots and nerves is a consistent feature.

b. In chronic or chronic relapsing polyradiculoneuritis, there is a slowly progressive (over weeks to months) polyneuropathy that may or may not include cranial nerve dysfunction and may or may not include sensory (proprioception, nociception) dysfunction. Muscle wasting is also a variable finding. Some patients will have either transient or sustained remissions of clinical signs that may or may not seem related to corticosteroid administration. A partial remission of clinical signs may also occur. In cauda equina polyradiculoneuritis, clinical signs of pelvic limb paraparesis with muscle atrophy, decreased proprioception, and loss of patellar reflexes have been described.

c. A tentative diagnosis is based upon clinical signs of a polyneuropathy, supportive electrodiagnostic and muscle/nerve biopsy results, and ruling out other potential causes (e.g. infectious, paraneoplastic) of a neuropathy.

d. Although some of these rare disorders seem to be corticosteroid-responsive, appropriate treatment and prognosis for these conditions remain to be elucidated.

5. Chronic inflammatory demyelinating polyneuropathy (CIDP)/chronic relapsing polyneuropathy[23, 24, 28, 41, 81, 99, 112, 186, 218, 302]

a. Chronic inflammatory demyelinating polyneuropathy is a suspected autoimmune polyneuropathy of mature dogs and cats (mean age of 6–7 yrs) that has recently been described. An analogous neuropathy occurs in people. This disorder is believed to be one of the more common neuropathies in dogs and cats. A polyneuropathy very similar to CIDP, referred to as chronic relapsing polyneuropathy, has been described in cats.

b. Clinical signs of insidiously progressive LMN paresis, with abnormal proprioception and normal sensation, have been described in CIDP and chronic relapsing polyneuropathy. The course of the disease is typically chronic, and patients tend to spontaneously recover and relapse. Clinical signs of dysfunction often occur in the pelvic limbs initially then progress to involve the thoracic limbs. The spectrum of potential clinical signs of dysfunction is broad and may include depressed spinal reflexes, muscle atrophy, paraparesis, tetraparesis, and tetraplegia.

c. Diagnosis is based upon historical and clinical features consistent with the disease, in conjunction with nerve/muscle biopsy results. Response to therapy (see below) also contributes to diagnosis. The predominant pathologic feature seen in nerve biopsies from these patients is evidence of demyelination and remyelination. Inflammatory cells have consistently been identified in ultrastructural studies of nerve biopsies from CIDP patients. Evidence of inflammation was lacking in nerve biopsies from patients with chronic relapsing polyneuropathy. Axonal degeneration is not a feature of CIDP, but was evident on the nerve biopsy of one cat with chronic relapsing polyneuropathy.

d. The prognosis is guarded to good. Most animals with CIDP and chronic relapsing polyneuropathy tend to be responsive to glucocorticoid therapy. In a recent report, 90% of dogs and 88% of cats with CIDP exhibited an initial positive response to oral prednisone therapy (1–2 mg/kg body weight q 12 hrs). Patients may relapse coincident with a reduction of glucocorticoid dosage or a discontinuation of glucocorticoid therapy. Some animals that initially respond to glucocorticoid therapy may subsequently become resistant to such treatment. If a positive response to glucocorticoid therapy is demonstrated in a patient with suspected CIDP or chronic relapsing polyneuropathy, dose reduction should proceed slowly once remission of clinical signs is achieved.

6. Protozoal polyradiculoneuritis[26, 28, 30, 68, 75, 85, 102, 103, 314]

a. Both *T. gondii* and *Neospora caninum* produce a severe polyradiculoneuritis in puppies, usually along with some degree of accompanying meningoencephalomyelitis and myositis.

b. Both organisms typically cause a polyradiculoneuritis in puppies less than 3 mos of age that is most profound in the lumbosacral nerve roots, especially the ventral roots. The puppies typically experience an acute paraparesis with rigid pelvic limb extension. Patellar and withdrawal reflexes are lost, and muscle wasting in the pelvic limbs develops. The patients retain nociceptive ability, and are often painful over the back and upon pelvic limb manipulation. Some dogs have a more fulminating course, with rapidly developing tetraparesis/tetraplegia and respiratory failure. There is evidence to suggest that *N. caninum* may be the more common offending organism in fulminating cases. Since many peripheral and cranial nerves can be affected—and concurrent infection of the brain, spinal cord, and muscles is often present—evidence of a multifocal disease process may be apparent. Although less common, adult dogs have been affected by these organisms.

c. The diagnosis is confirmed by identifying the organism's presence either serologically (antibody assays) and/or histopathologically (biopsy or necropsy specimens) in a patient with typical clinical signs of protozoal polyradiculoneuritis. Electrodiagnostic tests will be confirmative of a neuropathy, myopathy, or both.

d. Antimicrobial agents thought to be effective against these organisms include sulfa/trimethoprim combinations, pyrimethamine, and clindamycin. While the prognosis for survival in dogs with the typical pelvic limb dysfunction is favorable with treatment, the prognosis for a recovery of function is poor. *T. gondii* is a zoonotic disease.

7. Sensory ganglioradiculoneuritis (canine ganglioradiculitis, acquired sensory neuropathy)[28, 61, 83, 314]

a. This is an idiopathic inflammatory polyneuropathy primarily affecting dorsal root ganglia and dorsal nerve roots, as well as sensory cranial nerve ganglia. The pathogenesis of this nonsuppurative process is unknown, but viral and immune-mediated causes have been proposed.

b. Mature dogs are typically affected, and the Siberian Husky breed may be overrepresented. Clinical signs may develop acutely or insidiously, and are progressive over one to several months. The majority of clinical signs reported reflect dysfunction of sensory systems. These clinical signs may include pelvic limb ataxia without evidence of paresis, decreased conscious proprioception, decreased to absent spinal reflexes, hypermetric gait, decreased or altered (e.g. paresthesia/dysesthesia) facial sensation, dysphagia, megaesophagus, head tilt, Horner's syndrome, hearing loss, altered voice, and self-mutilation. Some dogs will also have masticatory muscle atrophy. This last feature has been attributed to secondary damage of motor axons of the trigeminal nerve as they traverse through the inflamed trigeminal ganglion.

   c. There is no treatment for this disorder and glucocorticoid therapy may even cause a worsening of clinical signs. Definitive diagnosis is made at necropsy (histopathologic findings). A tentative diagnosis is based mainly upon signalment, history, and supportive clinical findings. Electrodiagnostic tests and muscle/nerve biopsies may or may not support the diagnosis. CSF analysis may be normal or may have mild elevations of cells and/or protein levels.
   d. The prognosis for recovery is poor.

8. Trigeminal neuritis[23, 28, 50, 51, 167, 257, 261, 287]
   a. An idiopathic, bilateral, nonsuppurative inflammation of all motor branches of CN V (principally demyelination with some axonal loss) has been reported in both dogs (primarily) and cats. The pathogenesis is unknown, but an etiology is suspected.
   b. The typical clinical picture is acute onset of jaw paralysis, with an inability to close the jaw (Fig. 17.11). This occurs most commonly in adult (often older) animals. Most patients retain the ability to swallow, but mild dysphagia is occasionally observed. Unilateral Horner's syndrome has also been reported, presumably due to involvement of the postganglionic sympathetic fibers that travel with the ophthalmic branch of CN V. Facial sensation is normal in the majority of cases; however, unilateral or bilateral facial sensory deficits are possible. There is one case report of a young dog with purely sensory trigeminal neuropathy of unknown etiology. A variable degree of neurogenic atrophy of the masticatory muscles may develop. Although a dropped jaw is characteristic, trismus has been observed in some cases.
   c. A tentative diagnosis is based upon the typical clinical features of the disease. EMG and muscle biopsy results will support the diagnosis, but are often not pursued. Magnetic resonance imaging (MRI) may also be used to differentiate trigeminal neuritis from an MNST of the trigeminal nerve, particularly in dogs with unilateral nerve involvement. Other diseases that may affect the trigeminal nerves and/or masticatory muscles should be ruled out. In particular, multiple cranial nerve mononeuropathy due to mononuclear cell neoplasia (lymphosarcoma, myelomonocytic cancer) should be considered as a differential diagnosis, especially if clinical signs do not resolve within several weeks. Obtaining a vaccination history is important, as rabies can present with a similar clinical picture (i.e. dropped jaw). In masticatory myositis (see Chapter 18), trismus is the typical presentation, rather than a dropped jaw.
   d. This is a self-limiting disease, and most patients recover fully within 2–3 wks. Glucocorticoid therapy has been advocated early in the course of the disease, but there is little evidence of efficacy. Although glucocorticoid treatment of dogs with trigeminal neuritis is not contraindicated, such therapy may diminish subsequent responsiveness to combination chemotherapy in dogs whose trigeminal nerve dysfunction is due to mononuclear cell neoplasia. Some patients may have to be hand fed, or fed through a pharyngostomy, esophagostomy, or gastrostomy tube (i.e. those patients with dysphagia) during recovery.

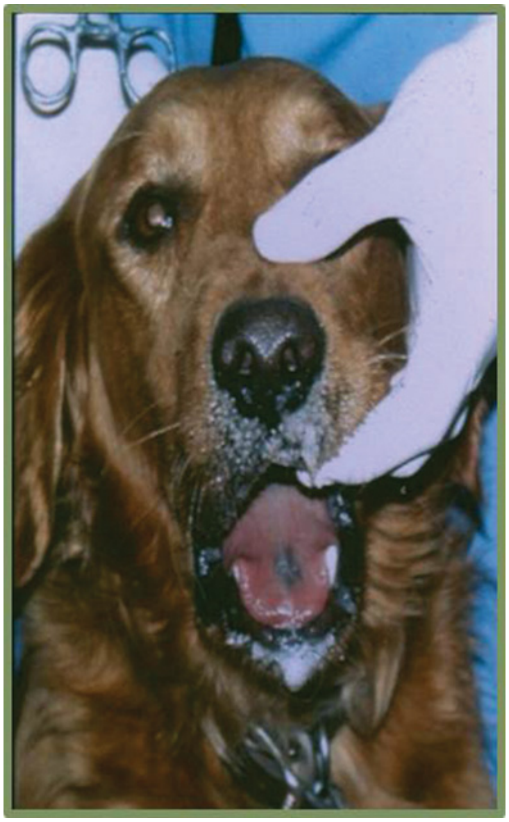

Figure 17.11 Dog with trigeminal neuritis and inability to close the jaw.

9. Hemifacial spasm[92, 114, 266]
   a. A rarely reported hyperactivity of the facial nerve in dogs and cats, this disorder probably reflects a secondary irritation of the facial nucleus and/or nerve. Potential diseases that could cause irritation include otitis media (facial nerve) or brain-stem disease (facial nucleus and/or nerve), such as neoplasia, or infectious/inflammatory disorders (e.g. GME).

  - **b.** The affected patient typically has an asymmetric facial countenance, with the nose and lips pulled toward the affected side. A small palpebral fissure with blepharospasm and a slightly elevated ear may also be appreciated on the affected side.
  - **c.** Diagnosis is based upon clinical signs. This syndrome can be confused with secondary facial muscle contracture due to prior facial nerve paralysis. The treatment and prognosis depend upon the underlying cause of the hyperirritability.

F. Ischemic: Ischemic neuromyopathy[23, 28, 99, 103, 314]

This is an ischemic insult due to vascular occlusion of the arterial supply to the limbs by an embolus. Both pelvic limbs are typically affected. This is usually reported in cats in association with cardiomyopathy, but has also been reported in dogs with a variety of underlying disorders. The vascular occlusion and resultant inflammatory mediators (which impair collateral circulation) result in damage to both peripheral nerves and muscles of the affected limbs. This disorder is discussed in more detail in Chapter 18.

G. Traumatic[7–9, 11, 12, 26, 28, 53, 55, 57, 94, 96, 99, 100, 103, 113, 128, 132, 133, 136, 141, 145, 153, 180, 195, 202, 232, 245, 260, 267, 281, 293, 301, 303, 306, 307, 309, 314, 319, 322, 344, 349] (Video 37)

1. Traumatic neuropathies are common in dogs and cats, and most often are a result of automobile accidents. Some of these neuropathies may be associated with fractures. Sciatic nerve injury occurs occasionally with pelvic fracture/luxations, especially sacroiliac luxations, sacral wing, caudal acetabular, and ischial fractures. The sciatic nerve may be injured at the time of trauma, or may be progressively compressed during the bone-healing process by proliferating connective tissue. Sciatic nerve entrapment by osteophytes associated with hip dysplasia has been reported in dogs, but is considered a rare phenomenon. Radial nerve injury may occur with humeral fractures, but it is extremely uncommon.

Extremity injuries may be complicated by osteofascial compartment syndrome or reflex sympathetic dystrophy, infrequent trauma-related phenomena that involve peripheral nerves. Osteofascial compartment syndrome occurs when hemorrhage and/or edema accumulate within a closed space whose borders are made up of skeletal muscle fascia or bone (osteofascial compartment). If the resultant pressure rise within the compartment is of sufficient magnitude and duration, damage to both muscle and nerve within that compartment may occur. Reflex sympathetic dystrophy is a poorly understood phenomenon, usually associated with extremity trauma, in which the affected limb becomes very painful and exhibits various autonomic abnormalities (e.g. edema, increase or decrease in temperature, sweating). This syndrome typically occurs weeks after the traumatic event in people and is thought to be mediated by the sympathetic nervous system. Reflex sympathetic dystrophy has been reported in the dog.

Most traumatic neuropathies are traction injuries, with no evidence of orthopedic problems (e.g. brachial plexus avulsion). Brachial plexus injury is commonly encountered in dogs and cats, and is thought to be caused by severe abduction and/or traction of the thoracic limb. These injuries may be partial or complete. Avulsion of the nerve roots appears to be a common form of brachial plexus injury, perhaps due to the lack of a perineurium over the nerve roots. The avulsions are typically intradural, in close proximity to the spinal cord. Ipsilateral Horner's syndrome and lack of a cutaneous trunci reflex often accompany brachial plexus avulsions, because of damage to the T1–T3 and C8–T1 roots, respectively. Other causes of traumatic neuropathies include missile injuries (e.g. gunshot wounds), bite wounds, and iatrogenic causes (e.g. inadvertent surgical trauma, injection injuries to the sciatic nerve). Iatrogenic injury is most common following pelvic surgeries, including iliosacral luxation repair, femoral fracture repair, perineal herniorrhaphy, or tibial plateau-leveling osteotomies. Entrapment of the sciatic nerve during forward positioning of the hindlimbs for perineal surgery has also been reported.

There are three general classes of peripheral nerve injury. From least severe to most severe, these are:

- **a.** Class 1 (Neurapraxia)—this refers to a transient lack of nerve function, with little or no structural damage to the axons or their supportive connective tissue structures. This temporary dysfunction may be due to ischemia (no structural damage) and/or mild paranodal demyelination. The degree of motor and proprioceptive dysfunction is variable, but nociceptive function is preserved for the most part (large-diameter axons are preferentially affected). Spontaneous recovery is expected within days to a month, depending upon the degree of demyelination. Neurogenic muscle atrophy is unlikely, as the axons are structurally intact.
- **b.** Class 2 (Axonotmesis)—in this type of injury, some or all of the axons of the nerve are disrupted structurally, but the connective tissue support (e.g. Schwann cell basal lamina, endoneurium) remains intact. These axons can regrow along the connective tissue scaffold. Substantial motor, proprioceptive, and nociceptive dysfunction is expected with this type of injury, the extent of which depends on the number of axons damaged. Neurogenic muscle atrophy is likely with this class of injury.
- **c.** Class 3 (Neurotmesis)—this class of injury reflects complete severance of the axons of the nerve, as well as the connective tissue support. These axons will not regrow (no guiding scaffold) without surgical intervention. Complete motor, proprioceptive, and nociceptive (i.e. no pain perception) dysfunction occurs

with this class of injury. Neurogenic muscle atrophy is to be expected. Note that a severe class 2 injury may be clinically indistinguishable from a class 3 injury.

2. Localization of peripheral nerve injuries and estimation of their severity is important both for deciding on treatment options and for judging prognosis. Cutaneous sensation can be utilized as a clinical tool in localizing peripheral nerve lesions. Autonomous zones are those sensory areas of the skin supplied only by a particular nerve (e.g. the dorsal aspect of the metacarpus is innervated by the radial nerve). The clinician should be aware of these autonomous zones (Fig. 17.12). With brachial plexus injuries, there may be inconsistency in the patterns of sensory versus motor deficits, as the ventral nerve roots appear to be more susceptible to damage than the dorsal nerve roots. Electrodiagnostic tests can be used both for localizing purposes and for providing prognostic information in some peripheral nerve injuries. These tests should be performed a minimum of 5–7 days post injury, as severed nerves will still conduct impulses, and denervated muscle may still be electrically silent prior to this period. MRI may also be helpful in the early recognition of nerve injury and regeneration. Experimental evidence in rats has shown T2 hyperintensities within damaged sciatic nerves within 24 hrs of injury, preceding electromyographic changes. Resolution of this T2 hyperintensity followed improvements in nerve function, as determined by electrophysiologic testing. However, MRI characteristics of nerve injury in dogs and cats is not yet available.
3. In most cases of peripheral nerve trauma, there is no specific treatment that will affect outcome. However, there are some instances (e.g. nerve anastomosis with isolated distal nerve injury, surgical repair of a fracture causing secondary nerve trauma, corrective tendon transposition, or joint fusion in partial brachial plexus injuries) in which accurate estimation of the location and severity of nerve trauma may assist in choosing what therapeutic course should be taken. Successful repair of injured peroneal and tibial nerves with cutaneous saphenous nerve grafts has been reported in a dog. Grafted nerve segments should be similar in width to the injured nerve(s). Experimental evidence of regeneration of chronically denervated peripheral nerves with the aid of transplanted neural stem cells has been described.

   The prognosis for the recovery of function following sciatic nerve injury is guarded. In one report of 27 dogs with iatrogenic injury of this nerve, only 13 patients recovered fully with treatment. Clinical improvement was seen in seven dogs, while seven remained unchanged 1 yr after surgical correction and/or nerve transplantation. The prognosis for most brachial plexus injuries is poor for the functional return of the limb. The majority of brachial plexus injuries are complete avulsions. The second most common scenario is damage to the caudal area of the plexus, including the contribution to the radial nerve. Cranial plexus injuries, which carry the most favorable prognosis (preservation of weight-bearing function), are rarely encountered. There is no chance of improvement with nerve root avulsion, but there may be improvement if the roots are still intact. It may be difficult or impossible to tell in many cases whether the nerve injury is permanent. In one report of 30 brachial plexus injuries, only eight dogs achieved functional limb recovery 4 mos or more following the injury. Preservation or return of triceps function is a favorable prognostic indicator for brachial plexus injuries. In general, the lack of deep pain perception to the toes is a poor prognostic indicator. Physical therapy for the affected thoracic limb and waiting several months for some return to function are indicated, before considering amputation. However, if self-mutilation due to paresthesia/dysesthesia or severely infected abrasions (due to dragging the foot without adequate protective covering) develop within that time, amputation may be indicated at an earlier date. The location of a class 2 or class 3 injury may also affect the prognosis. Axons regrow at a rate of 1–4 mm per day. In people, muscle motor endplate degeneration may occur if the damaged nerve does not reestablish contact with the muscle within 18 mos. So, with a very proximal injury, the prognosis may be poor, even if axonal regeneration occurs. Despite the unfavorable outlook for functional return with most brachial plexus injuries, most dogs and cats function extremely well with three legs.

H. Toxic
   1. Thallium poisoning[26, 28, 59, 99, 314, 338, 360, 361]
      a. This heavy metal is found in rodenticide preparations that are currently banned from use. Although the incidence is now quite low, dogs and cats will still occasionally ingest thallium-poisoned rodents and develop signs of toxicity.
      b. In addition to gastrointestinal, respiratory, and cutaneous signs of toxicity, neurologic dysfunction may be observed with thallium ingestion. Since thallium affects both the CNS and PNS, it may be difficult to discern which clinical signs are due to peripheral nerve damage and which to brain or spinal cord dysfunction. Clinical signs of neurologic dysfunction with thallium toxicity can include seizures, dementia, hyperesthesia, tremors, ataxic gait, and paraparesis or paraplegia.
      c. The tentative diagnosis of thallium toxicity is based upon a history of possible exposure in a patient with signs of toxicity. Finding thallium in the patient's urine confirms the diagnosis.
      d. If ingestion is known to have occurred within an 8-hr period, the treatment is induction of vomiting and administering activated charcoal. After this, the treatment consists of oral Prussian blue and potassium chloride as well as supportive care. The prognosis is guarded.

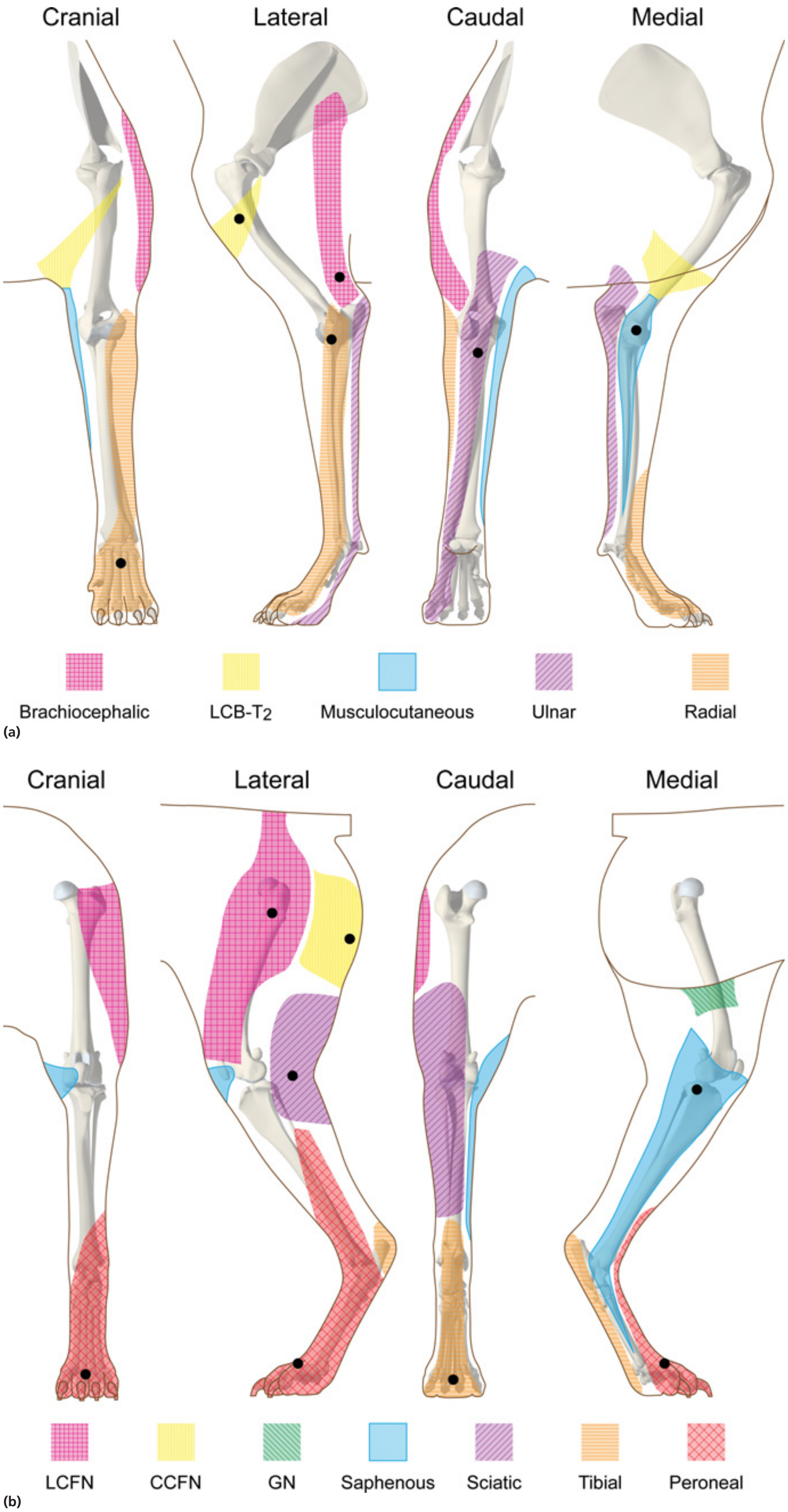
Cranial
Lateral
Caudal
Medial
Brachiocephalic
LCB-T2
Musculocutaneous
Ulnar
Radial
(a)
Cranial
Lateral
Caudal
Medial
LCFN
CCFN
GN
Saphenous
Sciatic
Tibial
Peroneal
(b)

Figure 17.12 (A) Schematic illustration of the cutaneous innervation of the left thoracic limb of the dog. Autonomous zones, innervated by only one nerve, are shown along with recommended sites for testing of sensation (dots). The median nerve does not have an autonomous zone. LCB–T2, lateral cutaneous branch of the second thoracic nerve. (Adapted from Kitchell *et al.*, 1982.[195] Redrawn by the Ohio State University. Reproduced with permission from the Ohio State University.) (B) Cutaneous innervation of the right pelvic limb of the dog. Autonomous zones and testing sites are shown as in A. LCFN (lateral cutaneous femoral nerve) L3, L4, (L5); CCFN (caudal cutaneous femoral nerve) (L7), S1–S2; GN, genitofemoral nerve L(2), L3–L4, areas of innervation and the autonomous zones (black dots) of the dog. (Adapted from Kitchell *et al.*, 1982.[195] Redrawn by the Ohio State University. Reproduced with permission from the Ohio State University.)

2. Pyridoxine poisoning[99, 164, 200, 314]
   a. Massive doses of vitamin B_6 can cause a sensory neuropathy in dogs.
   b. Clinical signs of toxicity include ataxia (especially in the pelvic limbs), dysmetria, and decreased conscious proprioception. There is usually no evidence of paresis.
   c. Diagnosis is based upon characteristic clinical signs in a patient receiving megadoses of pyridoxine.
   d. Treatment is discontinuation of pyridoxine supplementation. The prognosis for the resolution of the sensory deficits is unknown.
3. Vincristine neuropathy[26, 28, 59, 99, 142, 314]
   a. This alkaloid antineoplastic agent commonly causes neuropathies in humans, and has been shown both experimentally and clinically to cause neuropathies in dogs and cats. The suspected mechanism is impairment of axonal transport due to breakdown of neurotubules.
   b. Clinical signs include varying degrees of motor and sensory deficits to the limbs. Experimentally, cats develop an LMN paraplegia. A recent report of a dog with vincristine neurotoxicity described an ataxic gait with decreased proprioception and spinal reflexes in the pelvic limbs.
   c. Diagnosis is based on clinical signs of a neuropathy in a patient receiving vincristine, as well as confirmatory results of electrodiagnostic tests and muscle/nerve biopsies. Resolution of the neuropathy after vincristine discontinuation is important to distinguish vincristine as the cause of the disorder, rather than it representing a paraneoplastic neuropathy.
   d. Treatment is discontinuation of vincristine administration. The neuropathy will likely resolve with time.
4. Delayed organophosphate toxicity in cats[26, 28, 47, 59, 175, 209, 220, 285, 314]
   a. A polyneuropathy associated with prolonged exposure to chlorpyrifos has been described in cats. The mechanism by which the organophosphate causes the neuropathy is unknown.
   b. The reported cats exhibited varying degrees of decreased thoracic and pelvic limb proprioception, decreased spinal reflexes, generalized hyperesthesia, and paraparesis. Bilaterally dilated pupils (partially responsive to light) were also reported.
   c. Diagnosis in the reported cases was based upon history (exposure to organophosphates), decreased serum cholinesterase activity, neurologic examination findings, and an abnormal EMG.
   d. Treatment consisted of intravenous pralidoxime (2-PAM) and subcutaneous atropine. The cats recovered completely.
5. Walker Hound mononeuropathy[28, 178, 314]
   a. An unusual neuropathy involving the peroneal and tibial nerves of one pelvic limb has been described in unweaned Walker Hound puppies. There was degeneration of both axons and myelin in the peroneal and tibial nerves. The cause is undetermined, but a toxic agent in well water used to prepare milk replacement is suspected.
   b. Clinical signs occurred at approximately 2 wks of age and included paresis, lack of proprioception, absent spinal reflexes, muscle atrophy, and analgesia (except on the medial aspect of the limb), all in one pelvic limb. Progressive signs of worsening paresis as well as automutilation of the affected limb occurred over a 6-wk period.
   c. Diagnosis is based upon history, signalment, clinical findings, and results of histopathologic evaluation. All of the reported puppies were euthanized due to the progressive nature of the disease.
6. Salinomycin toxicity in cats[59, 99, 327, 343, 345]
   a. A severe polyneuropathy has been reported in cats in the United Kingdom and the Netherlands that had eaten food contaminated with salinomycin, the chickenfeed ionophore coccidiostat.
   b. An acute, progressive polyneuropathy occurred in affected cats. Clinical signs of neurologic dysfunction included paraparesis, tetraparesis, dysphagia, dyspnea, and generalized muscle atrophy. Paralysis of the pelvic limbs characteristically developed initially, followed by paralysis of the thoracic limbs.
   c. Diagnosis was based on clinical signs consistent with a polyneuropathy in cats exposed to food contaminated with salinomycin. Evidence of a distal axonopathy affecting both motor and sensory nerves was evident on a histopathologic evaluation of nerve samples.
   d. Many of the earliest reported cases were euthanized due to disease severity. However, removal of contaminated food and provision of supportive therapy is likely to lead to a full neurologic recovery in the majority of affected cats.

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Video Resources

Video resources are available on the companion website: www.wiley.com/go/dewey/neurology

See videos 13, 33, 34, 35, 36 and 37.

CHAPTER 18

Myopathies: Disorders of Skeletal Muscle

Curtis W. Dewey & Lauren R. Talarico

Introduction[8, 36, 40, 44, 61, 102, 141, 179, 214, 232, 301, 315]

Skeletal muscle is the effector organ for the somatic motor nervous system. In general, clinical signs of skeletal muscle dysfunction include weakness with preservation of sensory function—e.g. nociception (deep pain perception), proprioception—muscle atrophy, and muscle pain (myalgia). In some diseases, muscle hypertrophy is present rather than atrophy. Also, myalgia is not a feature of some myopathies.

Skeletal muscle is composed of multinucleated cells termed "myofibers" that are arranged in bundles called "fascicles." Each myofiber is innervated by an axonal process of a motor neuron at a specialized area of the sarcolemma (muscle cell plasma membrane) called the endplate (see Chapter 19). The myofibers contain the contractile apparatus, which comprises interlocking myofilaments (actin, myosin, troponin, tropomyosin). Muscle contraction occurs when calcium is released from the sarcoplasmic reticulum (the myofiber endoplasmic reticulum) following sodium influx into the myofiber (depolarization). Adenosine triphosphate (ATP) is required for the coordinated contraction and relaxation of the muscle fiber. A muscle enzyme called creatine kinase (CK) is required to immediately replenish ATP from adenosine diphosphate (ADP) by cleaving a high-energy phosphate group from the compound phosphocreatine, also found in the myofiber.

There are two main types of myofibers, differentiated upon the intensity of histochemical staining at different pHs (Fig. 18.1) with the ATPase reaction (muscle biopsy samples). Type I fibers are "slow-twitch" (relatively high levels of oxidative enzymes and lipid, low glycogen content) fibers and type II fibers are "fast-twitch" (relatively high levels of glycogen, lesser amounts of oxidative enzymes and lipid) fibers. A uniquely staining fiber type is also found only in masticatory muscle, called type IIM. One motor neuron will innervate a number of myofibers within a fascicle, and the fiber types of those myofibers will all be the same. The motor neuron and the myofibers it innervates comprise what is called a motor unit. The motor neuron dictates the fiber type of the myofibers of its motor unit. The myofibers of a single motor unit are normally scattered through a fascicle, giving a "checkerboard" appearance to the stained biopsy sample.

In some cases, it will be difficult to clinically discern a myopathy from a neuropathy or neuromuscular junction disorder. A diagnosis of myopathy is based upon neurologic examination findings as well as specific diagnostic tests. Typical diagnostic tests to pursue when a myopathy is suspected include serum CK measurement (elevations suggest muscle damage), and electrodiagnostics (remember that electromyographic [EMG] abnormalities can be seen with neuropathies and myopathies). However, these tests may yield abnormal results for reasons unrelated to neuromuscular disease. In particular, CK activity may be elevated in anorexic cats. Historical information, examination findings, and a decrease in CK activity with nutritional support may be used to help differentiate this elevation from that seen in neuromuscular disease. Muscle and/or nerve biopsies can be very helpful in elucidating the cause of a peripheral nervous system disorder. In addition to the ATPase reaction, there is a barrage of histochemical stains and reactions that can be applied to cryosections of properly frozen muscle biopsies to help characterize the nature of the muscle disorder (Fig. 18.2 to Fig. 18.9). A summary of myopathies of dogs and cats is shown in Table 18.1.

Fig. 18.2 is of hematoxylin and eosin (H&E) stained muscle cryosections showing a large pale staining necrotic fiber. H&E staining is used for the evaluation of general morphology. Fig. 18.3 is of modified Gömöri trichrome stained cryosections showing a prominent intramuscular nerve branch. Myelin stains pink with this stain. The modified Gömöri trichrome stain is a good general morphological stain, highlights intramuscular nerve branches and stains nemaline rods, and identifies ragged red-like fibers.

Fig. 18.4 shows staining with periodic acid-Schiff highlights glycogen or polysaccharide deposits that would suggest a glycogen or polysaccharide storage disorder. Note the figure has a glycogen deposit within a muscle fiber that is stained dark purple. Fig. 18.5 is of a nicotinamide adenine dinucleotide reductase reaction that identifies mitochondrial accumulations and tubular aggregates. In this muscle section, dark-blue reactions are

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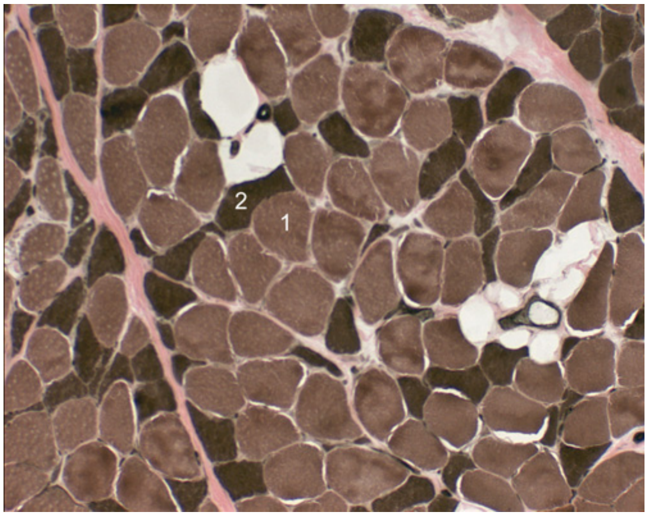


Figure 18.1 Cryosections from the vastus lateralis muscle reacted with myofibrillar ATPase at pH 9.8 shows type I fibers stained lightly and type II fibers stained dark. Type II fiber atrophy is present, consistent with an endocrine disorder such as hypothyroidism, or Cushing's syndrome. (G. Diane Shelton, University of California, La Jolla, CA, 2014. Reproduced with permission from G. Diane Shelton.)

present under the sarcolemma and extend into the sarcoplasm, consistent with lobulated fibers.

Fig. 18.6 demonstrates the oil red O stain that localizes the presence of lipid droplets composed of neutral triglycerides within muscle fibers supporting a metabolic myopathy which may be mitochondrial in origin, or resulting from a defect in fatty acid oxidation or carnitine metabolism. Fig. 18.7 shows how cryosections react with esterase to highlight large numbers of macrophages in a necrotizing myopathy. Esterase stains lysosomal accumulations in macrophages and also in degenerating muscle fibers. Fig. 18.8 shows the cryosection reaction highlighting the motor endplates. The acid phosphatase reaction also highlights increased lysosomal activity in macrophages and within muscle fibers (Fig. 18.9; note in this cryosection the red stained areas within macrophages).

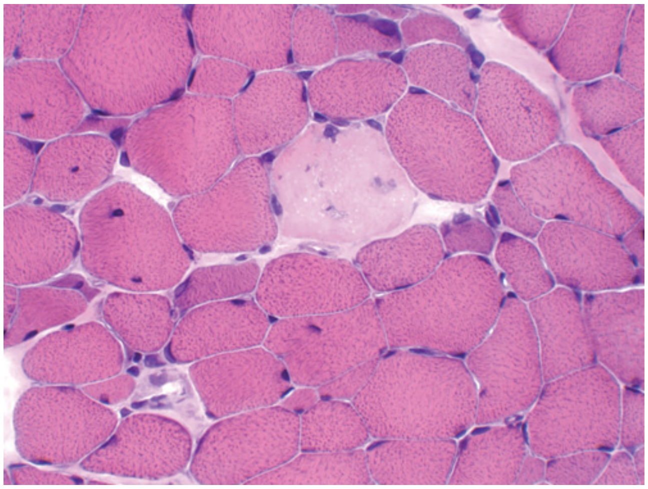


Figure 18.2 Hematoxylin and eosin stain muscle cryosections. (G Diane Shelton, University of California, La Jolla, CA, 2014. Reproduced with permission from G Diane Shelton.)

The immunoreagent Staphylococcal protein A-horseradish peroxidase identifies circulating serum antibodies that bind to the sarcolemma, to myofibers, to muscle nuclei in cases with anti-nuclear antibodies and to motor endplates in cases of myasthenia gravis following incubation of muscle cryosections with patient serum (Fig. 18.10). In the figure, distinct sarcolemmal labeling can be seen that is consistent with antibodies against an unidentified sarcolemmal protein(s) in a dog with polymyositis.

Table 18.1 Myopathies of dogs and cats.

Degenerative/ Developmental	Metabolic	Inflammatory/Infectious	Ischemic	Traumatic
Muscular dystrophy	Hypokalemic myopathy	Masticatory myositis	Ischemic neuromyopathy	Infraspinatus contracture
Centronuclear myopathy	Hyperkalemic periodic paralysis	Extraocular myositis		Iliopsoas muscle injury
Exercise intolerance and collapse of Labrador Retrievers	Hyperadrenocorticoid (Cushing's) myopathy	Laryngeal/pharyngeal myositis		Quadriceps contracture
Distal myopathy of Rottweilers	Hypothyroid myopathy	Autoimmune polymyositis		Coccygeal muscle injury
Myotonia congenita	Malignant hyperthermia	Dermatomyositis		
Fibrotic myopathy	Exertional myopathy	Feline hyperesthesia syndrome		
Nemaline myopathy	Lipid storage/mitochondrial myopathies	Infectious myositis		
Myositis ossificans (fibrodysplasia ossificans progressiva)	Glycogen storage disorders (glycogenoses)	Tetanus		
Pharyngeal/esophageal dysfunction of Bouviers				
Polysystemic disorder of English Springer Spaniels				
Cricopharyngeal achalasia				
Episodic muscle hypertonicity ("cramp")				
Myokymia and neuromyotonia				

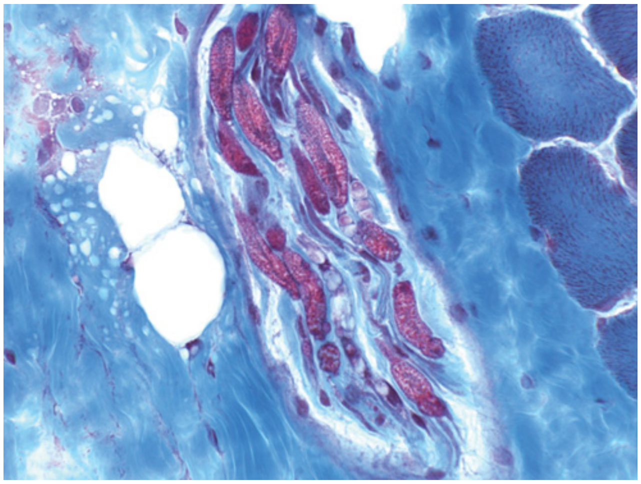


Figure 18.3 Modified Gömöri trichrome stained cryosections. (G Diane Shelton, University of California, La Jolla, CA, 2014. Reproduced with permission from G Diane Shelton.)

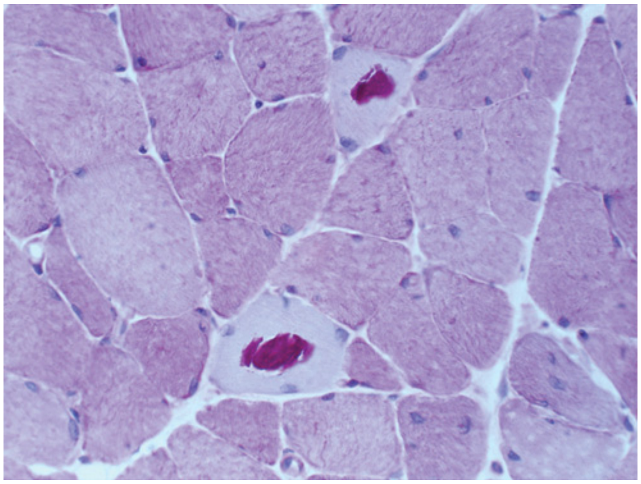


Figure 18.4 Staining with periodic acid-Schiff. (G Diane Shelton, University of California, La Jolla, CA, 2014. Reproduced with permission from G Diane Shelton.)

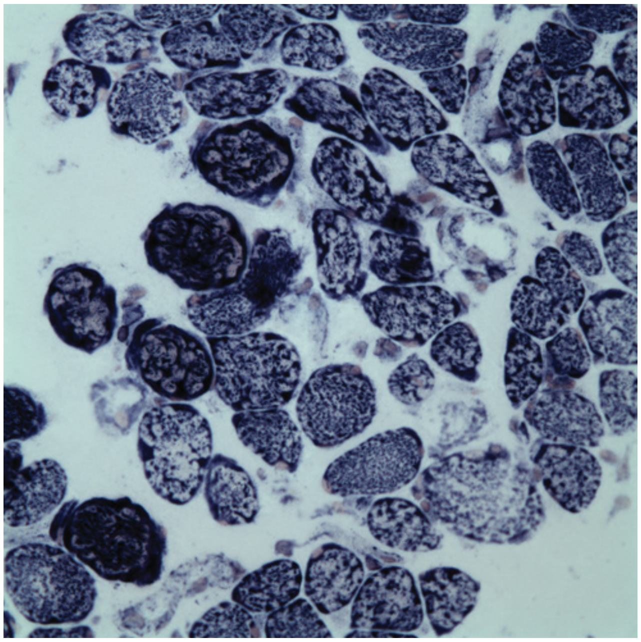


Figure 18.5 Nicotinamide adenine dinucleotide reductase reaction. (G Diane Shelton, University of California, La Jolla, CA, 2014. Reproduced with permission from G Diane Shelton.)

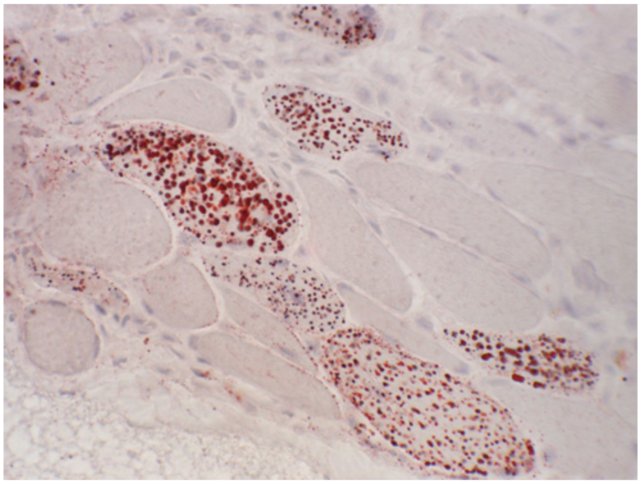


Figure 18.6 Oil red O stain. (G Diane Shelton, University of California, La Jolla, CA, 2014. Reproduced with permission from G Diane Shelton.)

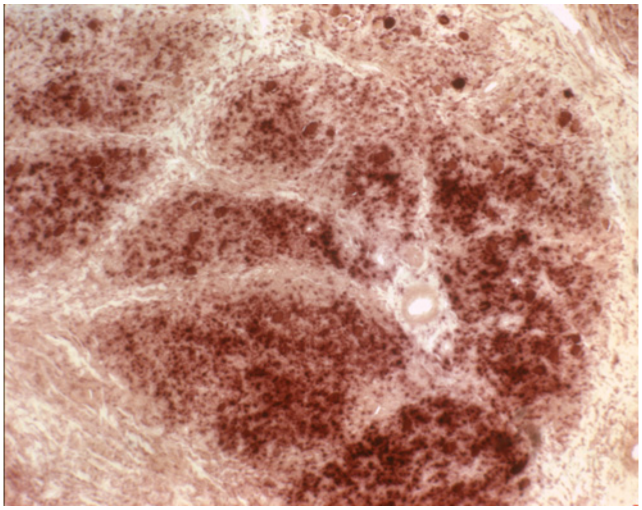


Figure 18.7 Cryosections reacting with esterase. (G Diane Shelton, University of California, La Jolla, CA, 2014. Reproduced with permission from G Diane Shelton.)

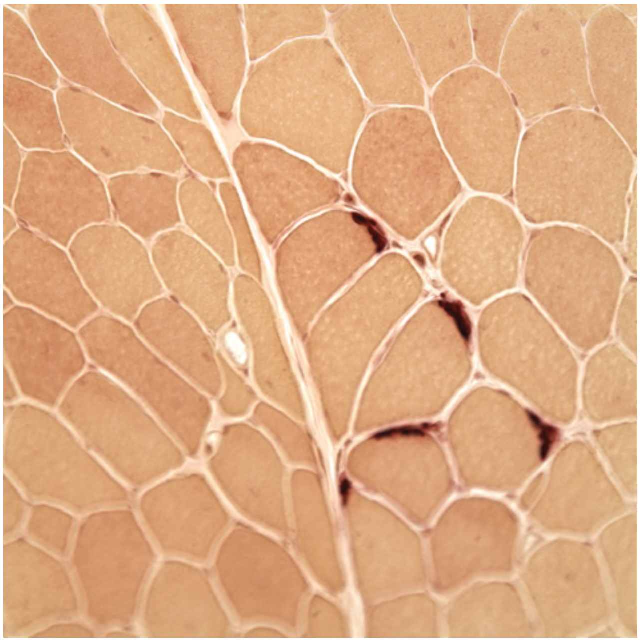


Figure 18.8 Cryosections reacting with esterase highlight the dark reddish brown stained motor endplates.

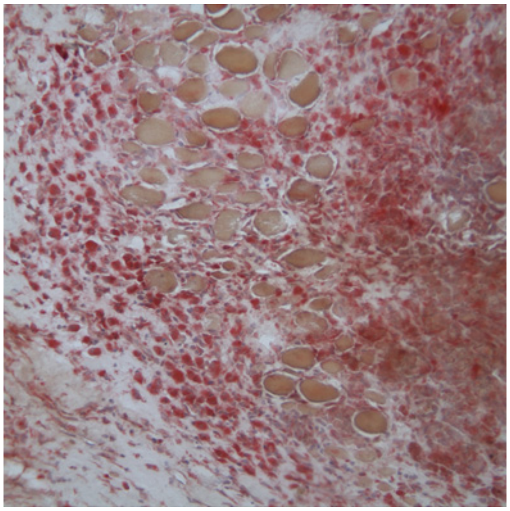


Figure 18.9 Acid phosphatase reaction. (G Diane Shelton, University of California, La Jolla, CA, 2014. Reproduced with permission from G Diane Shelton.)

Disorders of skeletal muscle in dogs and cats

A. Degenerative/developmental
   1. Muscular dystrophy (MD)[8, 15, 27, 53, 57, 58, 62, 64, 69, 71, 81, 83, 85, 95, 105, 110, 111, 118, 130, 148, 155, 156, 164, 165, 169, 176, 177, 179–181, 186, 190, 201, 235, 241, 245–248, 254, 258, 262, 288, 293, 295, 297, 301, 303–305, 310, 314, 333, 334, 337, 338, 346, 349, 354, 355, 357, 360, 365]

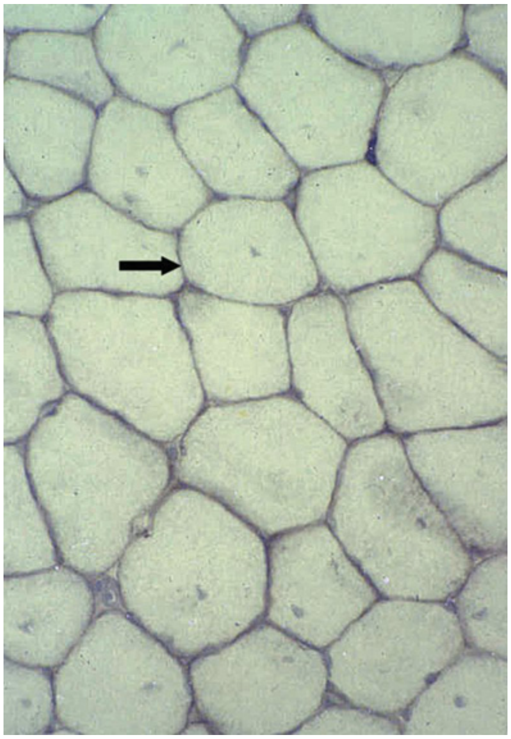


Figure 18.10 Immunoreagent Staphylococcal protein A-horseradish peroxidase. (G Diane Shelton, University of California, La Jolla, CA, 2014. Reproduced with permission from G Diane Shelton.)

a. The term “muscular dystrophy” refers to a wide variety of inherited myopathies with specific defects of skeletal muscle proteins. The most common form of MD in both humans and animals is associated with the sarcolemmal protein dystrophin. Dystrophin is located on the X-chromosome and thus is an X-linked disorder (X-linked muscular dystrophy, or XLMD). Dystrophin is thought to have an important structural role for myofibers and may also serve a vital role in cellular homeostasis, possibly as a regulator of intracellular calcium transport.

   X-linked dystrophin-deficient muscular dystrophies in dogs and cats are believed to be the veterinary analogs of Duchenne and Becker muscular dystrophy of humans, and have been described in various dog breeds (Golden Retriever, Rottweiler, German Shorthaired Pointer, Irish Terrier, Samoyed, Belgian Shepherd (Groenendael), Miniature Schnauzer, Rat Terrier, Wire-haired Fox Terrier, Samoyed, Brittany Spaniel, Japanese Spitz, Weimaraner, Labrador Retriever, Old English Sheepdog, Grand Basset Griffon Vendéen, Corgi) and cats (domestic shorthair, Siamese, Maine Coon). Specific gene mutations have been defined in Golden Retrievers, German Shorthaired Pointers, Cavalier King Charles Spaniels, Japanese Spitz dogs and Rottweilers. Progressive muscle atrophy predominates in dogs (although some muscle groups tend to hypertrophy), whereas muscle hypertrophy is the hallmark of XLMD in cats. The pathologic change in affected muscle is characterized histologically by variation in myofiber size (including both degenerating and regenerating myofibers), with necrosis and mineralization of myofibers (Fig. 18.11). A number of dystrophin-associated proteins (e.g. sarcoglycans, dystroglycans), as well as laminins (basement membrane proteins) may also be deficient in other forms of MD.

b. Dystrophin-deficient muscular dystrophy is best described in the Golden Retriever. Marked elevations in serum CK activity detected during the first few weeks of life are a hallmark of this disease. Clinical signs of partial trismus and a “bunny-hopping” gait may be appreciated as early as 6 wks of age in male puppies. Although MD is largely restricted to males, it has been reported in female dogs. Additionally, female carriers of dystrophin mutations often show elevations in their serum CK activities, without significant clinical disease. In affected dogs signs typically progress over 3–6 mos, after which time the disease often stabilizes. Common clinical signs include progressive muscle atrophy of the limbs, head, and trunk, exercise intolerance, a stilted gait, plantigrade stance (with associated tarsal joint

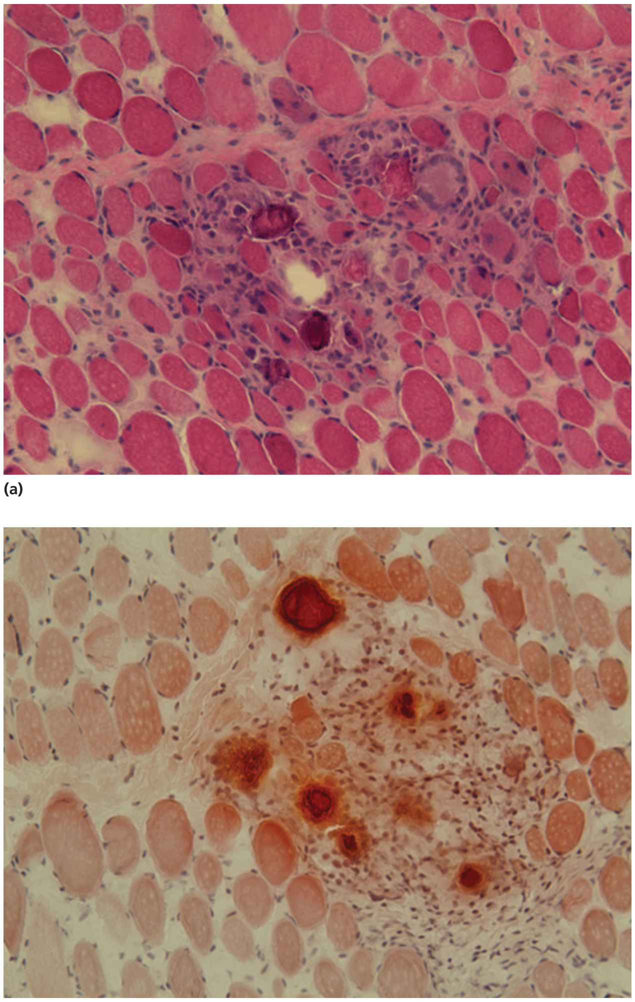


Figure 18.11 H&E (A) and alizarin red (B) stained muscle biopsy specimens from a dog with Duchenne muscular dystrophy. In A, a wide variation in muscle fiber size can be appreciated, and in B, there is evidence of intracellular calcium accumulation. (G. Diane Shelton, University of California, La Jolla, CA, 2014. Reproduced with permission from G. Diane Shelton.)

contracture), excessive salivation (pharyngeal dysfunction), weak bark (dysphonia), kyphosis that progresses to lordosis, and hypertrophy of the muscles of the base of the tongue. Proximal limb muscles, particularly the cranial sartorius muscle, may undergo hypertrophy in some dogs. Dysphagia and exercise-induced myalgia may present as sole clinical findings initially, prior to the onset of generalized weakness. Hiatal hernia and gastroesophageal reflux can be seen clinically, secondary to diaphragmatic and esophageal dystrophy, respectively. Spinal reflexes are normal initially but may become decreased due to muscle fibrosis. Inhalation pneumonia from pharyngeal/esophageal dysfunction and heart failure due to cardiomyopathy have also been reported. Uncommonly, some puppies display a more fulminant form of MD, and die within 10 days of birth.

There appears to be considerable variation in time of disease onset and severity of clinical signs in cats with XLMD. Although affected cats may exhibit characteristic signs, such as a "bunny-hopping" pelvic limb gait in the first months of life, they may also have mild or inapparent clinical signs of myopathy until approximately 2 yrs of age. Progressive "stiffness" in gait and muscle hypertrophy are prominent features of MD in cats, in contrast to the weakness and atrophy characteristic of the canine disorder. Stress may induce open-mouthed breathing and/or syncopal episodes in cats with MD, presumably due to a combination of cardiac and respiratory muscle involvement. A form of MD associated with laminin alpha 2 deficiency (normal dystrophin) has been described in two young female cats (Siamese and domestic shorthair). These cats exhibited progressive muscle atrophy and weakness, beginning in the pelvic limbs, at approximately 5–6 mos of age. Spinal reflexes were depressed to absent. Both cats progressed to nonambulatory status over 6–12 mos.

c. A diagnosis of MD is based upon signalment, characteristic clinical findings, marked serum CK elevations (often over 10,000 Units/L), bizarre high-frequency discharges on electromyograph, and muscle biopsy results (myofiber degeneration/regeneration with or without mineralization). Overall, the degree of elevation of CK in affected dogs does not correlate to the severity of their clinical signs. Serum CK levels in female dogs with MD have been less dramatically elevated compared with most males with the disorder. Cats with dystrophin-deficient muscular dystrophy frequently show myotonic discharges and fibrillation potentials on EMG evaluation, particularly in the proximal appendicular muscles. Motor nerve conduction studies remain normal. A lack or absence of dystrophin can be demonstrated immunocytochemically on a muscle biopsy specimen or by western blot analysis. Occasionally, dystrophin-associated proteins and laminins may also be deficient, with or without obvious lack of muscle dystrophin. Muscles of affected Golden Retrievers undergo fibrosis earlier than in other affected breeds, a process that appears to be cytokine-driven.

Golden Retrievers with MD may show consistent abnormalities on thoracic and pelvic radiographs. Diaphragmatic asymmetry, with an undulating pattern and either left crural flattening or ventral displacement, may be seen on thoracic radiographs, and can be accompanied by a hiatal hernia. Characteristic pelvic radiographic abnormalities include narrowing of the body of the ilia, ventral deviation of the tuber ischii, elongation of the obturator foramina, and lateral elongation of the wings of the ilia. The pelvis is overall tilted vertically, narrowed, and elongated. These pelvic changes may be secondary to myopathy-induced contractures resulting in bone remodeling and appear to be specific to the form of MD seen in Golden Retrievers. Cats with MD may develop marked diaphragmatic hypertrophy, with megaesophagus seen secondary to esophageal stricture.

d. There is no definitive treatment for and of the muscular dystrophies. Some patients may have an unexplained positive response when treated with glucocorticoids. Golden Retrievers with this disorder treated with daily prednisone therapy experience a combination of functional improvement but histopathologic deterioration. Growth hormone has been used clinically in human patients to decrease the severity of Duchenne muscular dystrophy. Additionally, lower IGF-1 concentrations (used as a measure of growth hormone) have been related to more severe forms of MD in Golden Retriever dogs. However, supplementation of growth hormone in such dogs has not yet been evaluated. There is active research concerning gene therapy for this myopathy, and preliminary studies have shown improvements in mobility and muscle function in dystrophic dogs using multiple gene therapy protocols. Pharmacologic upregulation of utrophin production (a paralogue of dystrophin) shows promise as a potential treatment for Duchenne muscular dystrophy and possibly the canine XLMD. However, continued research is needed before such treatments become available for clinical use. Stem cell therapy for dogs and humans with MD is also under investigation. The severity of dysfunction is variable, so the prognosis is guarded to poor. Clinical signs tend to progress more slowly after 6 mos of age in patients that survive that long.

2. Centronuclear myopathies (CNM)[2,5,8,22,30,31,35,65,100,104,112,122,179,184,189,203,212,213,215–218,297,303,328]

   a. Centronuclear myopathies are a group of congenital myopathies with characteristic histopathologic abnormalities affecting mainly type II myofibers. These abnormalities include central or internal location of myonuclei (often in areas devoid of myofibrils), central areas of mitochondrial aggregation, and type II fiber atrophy. The appearance of subsarcolemmal ring-like structures ("necklace fibers") has also been reported. In dogs, a causative genetic mutation has been identified for Labrador Retrievers (*PTPLA* gene) and Great Danes (*BIN1* gene) with CNM. These recessively inherited myopathies were previously termed *Labrador Retriever myopathy* and *inherited myopathy of Great Danes*, respectively; the Great Dane disorder had been described previously as a core myopathy, which is now known to be incorrect. A similar condition was reported in a Border Collie, although a specific genetic mutation was not identified in this dog. An X-linked form of CNM, specifically named myotubular myopathy, has been reported in young Labrador Retrievers with onset at weeks of age. This is a very severe disease and usually results in early euthanasia or death. X-linked myotubular myopathy is caused by a mutation in the gene that codes for the protein myotubularin. A similar X-linked myotubular myopathy with a confirmed mutation in the *MTM1* gene has recently been identified in Rottweiler puppies (Dr. Shelton, unpublished data).

   b. The age of onset as well as the severity and range of clinical signs are variable. For CNM of Labrador Retrievers, age of onset of clinical signs may range between 6 wks and 7 mos, but most dogs manifest obvious clinical signs of disease at about 3–4 mos of age. A short, stilted gait with "bunny-hopping" in the pelvic limbs is often observed. Some dogs display ventroflexion of the neck and arching of the back (kyphosis; Fig. 18.12). Abnormal joint posture—such as carpal hyperextension and valgus, splaying of the digits, and a "cow-hocked" pelvic limb stance—may also be apparent. Tendon reflexes are usually reduced or absent (especially patellar and triceps reflexes). Variable degrees of muscle atrophy, especially of the proximal limbs and head, develop as the disease progresses. Epaxial (paraspinal) musculature may also become atrophied. Weakness is often exacerbated by stress, excitement, exercise, and cold weather.

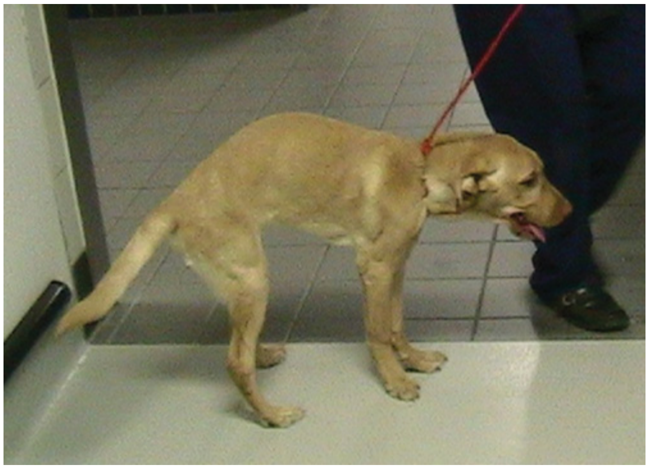


Figure 18.12 Characteristic posture of a dog with Labrador Retriever myopathy.

A few dogs with this disorder have developed megaesophagus. The condition typically stabilizes by 6–12 mos of age. The time of onset of clinical signs in Great Danes with CNM has ranged from 6 mos to 3 yrs in age in reported cases, although the majority present as older puppies (median age of 7 mos). Clinical signs may initially be mild and are often slowly progressive. These can include generalized muscle weakness that worsens with exercise, progressive muscular atrophy, a short-strided gait, "bunny-hopping," and tremors while standing. Depressed spinal reflexes have been reported in a small subset of affected dogs.

   c. Diagnosis of CNM in Labradors and Great Danes is confirmed by genetic testing. In addition to supportive clinical features of CNM, EMG findings are often abnormal. Serum CK levels may be normal or slightly elevated. In the Border Collie with CNM, EMG findings were abnormal, but CK levels were within reference range.
   d. There is no specific treatment for this disorder. However, some dogs with CNM have improved with a combination of L-carnitine, coenzyme Q and B vitamins. In general, Labrador Retrievers with CNM are only mildly disabled, so the patient's lifespan is often normal. Exposure to cold and stressful environments should be avoided. The Border Collie with CNM was reported to have normal exercise tolerance 14 mos after diagnosis. CNM of Great Danes appears to be more severe than the disorder in Labrador Retrievers. The majority of affected Great Danes appear to progress in their clinical signs and require euthanasia within months of the initial diagnosis (median survival time of 4 mos in one report). However, a subset of dogs with milder manifestations of the disease has been described, having a median survival time of 27 mos (range of 10 to 55 mos).

3. Exercise-induced intolerance and collapse (EIC) Labrador Retrievers[107]
   a. A congenital, autosomal recessive inherited disease seen in young adult, field trial Labrador Retrievers. Exercise-induced intolerance and collapse is characterized by episodic limb weakness followed by ataxia and collapse occurring 5–20 min after intense exercise. Dogs are normal between episodes and recovery is typically very rapid. Occasionally, death can occur. Spinal reflexes, specifically the patellar reflex during a collapse episode, are often absent and hyporeflexia/areflexia can progress to the thoracic limbs.
   b. A mutation in the dynamin 1 (*DNM1*) gene, specifically Arg256Leu, has been associated with EIC in Labradors. DNM1 belongs to an enzyme complex responsible for catalyzing hydrolysis of guanosine triphosphate (GTP), leading to conformation changes in other proteins needed for cellular homeostasis. DNM1 is responsible for endocytosis and neurotransmission during prolonged periods of stimulation, such as strenuous exercise. Clinical disease typically occurs in dogs which are homozygous recessive for the DNM1 mutation; however, heterozygous and dogs negative for DNM1 mutation can also be affected. The frequency of the DNM1 mutation in Labradors ranges from 17 to 38%. The homozygous DNM1 genotype frequency between conformation show, field trial/hunting, and pet/service dogs ranges from 1.8 to 13.6%. In a study of 211 dogs with clinical signs referable to EIC and confirmed DNM1 mutation, 33 dogs (15.6%) were heterozygous or lacked the Arg256Leu DNM1 mutation. Dogs homozygous for the DNM1 mutation are young (median age 12 mos old) when they experience their first collapse episode. Heterozygous dogs or those lacking the mutation are typically older (median age 23 mos) and can have a wide variety of characteristics of collapse not consistent with a particular disease.
   c. EIC has historically been a clinical diagnosis of exclusion, ruling out all other causes for exercise intolerance in a young adult, athletic dog. Affected dogs do not show cardiovascular, orthopedic, or neurologic abnormalities. All diagnostic tests and physical exam parameters are normal between episodes. Hyperthermia and elevated plasma lactate levels are commonly seen at the onset collapse, although an elevation in body temperature of up to 3° Celsius may be found in normal dogs of this breed following intensive exercise. Additionally, affected dogs show a change in their lactate/pyruvate ratio, while this should not be seen in normal dogs.
   d. A commercially available DNA test for the *Arg256Leu DNM1* gene mutation is now available to diagnosis EIC-affected dogs.
   e. There is no curative treatment for this disease. Most affected dogs make suitable pets and should refrain from intense exercises such as running, chasing balls or toys, and hunting and field trial events.

4. Distal myopathy of Rottweilers[82, 136, 210, 234]
   a. A presumably inherited myopathic disorder that preferentially involves distal appendicular muscles was described in four young Rottweiler dogs. Two of the four dogs were siblings, and one of the remaining two dogs evaluated had two reportedly similarly affected siblings (not evaluated clinically). The etiology of this disease is unknown. Distal myopathy of Rottweilers appears to be similar to distal myopathy of humans, a broad category of autosomally inherited myopathies that primarily affect distal appendicular muscles.

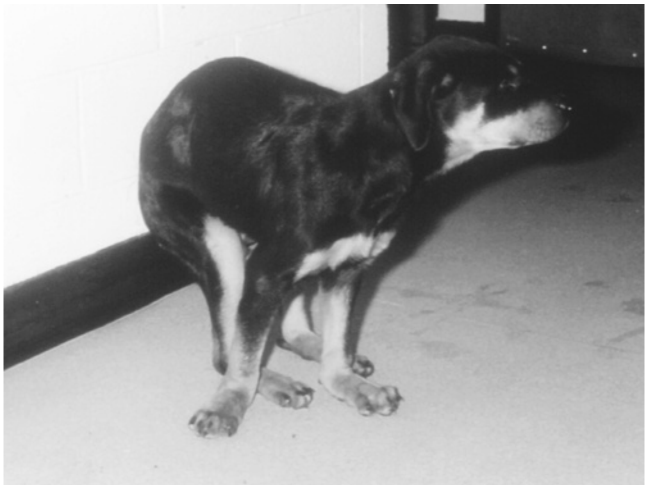


Figure 18.13 Characteristic posture of a Rottweiler with distal myopathy. (Courtesy of Dr. Stephen Hanson.)

b. The age at which the dogs were evaluated was between 4 and 7 mos, but all dogs had exhibited an abnormal gait and posture within the first several weeks of life. Characteristic clinical signs of dysfunction include a palmigrade and plantigrade stance (Fig. 18.13), splayed digits in the forelimbs (Fig. 18.14), generalized weakness, and exercise intolerance.

c. Diagnosis is based primarily on signalment, characteristic clinical features, and abnormal muscle biopsy histopathology results. CK levels were normal in one dog and only mildly elevated in the two others in which it was measured. EMG was performed in two of the four dogs. In one dog, rare fibrillation and positive sharp waves were identified. No EMG abnormalities were identified in the other dog. Both dogs had decreased amplitude of interosseous compound muscle action potentials, elicited during motor nerve conduction velocity testing. Plasma carnitine levels were decreased in all four dogs. Muscle carnitine levels were below normal levels in three dogs, and in the low–normal range in the remaining dog. Dystrophin immunocytochemical staining was normal in the two dogs for which this test was performed.

d. At present, the prognosis for this myopathy appears to be poor. All four dogs were euthanized, three due to the severity of the disease and one due to an unrelated behavioral disorder. This latter dog's clinical signs appeared to improve somewhat with oral carnitine supplementation, but did not deteriorate after carnitine withdrawal. The clinical significance of low plasma and muscle carnitine levels in this disorder is unknown but is felt to be a secondary, rather than a causative, phenomenon. The potential efficacy/inefficacy of carnitine supplementation for this myopathy remains to be determined.

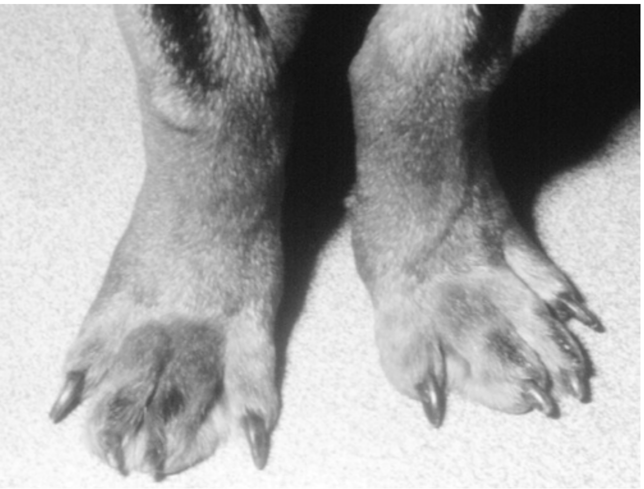


Figure 18.14 Splaying of the digits, characteristic of Rottweiler distal myopathy. (Hanson *et al.*, 1998. Reproduced with permission from Wiley.)[136]

5. Myotonia congenita[3, 8, 26, 28, 35, 37, 76, 96, 103, 129, 146, 147, 150, 178, 179, 183, 224, 225, 272, 285, 286, 297, 311, 314, 329, 331, 335, 343–345, 351, 358, 367, 368]

a. This disorder is believed to be inherited as an autosomal recessive trait in Chow Chow dogs and Miniature Schnauzers. Other breeds reported with a similar condition include the Staffordshire Terrier, Rhodesian Ridgeback, Great Dane, West Highland White Terrier, Samoyed cross, Australian Cattle dog, and Labrador Retriever. Myotonia congenita has also been described in six domestic shorthaired kittens. The four kittens in one report were from separate litters, but the queens of those litters were related. The discerning clinical feature of this disorder is sustained muscle contraction after cessation of voluntary movement. Failure of muscle relaxation is believed to be due to abnormal sarcolemmal chloride conductance. The decreased chloride conductance leads to hyperexcitability of the muscle membrane. Subsequent accumulation of potassium ions in the T-tubule system is responsible for sustained muscle contraction following initial depolarization. Abnormal sarcolemmal chloride channels, due to an autosomally inherited genetic defect, have been demonstrated as the cause of myotonia congenita in the Miniature Schnauzer. There are several forms of myotonia congenita in humans, some of which are due to abnormal sodium conductance across the sarcolemma.

b. Clinical signs are usually appreciated when affected puppies and kittens begin to ambulate. Affected animals typically appear worse after a period of rest. Cold temperatures also tend to cause exacerbation of clinical signs. The gait is stiff and tends to improve or even normalize with activity. The pelvic limbs are often more severely affected than the thoracic limbs; in canine myotonia, they may be advanced simultaneously in a "bunny-hopping" fashion. It may be difficult for affected dogs to flex the stifle joints. The thoracic limbs are often held abducted while ambulating, due to a decreased ability to flex the proximal limb joints. Myotonic patients may have difficulty rising from a sternal position. Myotonic kittens tend to snag their claws when walking on carpet. When myotonic kittens are startled, they may hyperextend all four limbs and fall into lateral recumbency for approximately 10 sec. Startling in these kittens may also result in bilateral prolapse of the nictitans, blepharospasm (due to spasm of the orbicularis oculi muscles), flattening of the ears, and retraction of the lips.

Generalized muscle hypertrophy (especially proximal appendicular and neck muscles and the tongue in dogs, gastrocnemius muscles most prominent in cats) is often appreciated and percussing the muscle may leave an indentation, referred to as a "myotonic dimple" (Fig. 18.15). Some patients will exhibit dysphagia and respiratory problems (e.g. stridor) because of sustained contraction of pharyngeal and laryngeal musculature, respectively. Affected kittens may exhibit signs of dysphonia, characterized by a hoarse meow and quiet purr. Unusual physical characteristics apparent in all of a group of related myotonic Schnauzers were prognathism (shortened mandible) and medially displaced canine teeth.

c. Diagnosis is based upon signalment, characteristic clinical signs, and electrodiagnostic findings (EMG abnormalities). CK levels are often either normal or only mildly elevated, and changes on muscle biopsy are usually mild and nonspecific (e.g. variation in myofiber size). Muscle biopsy results may contribute to the diagnosis, but may not be worth the risk of anesthesia in these patients. Anesthesia may be both difficult and dangerous due to stenosis of the laryngeal glottis. Also, people with myotonia are predisposed to anesthetic-induced malignant hyperthermia. The characteristic finding on EMG is bizarre high-frequency discharges that wax and wane (Fig. 18.16). These discharges are frequently referred to as "dive-bomber sounds," due to their waxing and waning nature. Others have likened their sound to a motorcycle engine. Myotonic discharges have also been reported on EMG evaluations of heterozygote (carrier) Miniature Schnauzers, although the length of these discharges is shorter than is seen in homozygote dogs of this breed. Lastly, polymerase chain reaction-based DNA tests have recently been reported for screening Australian Cattle dogs and Miniature Schnauzers for myotonia congenita.

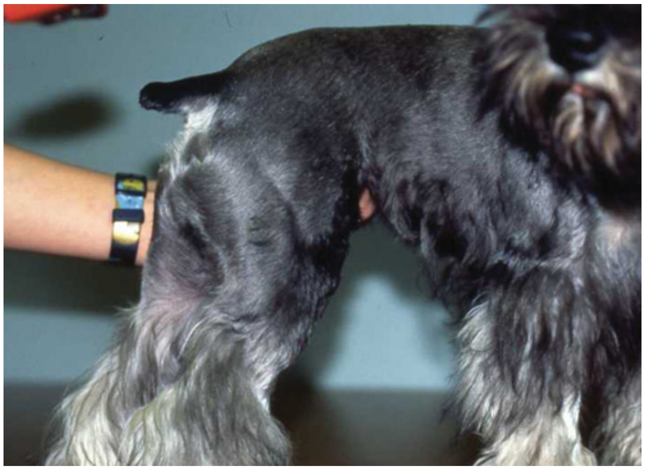


Figure 18.15 Myotonic dimpling in the caudal thigh musculature of a myotonia congenita patient. (Dr. G Kortz, 2014. Reproduced with permission from Dr. G Kortz.)

d. There is some evidence that using membrane-stabilizing agents may be helpful in relieving clinical signs in myotonic dogs. Procainamide is thought to be more effective than phenytoin or quinidine. Other drugs that have been used to treat myotonia in dogs include carbamazepine, tocainide, nifedipine, and mexiletine hydrochloride. Environmental modification alone is recommended to control clinical signs in myotonic cats. These kittens tend to be well managed without drug therapy, and drugs typically used to control canine myotonia have unacceptable toxicity risks in cats. Myotonia congenita is not considered a progressive disease, and clinical signs of dysfunction tend to stabilize between 6–12 mos of age. In general, most dogs and cats with myotonia congenita are not severely disabled, and therefore the prognosis for long-term survival is favorable. The prognosis for sustained improvement of clinical signs of myotonia is guarded, however.

6. Fibrotic myopathy (gracilis/semitendinosus myopathy) [39, 74, 196–200, 202, 297]

a. This is an idiopathic disorder characterized by replacement of muscle tissue with dense fibrous connective tissue. It occurs most commonly in dogs, especially adult male German Shepherd dogs (approximately 81% of reported cases). Other breeds reported with fibrotic myopathy include Belgian Shepherd, Boxer, Old English Sheepdog, Doberman Pinscher, Saint Bernard, and Bobtail. It has been reported in one cat. The gracilis muscle is most often affected (86% of cases), but the semitendinosus muscle may also be affected either alone or concurrently. Involvement of the supraspinatus and quadriceps muscles has been reported, but this is rare. The

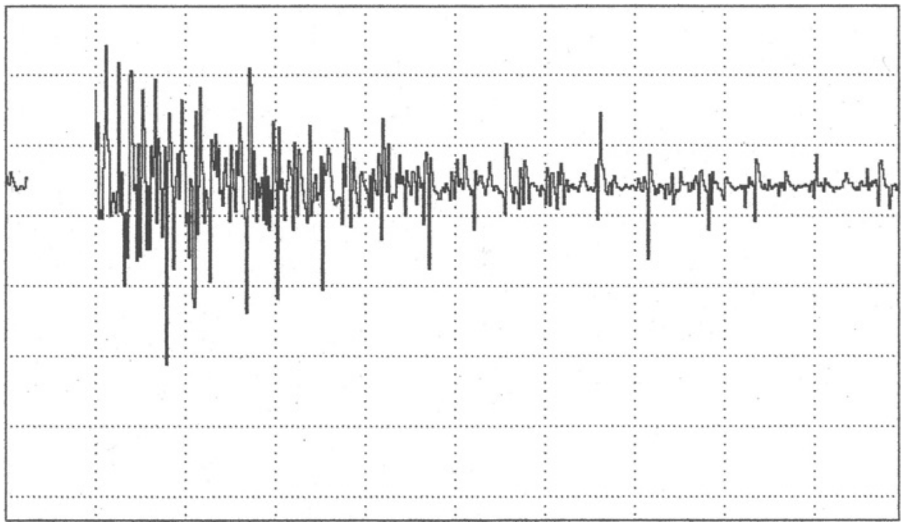


Figure 18.16 EMG tracing of a dog with myotonia.

fibrotic gracilis/semitendinosus muscle produces a tethering effect, interfering with coxofemoral joint abduction, as well as stifle and hock joint extension. The pathogenesis is unknown. Autoimmune myopathy, neuropathy, isolated muscle trauma, repeated microtrauma, and vascular compromise have all been suggested as possible etiologies.

b. Age of onset of dysfunction ranges from 8 mos to 9 yrs (mean, 5 yrs). Clinical signs are usually limited to apparently nonpainful pelvic limb lameness, which is more obvious at a trot than at a walk. In most cases, the lameness has an insidious onset and progresses over weeks to months before reaching a plateau. Occasionally, acute onset of lameness is reported. Bilateral involvement occurs in approximately 26% of cases. When both pelvic limbs are affected, the degree of dysfunction may not be symmetric; also, one limb may be affected initially, the other becoming dysfunctional at a later date. Although classically considered a nonpainful disorder, one study found that a painful response could be elicited from the majority of affected dogs with hip abduction and/or digital pressure applied to the distal aspect of the fibrotic muscle. The fibrous muscle prevents full extension of the pelvic limb during ambulation. The lameness in the affected limb is characterized by internal rotation of the stifle and external rotation of the hock as the limb is advanced (Fig. 18.17). The foot performs a “flipping” motion at the end of each stride. The resultant gait is often described as “jerky” or “goose stepping.” Affected muscle tissue may be visibly abnormal and the distal myotendinous area is often firm and hypertrophied when palpated (Fig. 18.18).

c. Diagnosis is based primarily upon signalment and characteristic clinical findings. Increased thickness may be appreciated in affected muscles with both radiographs and ultrasonography. CK values are typically normal or slightly elevated. EMG often fails to record any abnormal electrical activity. There are reports of both increased EMG activity and lack of normal insertional activity. Muscle biopsy reveals dense collagenous connective tissue.

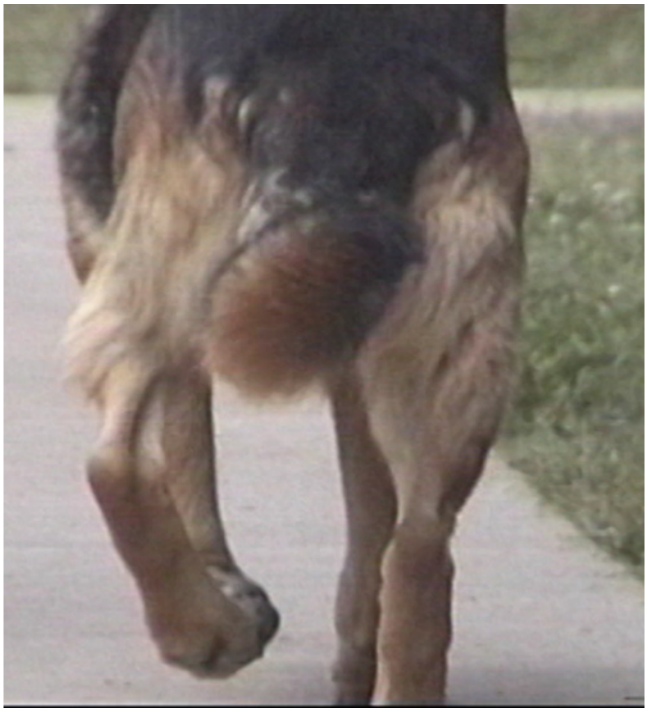


Figure 18.17 Typical pelvic limb gait of a dog with fibrotic myopathy.

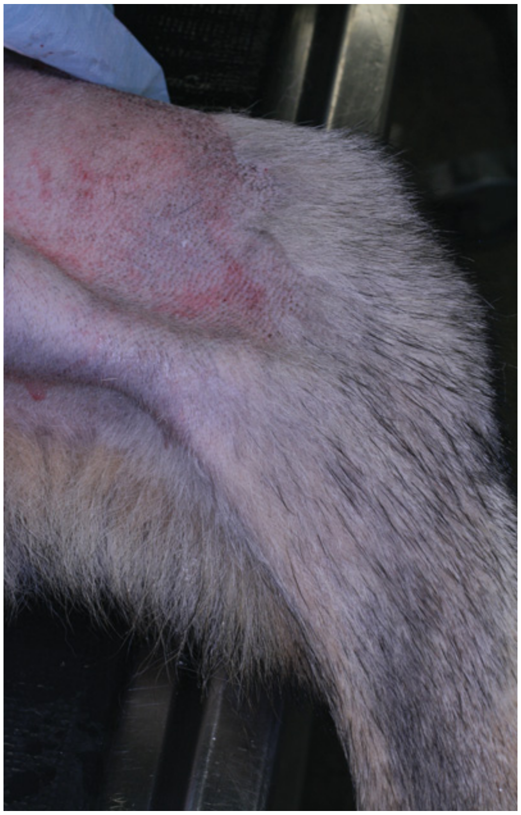


Figure 18.18 Bilateral fibrosis of the gracilis muscles in a dog with fibrotic myopathy.

d. Medical therapies for fibrotic myopathy (e.g. corticosteroids, penicillamine, colchicine) have been ineffective. Various surgical procedures (e.g. tenotomy, Z-plasty, excision of affected muscle) have met with poor long-term success. Improvement in gait post surgery is often substantial but transient, lasting only a few months. If the abnormal gait is not severely limiting the patient's lifestyle, no treatment is recommended.

7. Nemaline myopathy[75,77,88,185,204,231,292,303,308,309]

a. Nemaline myopathy is a rare, presumably inherited disorder described in young related cats. Congenital nemaline myopathy has also been reported in two dogs, a 10-mo-old Border Collie, and an 11-yr-old Schipperke. Nemaline rods were also observed in muscle biopsy specimens from a dog with hyperadrenocorticoid myopathy and a dog with hypothyroid myopathy. Finally, nemaline rods have been reported as incidental findings in muscle biopsies of dogs with neuromuscular disease. The presence of nemaline rods in a muscle biopsy is not necessarily specific for nemaline myopathy.

A diagnosis of nemaline myopathy should be suspected when there are numerous nemaline rods present in the absence of any other cause for a myopathy. The pathogenesis of nemaline myopathy is unknown, but special stains of muscle biopsy specimens reveal rod-shaped inclusions within myofibers (nemaline rods). In human nemaline myopathy, these rods have been shown to be composed of cytoskeletal proteins identical to those found in the Z-band area of the contractile filament apparatus. A myofiber cytoskeletal protein abnormality is suspected. Accumulations of tubulin-positive crystalline inclusions, and dystrophin and spectrin proteins in addition to nemaline rods, have been reported in cats as well. A myofibrillar myopathy showing accumulations of alpha-actin (Z-disc material) and desmin within the myofiber has been reported in an Australian Shepherd dog.

b. The reported cats had an acute onset of clinical signs between 6 and 18 mos of age. Clinical signs included weakness, a rapid and crouched hypermetric gait, muscle tremors, hyporeflexia, muscle atrophy, and reluctance to move. Only the muscle atrophy appeared to be progressive. Both congenital canine nemaline myopathy cases had slowly progressive clinical signs that included exercise intolerance, and reluctance to stand and walk. The Border Collie displayed tremors in all limbs, muscle atrophy, and absence of patellar reflexes. Additional clinical signs of dysfunction in the Schipperke included a stiff gait, spontaneous limb jerking, and decreased withdrawal reflexes in all four limbs. The endocrine myopathy cases had clinical signs of dysfunction typical for their respective myopathic disorders.

c. Diagnosis is based upon signalment, clinical signs, and demonstration of nemaline rods on muscle biopsy samples. CK levels were only mildly elevated in the reported cats and EMG evaluation was normal. Similarly, the CK level of one of the congenital canine cases was normal; the other was slightly elevated. EMG changes in these two dogs were mild.

d. Although only the muscle atrophy was progressive, the reported cats continued to lose condition and became inappetent. All the cats were eventually euthanized. The disorder in the reported dogs was slowly progressive over several years. There is no known treatment for nemaline myopathy and the prognosis for recovery is poor.

8. Dancing Doberman disease

This is an idiopathic syndrome in adult Doberman Pinschers that has characteristics of both a neuropathy and a myopathy. It is discussed in more detail in Chapter 17.

9. Myositis ossificans (fibrodysplasia ossificans progressiva)[7,39,75,161,204]

a. This is a rare idiopathic disorder of dogs and cats in which proliferation of fibrovascular tissue within muscle occurs, with secondary calcification and ossification. Intermuscular mineralization has also been reported. It is not known whether this disease represents a primary muscle disorder or is an abnormality of connective tissue adjacent to muscle (e.g. tendons, fascia) that leads to a secondary myopathy. Calcinosis circumscripta within lingual muscle has also been reported, secondary to a nutritional myopathy and idiopathic calcinosis.

  b. This disorder typically affects young adult to middle-aged animals of both sexes. Clinical signs include progressive weakness and stiffness of gait, enlargement of proximal limb muscles, and myalgia. Focal, firm swellings may be evident on muscle palpation.

  c. Diagnosis is based primarily upon signalment, clinical signs, and radiographic evidence of mineralized/ossified densities (usually multiple) within muscle tissue. CK levels are typically elevated, and EMG evaluation reveals abnormal potentials. Histopathologically, fibrosis, myofiber necrosis and phagocytosis, and areas of calcification/ossification may be seen.

  d. Since this tends to be a progressive disease, the prognosis is considered guarded to poor. However, focal lesions may regress or respond favorably to surgical excision.

10. Pharyngeal/esophageal dysfunction of Bouviers[46, 247]

  a. A myopathy primarily affecting pharyngeal and esophageal musculature has been described in 24 Bouvier des Flandres dogs from the Netherlands. The pathogenesis of this disorder is unknown, but muscle histopathology revealed abnormalities similar to those observed in dystrophin-related muscular dystrophy (DRMD). It has been suggested that this disorder may be the canine analog of oculopharyngeal muscular dystrophy in humans. Although suspected to be a heritable trait, the mode of transmission is unknown. Four adult female Bouviers with generalized muscle weakness and megaesophagus were described in the United States. These dogs also had histopathologic changes on muscle biopsies consistent with DRMD. It is unknown whether these dogs had a variation of the same disorder as the group in the Netherlands.

  b. Both males and females were affected, with an age range of presentation from 6 mos to 9 yrs of age. The predominant clinical sign of dysfunction was dysphagia. Seven of the 24 dogs with dysphagia also exhibited regurgitation. Regurgitation was the predominant clinical feature in three dogs.

  c. Tentative diagnosis of this myopathy was based upon historical and clinical signs, as well as abnormal pharyngeal and esophageal movement on fluoroscopic examination. Only seven dogs had radiographically obvious air accumulation in the esophagus. In 20 dogs in which serum CK levels were evaluated, seven dogs had normal values, and CK levels were elevated in 13 dogs. EMG abnormalities of the pharyngeal and/or esophageal musculature were found in all but one dog examined. A histopathologic evaluation of pharyngeal/esophageal muscles from affected dogs revealed changes characteristic of DRMD. In two dogs, these characteristic abnormalities were also apparent in temporalis, masseter, and laryngeal musculature.

  d. There is no known effective treatment for this disorder. Four dogs with dysphagia underwent cricopharyngeal myotomy. One of these dogs improved, but the other three died of aspiration pneumonia within two days of surgery. The majority of the affected dogs were euthanized due to continued dysphagia. The prognosis for dogs with this disorder appears to be poor.

11. Polysystemic disorder of English Springer Spaniels[149]

  a. Three related young English Springer Spaniels have been described with the combination of polymyopathy, dyserythropoiesis, and cardiac abnormalities. The etiology of this polysystemic disorder is unknown, but is suspected to be a heritable variant of MD.

  b. All three dogs developed clinical signs of dysfunction within the first 6 mos of life, and all were considered small for their age. One dog occasionally regurgitated, and the other two had decreased gag reflexes. Slowly progressive temporalis muscle atrophy developed in all dogs, with subsequent partial trismus. To a lesser degree, pelvic limb muscle atrophy occurred over time. One dog exhibited a stiff gait, most notable in the pelvic limbs, often "bunny-hopping" when ambulating. Exercise intolerance was not a notable feature in any of the three dogs.

  c. Diagnosis of this disorder was based upon both antemortem and necropsy evidence of concurrent polymyopathy, dyserythropoietic anemia (erythrocytes with abnormal morphology, including blast forms), and various cardiac abnormalities (e.g. right ventricular enlargement, enlargement of conus arteriosus, ascending aorta enlargement, ventricular premature complexes). Varying degrees of megaesophagus and abnormal esophageal motility were evident on thoracic radiographs and fluoroscopic evaluation, respectively. Serum CK levels were normal in one dog and slightly elevated in another. EMG abnormalities were not evident in the one dog in which electrodiagnostics were pursued. Abnormal muscle pathology in affected dogs included marked fiber size variation and fiber splitting.

d. There is no known effective therapy for this disorder and the prognosis for recovery is poor. All three dogs were euthanized.

12. Cricopharyngeal achalasia[52,120,188,211,233,251,277,281,298,350,352]

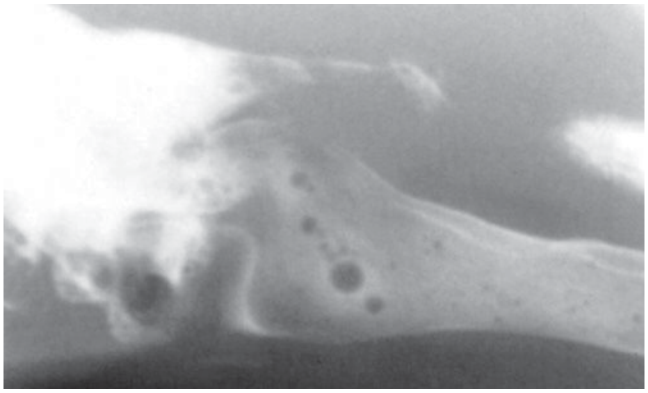
a. This is an uncommon and enigmatic disorder of young dogs. It is characterized by a failure to relax the cricopharyngeus muscle during the oropharyngeal phase of swallowing. The underlying reason for the lack of cricopharyngeus relaxation is unknown. Suggested etiologies include myopathy, neuropathy (affecting the glossopharyngeal nerve and the pharyngeal branch of the vagus nerve), junctionopathy, and central nervous system, or CNS, (brain-stem) lesion. Cricopharyngeal achalasia associated with hypothyroidism has been reported in one dog. A full recovery was seen following thyroid hormone supplementation, suggesting a possible role of hypothyroidism in the development of cricopharyngeal achalasia in this case.

b. Numerous dog breeds have been reported with cricopharyngeal achalasia. Spaniel breeds appear to be overrepresented in the literature; there is one report of cricopharyngeal achalasia occurring in Cocker Spaniel littermates. Clinical signs of dysfunction are usually evident at the time of weaning and remain static, unless aspiration pneumonia develops. Dysphagia is the hallmark clinical sign of dysfunction. Other characteristic clinical signs include regurgitation (typically immediately following attempted swallowing), nasal reflux of ingested food, coughing, and either weight loss or failure to gain weight. Dogs with this disorder may be more able to swallow liquids than solids, but ingesting liquids may lead to more nasal reflux than solids.

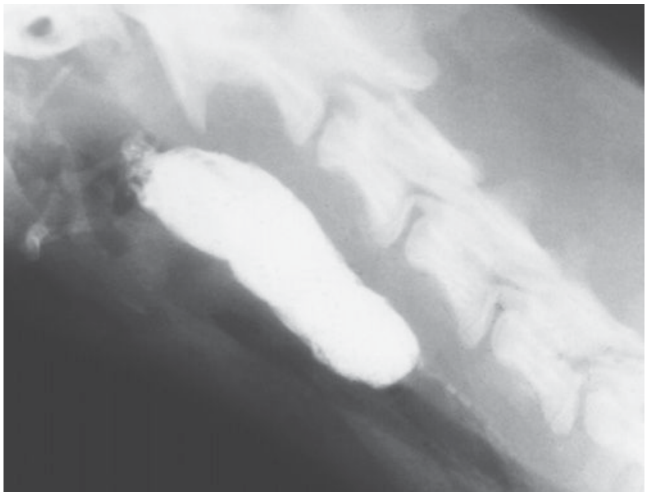
c. Diagnosis of cricopharyngeal achalasia is based primarily upon history, signalment, and characteristic clinical features, as well as ruling out other causes of dysphagia and regurgitation (e.g. idiopathic megaesophagus, myasthenia gravis, vascular ring anomalies). Radiographs of the pharyngeal area and thorax should be obtained to rule out pharyngeal foreign bodies and megaesophagus, respectively. Also, the presence or absence of aspiration pneumonia can be ascertained by thoracic radiographs. Crucial to diagnosis is evaluation of swallowing using contrast fluoroscopy (Fig. 18.19). This radiographic evaluation should confirm failure of cricopharyngeal relaxation during the swallowing reflex. Endoscopic evaluation of the pharyngeal area will be normal, and there is typically no appreciable impediment to passing the scope through the pharyngeal region.

d. Treatment of cricopharyngeal achalasia is myotomy or myectomy of the cricopharyngeus muscle. This surgical therapy is highly effective for this disorder. However, if the diagnosis is incorrect, cricopharyngeal myotomy/myectomy may not only be of no therapeutic value but also lead to life-threatening aspiration pneumonia. Lastly, inappropriate or insufficient treatment of aspiration pneumonia and/or malnutrition preoperatively in animals with cricopharyngeal achalasia frequently worsens postoperative outcome.

The authors have treated one case of cricopharyngeal achalasia with therapeutic Botox injections. The abnormal cricopharyngeal musculature was identified with an EMG. The Botox was injected into the abnormal muscle and repeated 3 wks later. This procedure was both therapeutic and used to prognosticate this patient's overall success with a permanent myectomy. This patient showed clinical improvement after this procedure and went on to have a permanent myectomy performed.



(a)



(b)

Figure 18.19 Fluoroscopic image of a dog with cricopharyngeal achalasia before (A) and after (B) cricopharyngeal myotomy. Prior to surgery, very little of the contrast bolus passed through the upper esophageal sphincter. (Ladlow and Hardie, 2000.)[188]

13. Episodic muscle hypertonicity ("cramp")[6,106,145,166,220–223,249,282,294,318,343,361–363]

    This uncommon disorder, initially reported in the Scottish Terrier breed ("Scotty cramp"), is characterized by episodic muscle hypertonicity. The episodes are of variable frequency and severity and are induced by stress, exercise, and excitement. The disease appears to be inherited as an autosomal recessive trait in Scottish Terriers. Although the pathogenesis is not completely understood, clinical manifestations of this disorder may be due to a functional deficiency of serotonin in the CNS. Drugs that potentiate CNS serotonergic effects (e.g. acepromazine) alleviate clinical signs, whereas those that decrease CNS serotonergic effects (e.g. amphetamine) either worsen or induce clinical signs. Similar conditions have been described in a number of different breeds. These and other movement disorders are covered in more detail in Chapter 10.

14. Myokymia and neuromyotonia[109,131,132,266,336,347,366]

    This category of disease (especially myokymia) is often discussed with tremor and movement disorders, but it is probably more accurately categorized as a neuropathy (see Chapter 17). It is discussed in this chapter because the manifestations of the disorder appear clinically more like a myopathy than a neuropathy. It is also briefly discussed in Chapter 10. The underlying pathophysiological cause for the intermittent and excessive muscle contraction characteristic of myokymia/neuromyotonia is thought to be hyperexcitability of motor axons; in humans, this hyperexcitability is thought to be due to abnormalities of voltage-gated potassium channels (VGKC) in these nerves, which is often due to an autoimmune process. In addition to autoimmune disorders of VGKC, there are some heritable disorders of these ion channels; for example, the disorder known as *episodic ataxia with myokymia* is due to a point mutation in the VGKC gene (*KNA1*). Whether acquired (autoimmune) or inherited, the VGKC involved in this disorder are fast potassium channels, also referred to as delayed rectifier channels, whose function is necessary for the cessation of depolarization as well as repolarization of the axon. If these channels are dysfunctional and/or decreased in density, prolongation of depolarization will allow more calcium to enter (calcium channels will remain open), with a subsequent excessive release of acetylcholine transmitter quanta into the synaptic cleft. This, along with delayed repolarization, will lead to excessive and repetitive muscle contraction. Confusion regarding this clinical phenomenon is likely perpetuated both by an unnecessary number of descriptive terms as well as the vast array of primary disorders that can lead to the manifestation of this type of muscular activity. The terms "myokymia" and "neuromyotonia" probably refer to the same class of disorders, differing solely in the frequency (in Hz) of the episodic involuntary muscle fiber contraction that characterizes the disease syndrome. The term myokymia, which is derived from the Greek word *kyma* (which means "wave"), is probably the most descriptive term for the vermicular ("worm-like"), rippling, or undulating motion of the skin (most notably on the proximal limbs) caused by the spontaneous intermittent contraction of subcutaneous musculature. Myokymic discharges are characteristically bursts of single motor unit action potentials that have a frequency of 5–150 Hz. Neuromyotonic discharges are described as similar episodic discharges of higher frequency (150–300 Hz, often with a waning amplitude), which are believed to be more likely than myokymic discharges to culminate in generalized contractions of large muscle groups (e.g. limb musculature). These intermittent bursts of motor unit action potentials occur as doublets, triplets, or multiplets on EMG examination, and sound (over the loudspeaker) like soldiers marching. These muscle fiber discharges persist during sleep and when the patients are under general anesthesia. The terms myokymia and neuromyotonia likely refer to different stages of severity of the same clinical condition. According to some sources, myokymia is considered a clinical manifestation of the overall disease syndrome of neuromyotonia. In other words, the umbrella term for the disorder is neuromyotonia, which includes the phenomenon of myokymia. Since the majority of reported cases in the veterinary literature describe patients that displayed myokymia and then rapidly progressed to generalized muscle contraction and collapse, this is probably the correct use of the terminology. In addition to these terms, neuromyokymia, continuous muscle fiber activity (CMFA), continuous motor unit activity (CMUA), neurotonia, pseudomyotonia, and episodic nonpostural repetitive myoclonus have been proposed. The list of disorders in humans that have been associated with concurrent myokymia and neuromyotonia is extensive and includes several autoimmune or suspected autoimmune disorders; it includes caudal fossa tumors, Guillain–Barré syndrome, multiple sclerosis, radiation-induced plexopathy, timber rattlesnake envenomation, chronic inflammatory demyelinating polyneuropathy (CIDP), thymoma, lymphoma, plasmacytoma, small-cell lung carcinoma, Hashimoto's thyroiditis, Addison's disease, rheumatoid arthritis, and acquired myasthenia gravis. The disorder has also been associated with penicillamine treatment. In addition to the multitude of terms already mentioned, the terms Isaacs' syndrome, Mertens' syndrome, Isaac–Mertens' syndrome, and Morvan's syndrome (also includes signs of encephalopathy) all refer to myokymia/neuromyotonia due to autoimmune response against VGKC.

Myokymia and neuromyotonia have been reported in eight dogs and one cat. The dogs included three Jack Russell Terriers, two Yorkshire Terriers, a Border Collie, a Cocker Spaniel, and a mixed-breed dog. The one feline report was a 6-yr-old domestic shorthaired cat. With the exception of one dog with facial myokymia (6-mo-old Cocker Spaniel, age at onset of 4 mos) who had occasional involvement of the left shoulder musculature, all of the other reported cases exhibited neuromyotonia with more generalized muscle stiffness, in addition to myokymia. Of the neuromyotonia cases, the cat was the least severely affected, remaining ambulatory despite the involuntary muscle contractions. With the exception of one Border Collie with an age at onset of 2 yrs, the other dogs with neuromyotonia had a very young age at onset of disease (2–11 mos). These dogs all had a similar clinical presentation, in which the excessive muscular contraction culminated in collapse. In all cases, the dogs were fully conscious during the collapsing episodes. The episodes in these dogs were typically triggered by stress, excitement, or exercise and lasted for several minutes to several hours. Between episodes, the dogs returned to normal, or their pre-episode condition (see comments below on the Jack Russell Terriers). Episodes were heralded in three dogs by intense facial rubbing, similar to what has been reported in hypocalcemic dogs. Common to all of these reported cases of myokymia/neuromyotonia was moderate to severe hyperthermia during the episodes. In two cases, death during an episode was attributed to hyperthermia. Another common feature was persistence of spontaneous muscle contraction during sleep and general anesthesia. All three reported Jack Russell Terriers exhibited generalized ataxia in addition to the myokymia/neuromyotonia episodes. Whether this finding represents concurrent hereditary ataxia or a condition similar to human episodic ataxia with myokymia is unknown. Two of the Jack Russell Terriers also exhibited mild cyanosis during episodes.

As with humans with myokymia/neuromyotonia, the diagnosis rests primarily on characteristic clinical features of the disease along with demonstrating the characteristic EMG abnormalities (i.e. episodic bursts of spontaneous muscle activity of specific frequencies). Other characteristic supportive features include serum elevations of ALT, AST, and CK concentrations. Muscle/nerve biopsy results in humans may be normal or indicative of axonal degeneration and/or demyelination. Muscle histopathology was normal in the four dogs for which it was performed. The Jack Russell Terriers had evidence of axonal degeneration and demyelination of peripheral nerves, with very mild muscle changes. One Yorkshire Terrier had normal muscle biopsy results. The cat had evidence of myofiber necrosis and regeneration, and intramuscular nerve branches were normal. Although none of the veterinary cases had an obvious underlying disorder for which the myokymia/neuromyotonia was considered a secondary or associated phenomenon, this should be addressed in such cases, based on what is known in the human literature on the subject. Unlike the scenario in human medicine, there is no assay for circulating anti-VGKC antibodies for dogs or cats (to diagnose autoimmune causes for myokymia/neuromyotonia), and no canine or feline hereditary mutations for the VGKC gene have been identified.

A variety of drugs have been effective in treating human myokymia/neuromyotonia, including procainamide, phenytoin, carbamazepine, acetazolamide, mexiletine, and gabapentin. These drugs have membrane-stabilizing properties and may also be of some benefit for veterinary cases of myokymia/neuromyotonia. In people with underlying autoimmune disorders, immunosuppressive drugs are used in addition to membrane-stabilizing agents. The cat responded favorably to oral phenytoin, and one Yorkshire Terrier responded well to procainamide. Two other dogs had transient responses to such therapy. The Border Collie responded for several months to oral mexiletine, and then reverted to the previous frequency of episodes. One Jack Russell Terrier responded to oral procainamide, but died during an episode in the second month of treatment. Four dogs either died during an episode (two dogs) or were euthanized due to disease severity (two dogs), suggesting at least a guarded prognosis for this disorder. However, more experience with this disease, especially with treatment options recommended for people with the disorder (only one of the deceased dogs was treated with one of these drug options), will be necessary before an accurate estimate for prognosis can be formulated for myokymia/neuromyotonia in dogs and cats.

B. Metabolic

1. Hypokalemic myopathy[29, 35, 38, 91–93, 151, 163, 174, 195, 229, 297, 324]

a. A relatively common myopathy associated with low extracellular potassium levels is encountered in cats. Most of these cats have chronic renal dysfunction with subsequent potassium loss through the urine. Other conditions associated with hypokalemic myopathy in cats include hyperthyroidism, dietary potassium deficiency, hyperaldosteronism (Conn's syndrome), fluid overadministration, chronic vomiting/diarrhea, and overuse of potassium-wasting diuretics. There is also a suspected hereditary condition of unknown pathogenesis in Burmese kittens with periodic hypokalemia and signs of myopathy. This is a suspected autosomal recessive condition. It may be similar to hypokalemic periodic paralysis of people. Hypokalemia leads to

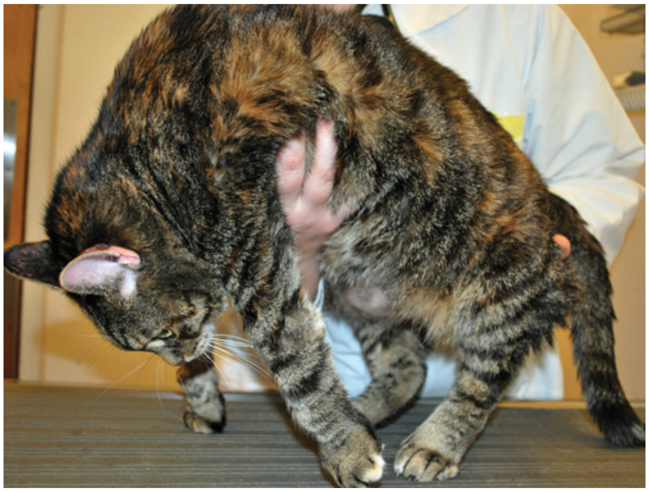


Figure 18.20 Cat with cervical weakness demonstrating cervical ventroflexion.

hyperpolarization of the sarcolemma resting membrane potential, making it refractory to depolarization and subsequent contraction.

b. Most cats with this condition are older and have evidence of renal dysfunction. The Burmese kittens with intermittent hypokalemia and myopathy ranged between 2 and 6 mos of age. Clinical signs are typically acute in onset and include neck ventroflexion (Fig. 18.20), myalgia, reluctance to ambulate, and a stiff, stilted gait. With severe hypokalemia, respiratory paralysis and rhabdomyolysis can occur.

c. Diagnosis is based upon signalment, historical and clinical findings, as well as supportive evidence of a myopathy in a cat with hypokalemia. An abdominal ultrasound is recommended to rule out an underlying adrenal tumor supporting Conn's disease and to evaluate renal status. The potassium level in affected cats is less than 3.5 mEq/L, and often is less than 3.0 mEq/L. CK levels are usually moderately to markedly elevated. EMG evaluation typically reveals abnormal activity such as fibrillation potentials, positive sharp waves, and bizarre high-frequency potentials. Muscle biopsy samples often reveal no or very mild abnormalities. Resolution of clinical signs with potassium supplementation also supports the diagnosis.

d. Treatment of this condition is oral potassium gluconate at an initial dose of 5–8 mEq/kg/day, divided into two doses. Normal potassium levels are often achieved within 1–3 days with this therapy. Maintenance therapy of 2–4 mEq/day is usually sufficient after achieving normal serum potassium levels. Potassium administration via intravenous fluids is usually counterproductive, because the dilutional and diuretic aspects of fluid administration actually further lower the potassium level.

In life-threatening hypokalemia, concentrated intravenous potassium solutions can be administered at a rate of 0.4 mEq/kg/hr. However, this is potentially dangerous and can lead to fatal cardiac arrhythmias without close monitoring of the serum potassium level and the electrocardiogram. An alternative is a dopamine infusion of 0.5 mg/kg/min. This may cause a transient increase in serum potassium, and allow time for oral potassium supplementation. The prognosis for this condition with proper therapy is generally favorable. Most cats exhibit obvious improvement within 1–3 days of potassium supplementation, although complete recovery may take several weeks.

2. Hyperkalemic periodic paralysis (HPP)[38, 91, 162, 174, 297]

a. Hyperkalemic periodic paralysis is an uncommon autosomal dominant genetic disease in people that has been reported in one dog. The clinical hallmark of HPP is episodic flaccid muscle weakness, which often leads to transient (usually of less than 1 hr) paralysis. The episodes are typically induced by exercise and exposure to cold environmental temperatures. Part of the clinical definition of HPP is exacerbation of clinical signs following oral potassium administration. The physiologic mechanisms involved in this disorder are not well understood, but are thought to involve excessive release of potassium from the myofiber across the sarcolemma and/or increased passive motion of sodium across the sarcolemma into the sarcoplasm. Abnormal glucose metabolism has also been implicated as a contributor to fluctuating serum potassium levels in patients with HPP. The weakness is thought to be due to muscle release of potassium ions, rather than a response of muscle to high serum levels of potassium. Although episodes are typically associated with elevated serum potassium levels, this is not always demonstrable. Also, the elevated serum potassium levels are increased as compared to precollapse levels, but are often still within the normal range.

b. In people with HPP, clinical signs of dysfunction initially occur in infancy or early childhood. The one reported case in a dog occurred in a 7-mo-old female Pit Bull. The dog began collapsing approximately once a day, usually coincident with playing. Weakness typically began with the pelvic limbs and would quickly progress to involve the thoracic limbs. The dog's neck became limp, her tongue would protrude, and she would collapse. The episodes lasted approximately 10–15 sec. After 3 mos, the episodes had increased in frequency to several times a day. There was no impairment of consciousness during the episodes.

c. Diagnosis of HPP is supported primarily by demonstrating an exacerbation of clinical signs following oral potassium administration, as well as a positive response to therapy. Sustained elevation of serum potassium levels associated with collapsing episodes also supports a diagnosis of HPP. There may or may not be EMG abnormalities in HPP patients, and CK levels are typically normal to slightly elevated. Muscle biopsy results are normal in HPP. In the reported dog, a few fibrillation potentials were documented in the lumbar musculature, and the CK was slightly elevated at one time, normal at another. A muscle biopsy revealed no abnormalities. A sustained elevation of serum potassium was demonstrated after a brief period of exercise, although this level remained within reference range. The dog experienced marked worsening of clinical signs following oral potassium administration on two separate occasions.

d. Treatment with acetazolamide in people with HPP is very effective, usually leading to the cessation of collapsing episodes within 24 hrs of treatment initiation. Acetazolamide is thought to stimulate the release of both insulin and glucagon, which subsequently promotes the movement of potassium ions into muscle cells. Other therapies reportedly used in human HPP include mineralocorticoids, salbutamol, and thiazide drugs. There is some evidence that glucocorticoids may worsen collapse episodes in HPP. Administration of carbohydrates may reduce episode severity. The dog with HPP was treated with oral acetazolamide and no further collapsing episodes occurred.

3. Hyperadrenocorticoid (Cushing's) myopathy[38,43,70,118,125,172,179,194,200,290,301]
   a. Excessive circulating glucocorticoid levels, whether due to endogenous production or exogenous administration of glucocorticoids, can lead to a myopathy in dogs and cats. The physiologic mechanism(s) behind the development of the myopathy is (are) not fully understood. There is some evidence that elevated plasma glucocorticoid levels may interfere with muscle fiber mitochondrial function. Additionally, a diminished muscular Na^+, K^+-ATPase concentration has been demonstrated in dogs with pituitary-dependent hyperadrenocorticism (PDH). This is believed to contribute to muscular weakness seen in dogs affected by PDH. Type II fiber atrophy is a consistent histopathologic feature of this myopathy.
   b. Most dogs with naturally occurring hyperadrenocorticism are middle-aged, small-breed dogs. Clinical signs of glucocorticoid excess (polyuria/polydipsia, polyphagia, pendulous abdomen) are typically noted prior to clinical signs of myopathy. A stiff, stilted gait (especially in the pelvic limbs), weakness, and muscle atrophy may be apparent with hyperadrenocorticoid myopathy. Both clinical signs and diagnostic test results may be consistent with myotonia, hence the terms "Cushing's myotonia" and "pseudomyotonia."
   c. Diagnosis is based upon clinical signs of a myopathy in a patient with hyperadrenocorticism, as well as upon specific diagnostic tests. Subclinical myopathy has also been documented in dogs with hyperadrenocorticism. The authors have witnessed one dog (12-yr-old female spayed Miniature Poodle) with confirmed atypical hyperadrenocorticism develop similar myopathic signs. This patient had significantly elevated sex steroid levels and a normal cortisol. Other abnormalities supporting the diagnosis may include elevated CK levels, abnormal discharges on EMG examination (sometimes including waxing and waning "dive-bomber" potentials and other bizarre high-frequency discharges), and both type I and type II fiber atrophy (type II atrophy may predominate) apparent on muscle biopsy samples. Accumulation of intramyofiber lipid droplets and "ragged red fibers" (see "Lipid storage and mitochondrial myopathies" section below) has also been reported in cases of hyperadrenocorticoid myopathy.
   d. Treatment of this myopathy depends upon correcting the underlying problem causing the hyperadrenocorticism (e.g. mitotane treatment for PDH, discontinuing oral prednisone therapy with iatrogenic hyperadrenocorticism). The prognosis for resolution of the myopathy after correcting the underlying disorder is guarded to good.
4. Hypothyroid myopathy[38,42,67,159,172,179,194,301]
   a. There is evidence in humans as well as in dogs that hypothyroidism may cause a myopathy. The pathogenesis is unknown. Potential mechanisms include abnormal carbohydrate metabolism, abnormal myofiber mitochondrial activity, problems with triglyceride turnover, and deranged cation transfer across the sarcolemma. On muscle biopsy, type II fiber atrophy, predominates.
   b. The best-documented cases of hypothyroid myopathy in dogs were subclinical. However, the lethargy and intolerance to exercise exhibited by some hypothyroid dogs may be due in part to myopathic changes. The clinician should bear in mind that hypothyroid neuropathy may produce similar nonspecific signs of weakness.
   c. Diagnosis of this condition may be difficult (see the "Hypothyroid neuropathy" section in Chapter 17). An abnormal thyroid-stimulating hormone response test supports the diagnosis of hypothyroidism. CK levels may be elevated and EMG examination may reveal abnormal muscle activity. Muscle biopsy may reveal preferential type II fiber atrophy. Similar to hypothyroid neuropathy, resolution of clinical signs with thyroid supplementation should support the diagnosis.
   d. The prognosis for recovery is unknown, due to the absence of well-documented clinical cases.

5. Malignant hyperthermia[9, 12, 14, 23, 38, 49, 54, 84, 94, 97, 167, 168, 175, 193, 226–228, 236, 237, 265, 353]
   a. This is a potentially life-threatening disorder described primarily in dogs, but also in cats. The human disorder is very similar to the canine disease. There is some evidence that malignant hyperthermia may be inherited as an autosomal dominant trait in dogs. The underlying disorder is abnormal calcium (Ca^{++}) release channels in the sarcoplasmic reticulum of myofibers. Sustained calcium release causes sustained muscle contraction with subsequent elevations in body temperature. Although symptoms vary in both severity and the rate of onset, severe and progressive hyperthermia (exceeding 107 °F) with accompanying acidosis and hypoxia can sometimes rapidly lead to death without prompt and aggressive therapy. The most common triggers for hyperthermic episodes appear to be volatile anesthetic agents (halothane, isoflurane, sevoflurane) and depolarizing neuromuscular agents (succinylcholine). In some patients, excitement, stress, or exercise can induce hyperthermic episodes. Finally, one report suggests that the ingestion of hops from home-brewing kits can induce malignant hyperthermia episodes in dogs.
   b. Unfortunately, clinical signs may not be apparent until a life-threatening hyperthermic episode is triggered. However, susceptible dogs may have hyperactive temperaments, hypertrophic-appearing muscles, and high normal to slightly elevated resting rectal temperatures. Some of these patients may also have mild elevations of serum CK levels. Clinical signs of a hyperthermic episode can occur within minutes to a few hours after a triggering event and may include tachypnea, tachycardia, elevated temperature, limb muscle rigidity, and myoglobinuria. Severe metabolic acidosis can develop rapidly. CK levels may also be increased. Respiratory and cardiac arrest may occur quickly, especially if appropriate therapy is not instituted immediately. In anesthetized patients, increased CO_2 production appears to be the earliest indication of a hyperthermic episode, so capnography is recommended in suspect patients. Some dogs with the exercise-induced form of the disease may have a history of intolerance to mild to moderate exercise with clinical signs of muscle weakness of varying severity.
   c. Definitive diagnosis of malignant hyperthermia can be attained with in vitro caffeine- or halothane-contracture tests, using muscle biopsy tissue from a suspect patient. Unfortunately, this mode of testing is difficult to perform and is not widely available. The muscle sample is exposed to a level of caffeine or halothane that will not cause muscle contracture in a normal animal. A contracture response by the muscle tissue supports a diagnosis of malignant hyperthermia. Histopathologic changes in muscle biopsy samples tend to be either inapparent or mild and nonspecific. A tentative diagnosis is based upon observing a hyperthermic episode associated with a known triggering incident. When confronted with an exercise-intolerant animal in which malignant hyperthermia is suspected, the clinician must be extremely cautious when attempting to reproduce the reported symptoms by exercising the patient. An inordinate increase in rectal temperature (e.g. from normal to 105 °F or above) after a short period of mild exercise in a relatively cool environment is very suspicious for the exercise-related form of malignant hyperthermia. A suspect patient should not be exercised to the point of collapse, and provisions should be made to allow for the rapid cooling of the patient at a moment's notice. In other words, the clinician should not assume that a severe positive response will not be induced in a suspect patient; prepare for the worst-case scenario.
   d. Treatment of the patient experiencing a hyperthermic episode will vary somewhat depending upon the severity of the episode. In all suspected cases, all potentially triggering anesthetics and/or neuromuscular blocking agents should be discontinued. Measures to reduce the body temperature are instituted immediately as well, such as cold-water lavages and enemas, and placing ice packs over large superficial veins. Non-calcium-containing intravenous fluids may be used to manage hyperthermia, and must frequently be used to treat hypotension. Dantrolene sodium is a drug that blocks calcium release from the sarcoplasmic reticulum; it is recommended intravenously at a dosage of 2–3 mg/kg in cases of malignant hyperthermia. If metabolic acidosis is suspected or confirmed, intravenous sodium bicarbonate should be administered as needed. Hyperkalemia, if present, may be treated with intravenous fluids, insulin, and glucose. There is no maintenance treatment to prevent further hyperthermic episodes in malignant hyperthermia patients, other than avoiding likely triggers of these episodes. The prognosis is guarded, but may be improved by early recognition and treatment of this disorder.
6. Exertional myopathy[8–10, 38, 87, 249, 260, 342]
   a. Also referred to as exertional rhabdomyolysis, this disorder has been described primarily in racing Greyhounds. The pathogenesis is unknown but may involve abnormal myofiber glycogen metabolism or electrolyte abnormalities. Exercise induces a series of events culminating in muscle swelling and necrosis.
   b. Clinical signs typically occur associated with a race and include myalgia, tachypnea, and extreme distress. Myoglobinuria may develop in severe cases.

c. Diagnosis is based upon characteristic clinical features of the disorder in a susceptible dog (e.g. racing Greyhound). CK levels will be markedly elevated and muscle biopsy samples reveal multifocal hemorrhage and myofiber necrosis. These patients may also have varying degrees of metabolic acidosis.

d. Treatment consists of intravenous fluid therapy to prevent or correct hypovolemic shock and to aid in the renal excretion of myoglobin. Some dogs will be hyperthermic and will need to be cooled down (see "Malignant hyperthermia" section above). Intravenous sodium bicarbonate may also be indicated in severely acidotic patients. Suggested preventative measures include proper air-conditioning of kennels, decreasing the frequency of racing in susceptible dogs, oral potassium and sodium bicarbonate supplementation, and cool-water baths to reduce body temperature immediately prior to racing. The prognosis for this condition is guarded and depends upon the severity of clinical signs. Dogs with severe symptoms and myoglobinuria are in danger of dying of renal failure within 48 hrs.

7. Lipid storage and mitochondrial myopathies[22, 47, 98, 99, 127, 138, 152, 153, 157, 207, 238, 242, 250, 254, 287, 289, 296, 301, 306, 313, 332]

a. Defects in myofiber energy metabolism leading to myopathies are well characterized in humans. Though the specific metabolic defects have not been fully characterized, analogous disorders occur in dogs. Glycogenolysis provides energy to myofibers for rapid and strenuous activity (mainly type II fibers), but most of the energy provided to myofibers at rest, for normal levels of activity, and for sustained low-intensity exercise, is derived from free fatty acids via beta-oxidation in the mitochondria (mainly type I fibers).

Fatty acids undergo an ATP-dependent acylation reaction with coenzyme A (CoA), prior to oxidation, forming fatty acyl-CoA molecules. The amino acid carnitine is required to transport these "activated" fatty acids across the inner mitochondrial membrane so that they can be oxidized by the mitochondrial respiratory chain enzymes to produce energy. An enzyme called carnitine palmitoyl transferase (CPT) is necessary for binding of the carnitine molecule to the free fatty acid (with subsequent release of the CoA molecule), prior to transport across the inner mitochondrial membrane. The fatty acyl-carnitine ester is transported across the inner mitochondrial membrane by a carrier protein.

Carnitine also has an important buffering function in the myofiber. If short and medium chain fatty acyl molecules accumulate within the mitochondria, they can interfere with mitochondrial function. Carnitine is required to bind to these fatty acyl groups, forming acyl-carnitine esters that can be transported out of the mitochondria and excreted in the urine.

Lipid storage myopathies include primary (uncommon) and secondary carnitine deficiency, as well as deficiency of the CPT enzyme. Histopathologically, myofibers exhibit increased levels of lipid inclusions in most of these disorders, especially in type I fibers. The mitochondrial myopathies include a wide spectrum of possible defects in energy substrate transport and utilization, particularly defects in electron transport and oxidative phosphorylation. The majority of mitochondrial myopathies are due to mutations of mitochondrial DNA. Histopathologically, abnormal subsarcolemmal accumulations of mitochondria may give the characteristic appearance of "ragged red fibers" when a trichrome stain is used. However, many mitochondrial myopathies are not associated with "ragged red fibers."

There is considerable overlap between lipid storage and mitochondrial myopathies and the distinction between the disorders is often unclear. Some mitochondrial myopathies may be characterized by lipid accumulation within myofibers, and many cases of secondary carnitine deficiency may be due to an underlying mitochondrial defect. A defect in the mitochondrial respiratory enzyme chain is likely to lead to mitochondrial accumulation of short and medium chain fatty acyl molecules, proximal to the defect. By virtue of its buffering capacity, carnitine is likely to become depleted secondarily, with carnitine being lost in the urine as acyl-carnitine esters. Therefore, a carnitine-associated lipid storage myopathy may develop secondarily to an underlying mitochondrial myopathy.

b. There are a number of reports of suspected lipid storage and mitochondrial myopathies in dogs. In one report, the clinical pathologic features of 25 dogs with lipid storage myopathies were described. Most of the reported dogs with lipid storage myopathies have been adults. Clinical signs of dysfunction include acute and chronic myalgia (often difficult to localize), weakness, muscle atrophy, stiffness, lameness, exercise intolerance, and tremors. Cardiomyopathy appears to be a rare presentation in dogs, and is usually associated with primary carnitine deficiency in humans. Suspected mitochondrial myopathy has been reported in juvenile Clumber and Sussex Spaniels, as well as young adult Old English Sheepdog littermates. These patients exhibited exercise intolerance, as well as exercise-induced metabolic acidosis. Serum levels of both lactate and pyruvate were elevated in these dogs after exercise. A deficiency of pyruvate dehydrogenase phosphatase has been demonstrated in the

Clumber and Sussex Spaniels and a specific mutation identified in the *PDP1* gene in both breeds. The exact biochemical defect in the sheepdogs is currently unknown.

c. Diagnosis of these disorders rests heavily on the histopathologic demonstration of intramyofiber lipid accumulation (lipid storage myopathies) and/or "ragged red fibers" (mitochondrial myopathies) in fresh frozen muscle biopsy samples of patients with clinical evidence of myopathy. These abnormalities are found mainly in type I fibers. CK levels may or may not be elevated in these disorders, and EMG findings may or may not reveal abnormalities. Abnormal levels of various urinary organic acids and plasma amino acids often support a metabolic abnormality in fatty acid oxidation as a cause for myopathy. Serum lactate and pyruvate levels may be helpful both in differentiating between lipid storage and mitochondrial myopathies and in identifying the specific defect in mitochondrial disorders.

In the report of 25 dogs, all cases demonstrated lactic acidosis, as well as increased urinary levels of lactate, pyruvate, and alanine. A defect in mitochondrial oxidative function (mitochondrial myopathy) was suspected in the majority of cases. Carnitine levels in serum, muscle, and urine can also help identify primary and secondary carnitine deficiency myopathies. In the 25 dogs with lipid storage myopathy, elevated urinary levels of carnitine and carnitine esters were found in all but two cases, but plasma carnitine levels were normal in all but two dogs. A secondary loss of carnitine due to a mitochondrial defect was suspected.

d. Information concerning treatment and prognosis is scant, although there is anecdotal evidence that dogs with lipid storage and mitochondrial myopathies may respond to various treatments. Some patients with carnitine deficiency will show a clinical response to oral L-carnitine supplementation (50 mg/kg, q 12 hrs). Oral supplementation with riboflavin (50–100 mg per day), vitamin C (50 mg/kg per day), and coenzyme Q (1 mg/kg/day) have been recommended for people with mitochondrial myopathies, but the efficacy of these treatments is questionable. There is some evidence in people with mitochondrial myopathies that creatine monohydrate may be beneficial. Finally, dietary management, including a low-fat, high-carbohydrate, high-protein diet, supplemented with medium-chain triglycerides, may provide some benefit by bypassing the nonfunctional pathway(s) in some of these disorders.

8. Glycogen storage disorders (glycogenoses)[35, 37, 75, 108, 113, 114, 126, 142, 179, 191, 301, 348]

   a. This is a group of rare inborn errors of metabolism in which an enzyme necessary for the synthesis or degradation of glycogen is deficient. Histopathologically, vacuolated myofibers are often observed, the vacuoles being filled with glycogen.

   b. Clinical signs of glycogen storage diseases usually develop in the first year of life and typically include progressive muscular weakness (often exercise related), muscle atrophy, and poor growth, as compared to normal littermates. However, a glycogen storage disorder with delayed manifestations of clinical signs was reported in a 10-yr-old Abyssinian cat with a 4-yr history of neuromuscular dysfunction. Some patients may have megaesophagus with resultant regurgitation and aspiration pneumonia, and some may have cardiac abnormalities. The glycogen storage diseases reported in dogs and cats include:

      1. Glycogenosis type II (acid maltase or a-1, 4-glucosidase deficiency)—described in Lapland dogs.
      2. Glycogenosis type III (amylo-1,6-glucosidase deficiency)—described in German Shepherd and Akita dogs. Glycogenosis type III with autosomal recessive inheritance has been reported in curly-coated retrievers. Progressive hepatomegaly is an additional clinical feature in these dogs.
      3. Glycogenosis type IV (a-1,4-D-glucan deficiency)—described in Norwegian Forest cats.
      4. Glycogenosis type VII (phosphofructokinase deficiency)—reported in English Springer Spaniel dogs. These dogs rarely exhibit clinical signs of myopathy. They usually exhibit compensated intermittent hemolytic anemia and hemoglobinuria, due to defective erythrocytes. This has also been reported in an American Cocker Spaniel dog. A syndrome of dyserythropoiesis, myopathy, and cardiac dysfunction has been described in related English Springer Spaniel dogs. However, this is not thought to represent a glycogen storage disease, but rather a defect in DNA synthesis and replication.

   c. Definitive diagnosis requires demonstrating deficient enzymatic activity for the enzyme of interest (e.g. leukocyte assay). Other supportive evidence includes clinical signs of myopathy in a young dog or cat of a suspect breed, abnormal CK levels and/or EMG activity, and evidence of myofiber glycogen accumulation on muscle biopsy. A genetic test has been developed to identify curly-coated retriever carriers for glycogenosis type III.

   d. There are no effective treatments for these diseases and most patients are euthanized due to progressive debilitation within the first 1–2 yrs of life.

C. Inflammatory/infectious

1. Masticatory myositis[4, 8, 38, 101, 116, 118, 179, 192, 219, 230, 240, 243, 252, 255, 263, 270, 274, 297, 299–302, 307, 316, 341, 364] (Video 38)

a. This is an autoimmune disorder in which antibodies are directed against the muscles of mastication (e.g. temporalis, masseter, pterygoid muscles). The pathogenesis of this disease is uncertain, although recent studies have uncovered a primary role of lymphocytes, particularly T cells, in this disorder. The distinct myosin isoform and myofiber type (type II M) of masticatory muscles may explain why they are preferentially targeted by the immune response. These type II M myofibers have a different embryologic origin (branchial arch mesoderm) than appendicular myofibers (paraxial mesoderm), and are believed to be antigenically distinct from these latter fiber types.

b. Dogs of numerous breeds (usually large breeds) and both sexes have been reported with this disorder, but the German Shepherd dog seems to be particularly predisposed to it. Most dogs with masticatory myositis are young adults. However, juvenile onset of masticatory myositis has been reported in 12-wk-old Cavalier King Charles Spaniel dogs. Cats are rarely reported with this disorder. Clinical signs typically include painful swelling of the masticatory muscles and varying degrees of trismus (Fig. 18.21). Clinical signs are often acute in onset and may be recurrent. Exophthalmos and fever are also occasionally observed. Palpation of the masticatory muscles and attempts to force the jaws open often elicit a painful response (Fig. 18.22). Some dogs have a history of chronic masticatory muscle atrophy without obvious painful swelling. These dogs may represent a more chronic form of masticatory myositis, neurogenic atrophy from trigeminal neuritis, or a distinct atrophic myopathy of masticatory muscles.

c. Diagnosis of masticatory myositis is attained by demonstrating antibody localization to type II M myofibers with the immunoreagent staphylococcal protein A conjugated to horseradish peroxidase (SPA-HRP). This can be done using frozen sections of the patient's temporalis muscle or incubating the patient's serum with normal stored frozen canine muscle and the immunoreagent. Although this test has a high sensitivity and specificity, testing for circulating autoantibodies against type II muscle fibers may yield falsely negative results in a small subset of dogs with masticatory myositis. CK levels may also be elevated and EMG examination often reveals abnormalities. Computed tomography (CT) and/or magnetic resonance imaging (MRI) may aid in the diagnosis of dogs with this disorder, by showing inhomogeneous contrast enhancement, changes in size, and focal changes in attenuation of masticatory muscles. EMG evaluation of the masticatory muscles is likely to reveal fibrillation potentials and positive sharp waves. Muscle biopsies may reveal mixed inflammatory infiltrates, including lymphocytes, macrophages, histiocytes, and, less frequently, eosinophils. Neutrophils are rarely seen. Biopsy results may also reveal myofiber necrosis and phagocytosis, and can be helpful in determining the prognosis for recovery.

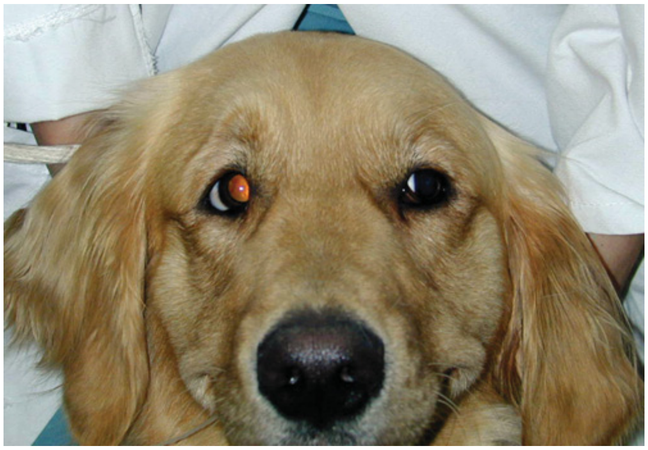


Figure 18.21 Golden Retriever dog in the acute phase of masticatory myositis showing swelling of the temporalis muscles.

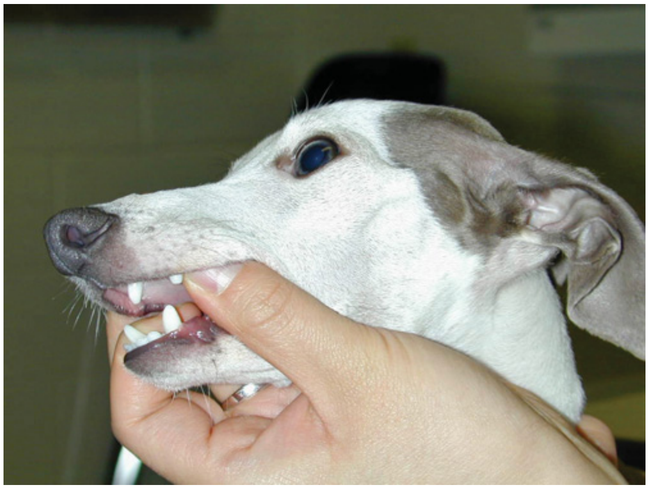


Figure 18.22 Dog with profound atrophy of the muscles of mastication due to masticatory myositis. The mouth could only be opened a few millimeters.

d. Treatment is immunosuppressive doses of prednisone (1–2 mg/kg per os, q 12 hrs) for 3–4 wks, after which the dosage is tapered to every other day. Tapering is slowly continued in order to achieve the lowest every-other-day dosage that will control clinical signs. Most dogs will show a favorable response to therapy, but relapses are common. In some cases, prednisone can be replaced by azathioprine or cyclosporine as the maintenance immunosuppressant drug, relieving some or all of the side effects associated with glucocorticoid therapy. In general, the prognosis for this disease is favorable, although muscle atrophy and/or reduced function may persist.

2. Extraocular myositis[33, 63, 101, 255, 263, 324]
   a. An inflammatory myositis restricted to the extraocular muscles has been reported infrequently in dogs. The pathogenesis is unknown but may involve an autoimmune reaction to antigenically distinct muscle fibers unique to extraocular muscles, similar to the situation in masticatory myositis.
   b. Dogs reported with disorder have ranged between 6 mos and 8 yrs of age. No sex predilection has been found. Six of the 10 dogs were Golden Retrievers in one report. Other breeds have included a German Shepherd dog, a Doberman Pinscher, a Bull Mastiff, a Dachshunds, and a mixed-breed dog. The predominant clinical sign seen is bilateral exophthalmos of acute onset (Fig. 18.23). One dog exhibited unilateral exophthalmos. Visual deficits and increased intraocular pressures have been noted in one dog.
   c. Diagnosis is based primarily upon clinical signs and muscle biopsy results. Fine-needle aspiration cytology of affected muscles is an alternative to muscle biopsy, and may provide evidence of an inflammatory infiltrate. EMG of the extraocular muscles may reveal abnormalities. A CK level was measured in one dog with this disorder and found to be normal. In one report, marked swelling of the dorsal rectus muscles was evident on ultrasonography of the globe. Histopathologic findings on muscle biopsy include inflammatory infiltrates with myofiber necrosis and phagocytosis, as well as areas of hemorrhage. In one dog that was euthanized and necropsied (no therapy attempted), all extraocular muscles except the retractor bulbi muscles were abnormal. No other muscle groups were affected.
   d. Clinical signs resolved spontaneously in one dog and in all the remaining dogs that were reportedly treated with oral immunosuppressive glucocorticoid therapy. One dog relapsed following glucocorticoid discontinuation, but responded favorably to a reinstitution of therapy. The prognosis for this disorder appears to be favorable.

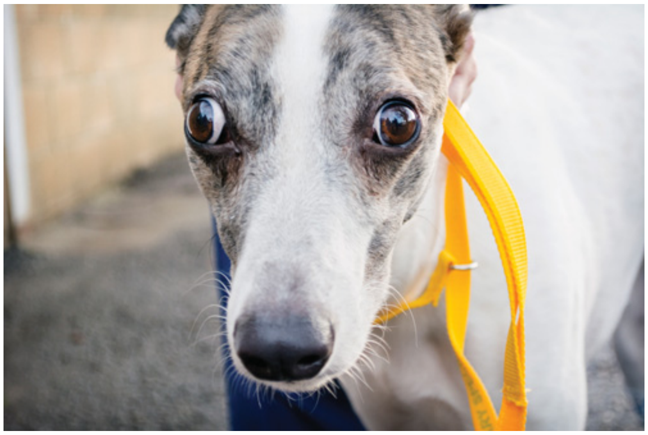


Figure 18.23 Extraocular myositis in a dog.

3. Laryngeal/pharyngeal myositis[34, 187, 263, 279, 298]
   a. Laryngeal and pharyngeal dysfunction associated with evidence of a localized inflammatory myopathy has been described in three dogs, including a 7-yr-old male Boykin Spaniel, a 10-yr-old male Alaskan Malamute, and a 3-yr-old female Bouvier des Flandres. Additionally, an inflammatory myopathy resulting in pharyngeal dysfunction alone has been reported in three Boxer dogs (4, 6 and 7 yrs old) and a 2.5-yr-old Briard. The pathogenesis for this disorder is unknown.
   b. Clinical signs may be consistent with laryngeal paralysis (see Chapter 17) and/or functional dysphagia of chronic duration.
   c. Elevated CK levels were seen in the Boxers and the Briard with functional dysphagia. Esophagraphy can be used to distinguish functional from morphologic dysphagia. EMG abnormalities (fibrillation potentials, positive sharp waves, complex repetitive discharges) and histopathologic evidence of an inflammatory myopathy (e.g. inflammatory infiltrates, myofiber necrosis and phagocytosis) may be restricted to the laryngeal and/or pharyngeal musculature. Evidence of mild focal inflammation has been reported in the temporalis musculature, the masseter muscles, and in tongue, diaphragmatic, and gluteal muscles in dogs with laryngeal/pharyngeal myositis. Testing for autoantibodies against type IIM muscle fibers was negative in all four dogs in which this test was performed.
   d. Treatment protocols and prognosis for this disorder are as of yet undetermined, due to the small number of cases. One dog was euthanized due to respiratory distress, one was treated surgically (laryngoplasty), and one responded to a combination of corticosteroids and thyroid replacement therapy.
4. Autoimmune polymyositis[8, 25, 38, 80, 90, 101, 115, 121, 133, 134, 179, 182, 199, 209, 230, 255, 261, 263, 283, 297, 301, 326, 330, 356] (Video 39)
   a. This is an autoimmune inflammatory disease of unknown pathogenesis, primarily affecting the appendicular muscles. It is more commonly reported in dogs than cats. While there is usually no identifiable cause for the immune response, systemic lupus erythematosus, the use of trimethoprim-sulfa drugs in Doberman Pinschers, and thymomas (usually in conjunction with acquired myasthenia gravis) have all been associated with the development of this condition. Breed-associated polymyositis has been reported in Newfoundlands, Boxers, and Hungarian Vizsla dogs, frequently demonstrating circulating autoantibodies

against a sarcolemmal antigen. In the Hungarian Vizslas, an association between an MHC-2 haplotype and increased risk of polymyositis was found. This supports an autoimmune etiology. A unique inflammatory myopathy with secondary tongue atrophy has also been identified in Pembroke Welsh Corgi dogs.

b. While any breed of dog can be affected with this disorder, large-breed dogs, Boxers and Newfoundlands appear to be overrepresented. Dogs of any age or sex may develop autoimmune polymyositis, although most are middle-aged. Clinical signs may be acute or chronic and can include generalized weakness that is often worsened by exercise, hyperesthesia upon muscle palpation (myalgia), regurgitation (due to megaesophagus), dysphagia, depression, fever, muscle swelling in the acute phase, muscle atrophy in the chronic phase, shifting leg lameness, and voice change. Pembroke Welsh Corgi dogs exhibited dysphagia with severe tongue atrophy, facial muscular atrophy, and occasional walking difficulty. Histopathologic examinations of the two dogs with clinical symptoms revealed moderate to severe inflammatory lesions characterized by lymphohistiocytic infiltration and muscular atrophy in the tongue and/or femoral muscles. Decreased or absent spinal reflexes may be infrequently seen in dogs with generalized weakness. Affected Newfoundlands appear to present with clinical signs earlier than dogs of other breeds (reported age range from 6 mos to 5 yrs), and more frequently present with dysphagia and/or megaesophagus. None of the reported Newfoundlands exhibited myalgia. A recent study reported eight Boxers diagnosed with round cell tumors (lymphoma, plasmacytoma, and anaplastic round cell tumor) months after developing autoimmune polymyositis, suggesting that the latter may represent a preneoplastic syndrome in this breed. In these cases neoplastic cells were not seen in the original muscle biopsies, but could be detected in subsequent biopsies. The recently reported polymyositis disorder of Hungarian Vizsla dogs is characterized by masticatory muscle atrophy and pharyngeal dysphagia.

A combination of autoimmune polymyositis and masticatory myositis, defined as an overlap syndrome, has been reported in dogs. In these cases, biopsy results were most consistent with generalized autoimmune polymyositis, although testing for type IIM autoantibodies was also positive. This syndrome was hypothesized to be a more severe disorder than the individual types of inflammatory myositis, due to the demise of two out of the three affected dogs (the third dog was lost to follow-up).

Additional subtypes of generalized, presumed autoimmune, polymyositis have been described. These disorders were described recently under the category of unclassified myopathies. Affected dogs in this report overall resembled those with autoimmune polymyositis clinically, although mean ALT levels were significantly higher in dogs with unclassified myositis. Two out of the seven dogs in this report showed myalgia, while six out of seven were febrile. An additional report describes five dogs with inflammatory myopathies with primarily histiocytic inflammatory infiltrates on muscular biopsies. Interestingly, two of the dogs in this report also showed myalgia and two were febrile on physical examination. A similarity to human histiocytic muscle disorders was proposed.

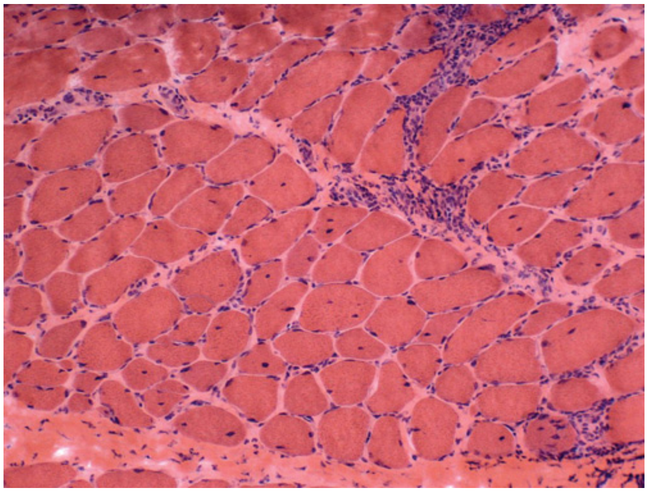


Figure 18.24 Histopathology of a muscle biopsy of a dog with polymyositis showing endomysial and perimysial nonsuppurative cellular infiltration (H&E stain).

c. Diagnosis is based upon typical clinical findings, as well as results of various diagnostic tests. CK and AST levels may be elevated. EMG examination typically reveals multifocal or diffuse abnormalities, and muscle biopsy reveals myofiber necrosis, phagocytosis, and regeneration, with a nonsuppurative inflammatory infiltrate (Fig. 18.24). Immunoglobulin localization to the sarcolemma may also be demonstrable immunohistochemically. Reports of MRI in dogs with myositis describe diffuse increases in signal intensity on T2-weighted (T2-W) images, decreased signal intensity on T1-weighted (T1-W) images, and marked contrast enhancement within affected muscles.

d. Initial treatment consists of oral prednisone therapy at immunosuppressive doses (e.g. 1–2 mg/kg, q 12 hrs) until clinical remission is achieved, with subsequent tapering of the dose. Other immunosuppressive drugs are also often effective and can ameliorate glucocorticoid side effects, though some may have a more delayed onset of clinical effect (e.g. azathioprine)

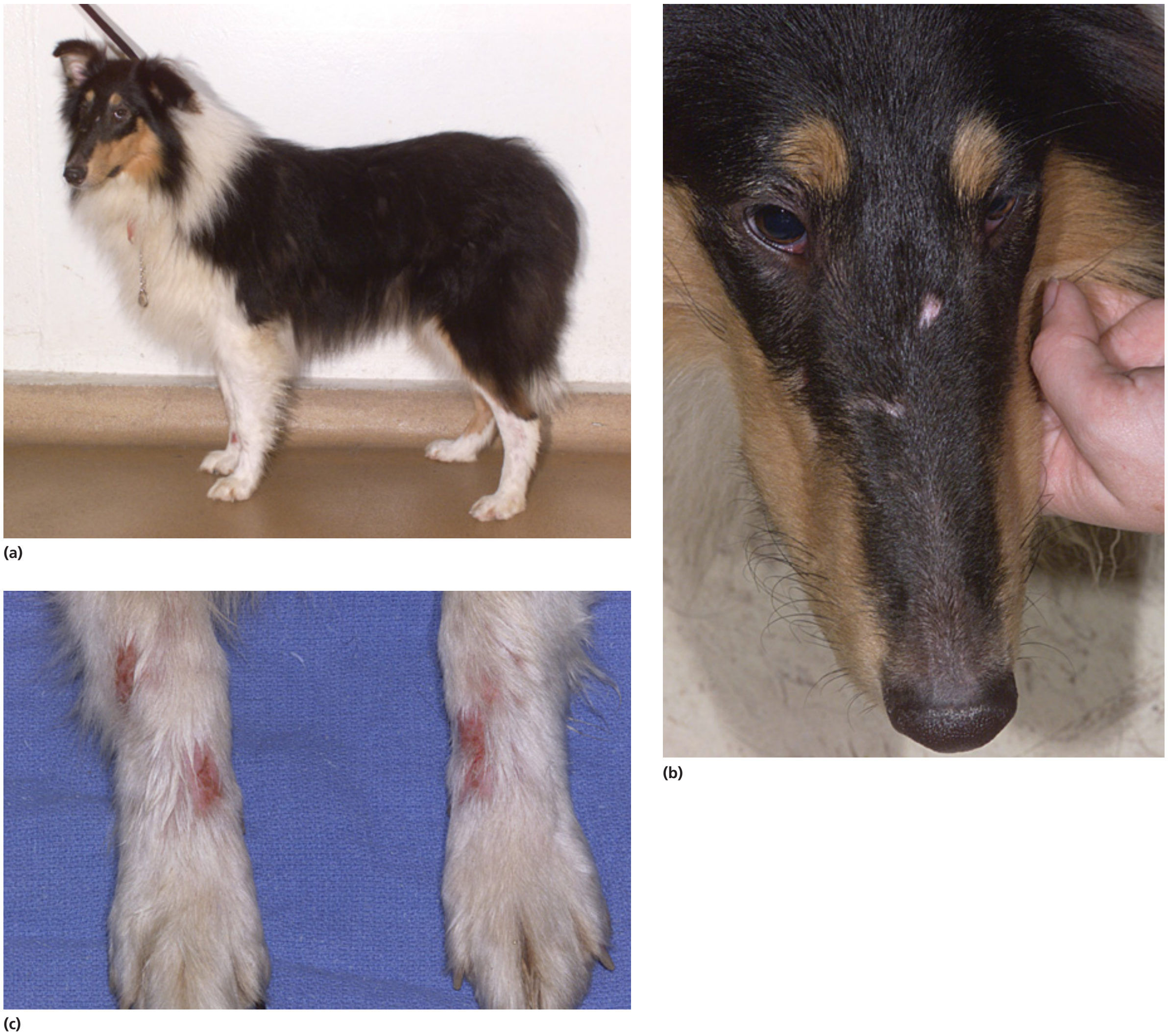


Figure 18.25 (A, B, C). Characteristic skin lesions in a Collie with dermatomyositis. (Dr. L Cole, The Ohio State University, Columbus, OH. Reproduced with permission from Dr. L Cole.)

compared with prednisone. Muscle regeneration may occur if the inflammatory process is halted prior to exhaustion of the muscle's regenerative capacity. The prognosis is generally favorable, although relapses may occur.

5. Dermatomyositis[35, 38, 59, 73, 121, 139, 140, 143, 144, 154, 170, 179, 188, 253, 267, 297, 301, 359]
    a. Best described in Collie dogs, this is an inflammatory disorder of skin, and to a lesser extent muscle, that is believed to be immune-mediated (autoimmune) and heritable as an autosomal dominant trait. This disorder is also recognized in Shetland Sheepdogs and has been reported in a Pembroke Welsh Corgis, as well as an Australian Cattle dog.
    b. Clinical signs of dermatitis usually begin between 2 and 6 mos of age in Collies and Shetland Sheepdogs. Skin lesions predominate in the facial area, especially the nose, lips, and tips of the ears (Fig. 18.25). Some dogs will develop lesions around bony prominences of the lower limbs and sternum. Clinical signs of myositis are typically mild or inapparent (especially in Shetland Sheepdogs) and develop after the skin lesions are noticed. Some dogs may have only temporalis and masseter muscle atrophy. Other dogs may develop more prominent signs of a myopathy, such as a stiff gait with exercise intolerance, megaesophagus, and dysphagia. Clinical signs associated with both the dermatitis and myositis tend to wax and wane and most dogs resolve spontaneously by 6–8 mos of age.
    c. Diagnosis is based mainly upon signalment and clinical signs. CK levels are usually normal, but EMG evaluation usually reveals abnormalities in patients with myositis. Skin and muscle biopsies confirm the

inflammatory disorder. In addition to inflammatory infiltrates in these biopsies, vasculitis is sometimes evident.

- **d.** Although the efficacy of immunosuppressive oral prednisone therapy is questionable, an initial dose of 1–2 mg/kg q 12 hrs, with subsequent tapering, is recommended. Since the disease tends to resolve spontaneously without therapy, it is difficult to assess the efficacy of this treatment. Hypoallergenic shampoos are recommended. Treatment with pentoxifylline appears to help resolve clinical signs in affected dogs as well. The prognosis is typically good for recovery.

6. Feline hyperesthesia syndrome (FHS)[68, 72, 208, 239, 264]

- **a.** Feline hyperesthesia syndrome is a well-described, yet poorly understood, disorder of unknown etiology. Affected cats intermittently display clinical signs suggesting an irritative phenomenon, and proposed causes have included behavioral and seizure disorders. There is recent evidence that FHS represents a myopathy, with histopathologic muscle biopsy features similar to inclusion body myositis in humans. Inclusion body myositis is a common idiopathic inflammatory myopathy of elderly people. Muscle biopsies from such patients contain numerous rimmed vacuoles (inclusion bodies) containing proteins that are commonly found in the brains of Alzheimer's patients (e.g. paired helical filaments, presenilin I, beta-amyloid precursor protein). Similar inclusions were recently identified in epaxial muscle biopsy samples from cats with FHS. Inclusion body myositis is believed to be a degenerative myopathy, with a secondary immune-mediated inflammatory response.
- **b.** Any age, breed, or sex of cat can develop FHS. There may be a predisposition for FHS to develop in Abyssinians, Burmese, Himalayans, and Siamese breeds. In a recent report, affected cats were all between 5 and 8 yrs of age at the onset of dysfunction. Clinical signs of the disorder include: rippling of the skin over the dorsum; muscle spasms in the thoracolumbar epaxial region; violent licking and biting at the back, flank area, pelvic limbs, and/or tail; agitated demeanor, apparently startling easily; excessive vocalization (e.g. growling, hissing, meowing); pupillary dilation; exaggerated tail motion; attacking inanimate objects or people; and running frantically. These abnormalities tend to occur episodically. Affected cats resent palpation of the thoracolumbar epaxial musculature. There are no neurologic deficits in cats with FHS.
- **c.** Diagnosis is based primarily on historical complaints and clinical signs. Bloodwork, spinal imaging, infectious disease titers, CSF analysis, and EEG evaluations are typically normal. Spontaneous EMG activity was documented in the thoracolumbar epaxial muscles of FHS cats in one report. All cats in this study had epaxial muscle biopsy findings similar to those found in human inclusion body myositis. Rimmed intramyofiber vacuoles, containing paired helical filaments and beta-amyloid, were found in biopsies from all affected cats.
- **d.** Feline hyperesthesia syndrome tends to progress over one to several years. Similar to human inclusion body myositis, no consistently effective therapies have been identified for FHS. Proposed treatment options include corticosteroids (prednisolone), tricyclic antidepressants (clomipramine, amitriptyline), and/or selective serotonin reuptake inhibitors (paroxetine, fluoxetine). Phenobarbital or pregabalin may also be used if the aforementioned options are not effective. Lifestyle changes—such as minimizing environmental stressors and/or preservative-free diets supplemented with coenzyme Q_{10}, carnitine, and omega-3 fatty acids—may be helpful as well. The prognosis for control of this syndrome is poor.

7. Infectious myositis[8, 17, 20, 35, 41, 55, 66, 78, 79, 118, 124, 160, 179, 204–206, 256, 259, 268, 291, 297, 325, 340]

- **a.** Although infectious myositis is relatively uncommon, there are numerous microbial agents that can lead to myopathies in dogs and cats. A detailed description of all these infectious myopathies is beyond the scope of this text. Most infectious myopathies are polymyopathies and represent a facet of multisystemic illness. Viral-associated myopathies are rare, but feline immunodeficiency virus (FIV) has been shown to induce a subclinical myopathy in experimentally infected cats. *Clostridium* species are most commonly implicated in bacterial myositis; these infections may be focal, involving one or several muscles in one limb. *Leptospira* species have also been associated with myositis in dogs. Protozoal myopathies include those due to *Toxoplasma gondii*, *Neospora caninum*, *Hepatozoon canis*, and *Babesia canis* and *B. gibsoni*. *Sarcocystis* species have been identified in canine and feline skeletal muscle. Two reports describe clinical disease in dogs due to sarcocystis-induced myositis. However, evidence of clinical disease in cats is lacking. Myositis can also be due to rickettsial infection (e.g. ehrlichiosis, Rocky Mounted spotted fever). Rarely, parasitic infestations (e.g. *Trichinella spiralis*, *Ancylostoma caninum*, *Trypanosoma cruzi*) are associated with myositis.
- **b.** Clinical signs typically include fever and myalgia. With bacterial infections, there may be a recent history of a bite wound or surgery. Clostridial infections are often characterized by palpable crepitus, due to gas accumulation in tissues. *Toxoplasma* and *Neospora* infections in young dogs often result in rigid hyperextension of the pelvic limbs, due to a combined

neuropathy/myopathy (see Chapter 17). Typical clinical findings in dogs with hepatozoonosis often include chronic myalgia, fever, cachexia, anorexia, lethargy, paresis, oculonasal discharge, and bloody diarrhea.

  c. Diagnosis of an infectious myositis is based upon demonstrating the presence of a likely causative infectious organism in a patient with myositis. In some cases, organisms are found in muscle biopsy samples; in others, serial serology or wound culture is necessary to identify the organism's presence. CK levels are likely to be elevated, and basic bloodwork may reveal evidence of a systemic inflammatory response (e.g. neutrophilic leukocytosis). Radiographic evidence of periosteal bone proliferation is a common finding in *Hepatozoon* infections of dogs.

  d. Treatment and prognosis are variable and depend upon the organism in question and the extent of the disease. The suggested references should be consulted for specific treatment regimens and prognostic information for these various diseases. Culture and sensitivity testing should be pursued with bacterial infections, to help guide antimicrobial therapy. Surgical drainage may be required in some cases. Antibiotics effective against anaerobes (e.g. penicillin, clindamycin, metronidazole) are recommended to combat clostridial infections. Penicillin, tetracyclines, and erythromycin are often initial drug choices for infections with *Leptospira* organisms. Trimethoprim-sulfa drugs, pyrimethamine-sulfonamide combination, and clindamycin are appropriate drug choices for *Toxoplasma* and *Neospora* infections. These drugs as well as the antiprotozoal/anticoccidial drugs toltrazuril and decoquinate are often used to combat *Hepatozoon* infections. Numerous drugs have been used for *Babesia* infections in dogs; diminazene aceturate and phenamidine isethionate appear to be most effective. Doxycycline is often used to treat rickettsial infections; chloramphenicol is also often effective.

8. Tetanus[1, 11, 13, 16, 18, 56, 86, 117, 119, 123, 135, 171, 244, 257, 276, 280, 284, 323, 369]

  a. Tetanus is not technically a disease of skeletal muscle. However, because the clinical effects primarily are associated with skeletal muscle, it is included in this chapter. This disorder is uncommon in dogs and rare in cats, and is caused by a tetanospasmin toxin (an exotoxin) produced by the vegetative form of the bacterium *Clostridium tetani*, an anaerobic, spore-forming bacillus. Dogs are very resistant to the effects of tetanus toxin, and cats are over 10 times more resistant than dogs. Spores of *C. tetani* are ubiquitous in the environment, and can be found in the feces and on the skin of normal dogs and cats. When spores are introduced into tissues under anaerobic conditions—such as penetrating wounds, contaminated body cavity surgery (e.g. ovariohysterectomy), or dental infections—they may germinate to become the vegetative exotoxin-producing form of the organism.

  Tetanospasmin toxin enters the telodendria of motor nerve axons at neuromuscular junctions of skeletal muscle (endplates), and then travels retrograde to eventually reach the CNS. The toxin may enter the endplate region directly from a nearby wound, or localize at endplates in several areas of the body following hematogenous dissemination. With hematogenous dissemination, some toxin may cross the blood–brain barrier directly to enter the CNS. The toxin interferes with the release of inhibitory neurotransmitters (primarily glycine, also GABA) by inhibitory interneurons in the spinal cord (Renshaw cells) and brain. The clinical result is uncontrolled and sustained skeletal muscle contraction, most evident in extensor muscles. The autonomic nervous system can also be affected by tetanospasmin toxin.

  b. Tetanus can be localized (i.e. involving one region of the body, such as the head or one limb) or generalized. Localized tetanus often progresses to generalized tetanus, but some cases may remain localized throughout the disease course. The onset of clinical tetanus after sustaining a wound or surgical contamination (if this is part of the history) is variable. The range is from 3 to 18 days, most often 5–10 days. Since cats are more resistant to the tetanus toxin, the delay may be up to 3 wks. In dogs, evidence of an active infection is often elusive and may not be present. Cats with tetanus typically will have a readily evident source of infection and toxin production. Muscle stiffness is the hallmark of tetanus in dogs and cats, whether it is localized or generalized. Localized tetanus of a limb is often associated with a wound on the affected limb. The affected limb is typically stiff and hyperextended. The stiffness may spread to the opposite limb (e.g. both pelvic limbs) and continue to progress to the thoracic limbs. Localized tetanus of the head region can also occur. This may represent an early stage of generalized tetanus after the hematogenous spread of the toxin, with the shorter cranial nerves affording a more rapid delivery of toxin to the CNS than the motor nerves of the extremities.

  Involvement of muscles around the head usually leads to very characteristic features. Facial muscle contraction is seen as narrowed palpebral fissures and a drawing back of the lips (*risus sardonicus*, or "rictus grin") as well as a wrinkling of the forehead with the tips of the ears being pulled toward each other (Fig. 18.26). Extraocular muscle involvement leads to enophthalmos with protrusion of the third eyelids, and masticatory muscle contraction results in an inability to open the mouth (trismus, or "lockjaw"). Ocular changes (including enophthalmos,

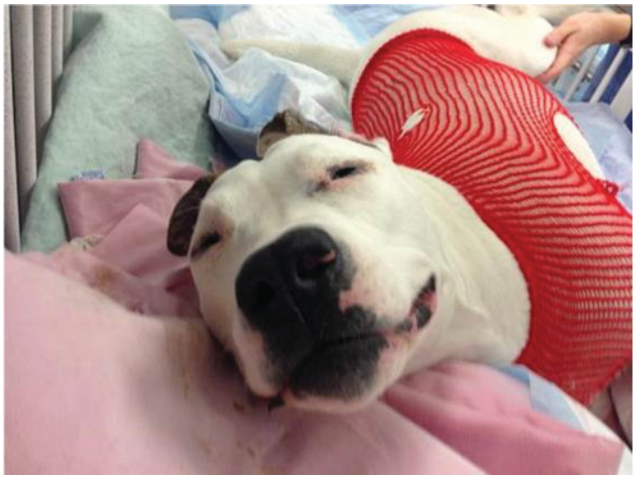


Figure 18.26 Typical facial features of tetanus in a dog. (Courtesy of Dr. Edward Copper, The Ohio State University.)

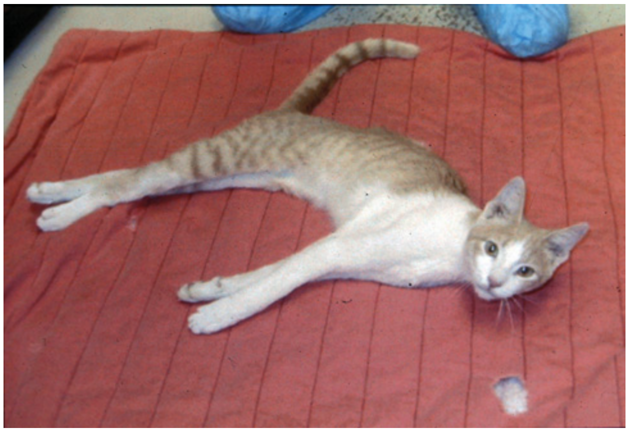


Figure 18.27 Cat with generalized tetanus, exhibiting rigid extension of all limbs and dorsiflexion of the tail.

blepharospasm, and strabismus) may be the only signs seen in early-stage tetanus. Laryngeal and pharyngeal musculature may also be affected, with resultant dyspnea (due to laryngospasm) and dysphagia, respectively. Ptyalism may also be seen. An increased respiratory rate is common in tetanus, due to the involvement of both the laryngeal and lower respiratory musculature. Affected animals often seem willing to eat, but have difficulty prehending and swallowing food.

Generalized tetanus is more common than localized, and many localized cases progress to become generalized. Generalized tetanus is usually characterized by stiffness and extensor rigidity of all limbs, along with the above-described clinical abnormalities involving the head region. If the patient remains ambulatory, the gait will be stiff and stilted, and a wide-based, “saw-horse” stance will be evident. If the patient is recumbent, the limbs are often held out in rigid hyperextension, with the tail curved dorsally (Fig. 18.27). Reflex muscular spasms tend to occur in response to tactile or auditory stimuli. Because of increased urethral and anal sphincter tone, urine retention and constipation often occur in tetanus patients. Some animals develop a hiatal hernia or megaesophagus with resultant regurgitation. Autonomic dysfunction (autonomic storms) may occur, leading to tachycardia, bradycardia, other cardiac arrhythmias (e.g. atrioventricular block, ventricular escape beats), hypotension, or hypertension. Parasympathetic overactivity has been reported to occur more frequently than sympathetic signs. Rectal temperature is often elevated in dogs and cats with tetanus, due either to sustained muscle contraction, persistent clostridial infection, or both. With generalized tetanus, death may result from progressive respiratory compromise.

c. Diagnosis of tetanus is usually based upon characteristic clinical features in addition to historical information (e.g. prior wounding or surgical procedure). Identifying an active source of infection and toxin production supports the diagnosis. However, in a subset of dogs with tetanus a wound or active infection may not be clinically evident. If an active infection is present, this may be reflected in bloodwork results (e.g. neutrophilic leukocytosis). EMG abnormalities and elevated serum CK levels may be evident, but muscle biopsy (not recommended) results are likely to be normal. Attempts at culturing *C. tetani* from wounds are often unproductive. The reliability of measuring serum antibody levels against tetanus toxin is questionable.

d. Treatment of tetanus is aimed at prevention of continued toxin production, neutralization of any tetanus toxin not yet bound to the CNS, and supportive care. Continued toxin production occurs in the presence of an active infection. A thorough search for an infection source should be undertaken. If found, the source should be drained and debrided. Depending on the location of the wound, flushing with hydrogen peroxide may inhibit clostridial growth by increasing oxygen tension in the wound. Regardless of whether an active clostridial infection is located, antibiotics effective against *C. tetani* should be administered for 10–14 days. Penicillin G is often considered the antibiotic of choice, but there is evidence that metronidazole may be more effective. Other drugs with activity against *C. tetani* include clindamycin and tetracycline. If a wound site is located, small doses of antibiotic (e.g. penicillin G) can be infiltrated around the wound area, in addition to parenteral therapy.

Antitoxin administration may be used in order to prevent further binding of circulating tetanospasmin toxin to the CNS. The major side effect and concern associated with antitoxin administration is anaphylaxis. The dose of equine antitoxin for small animals is 100–1000 units/kg, given intravenously over 10 min. Larger animals receive a proportionally smaller dose than smaller animals. Prior to administration, a test dose of 0.1–0.2 mL of antitoxin should be administered either subcutaneously or subdermally. The test site should be observed for wheal development for 15–30 min. If a wheal develops, an anaphylactic reaction is likely to occur. The clinician may decide to forgo antitoxin in this scenario or proceed with extra caution, depending on the particular nature of the individual case. Premedication with glucocorticoids and antihistamines is advisable prior to the intravenous injection of antitoxin, regardless of the results of the test dose. If an anaphylactic reaction develops, or is strongly suspected to develop (based on test dose results), intravenous epinephrine (diluted to 1:10,000) at 0.1 mL/kg is the therapy of choice. It is advisable to have this drug drawn up and ready to administer before antitoxin is given. A small amount of the antitoxin dose (e.g. 1000 units) may also be infiltrated around the wound site, if one is identified.

Supportive care of the tetanus patient can be very labor-intensive. Nutritional and hydration needs must be met, and may require tube-feeding in some animals. Enemas and urinary expression/catheterization may be required in some patients. Because of hypersensitivity to auditory and tactile stimuli (reflex muscle spasms), severely affected tetanus patients may need to be sedated. Combinations of promazine drugs (e.g. acepromazine, chlorpromazine) in combination with either diazepam or barbiturates are most effective. Caution is advised with barbiturate use, as tetanus patients are often respiratory-compromised, and barbiturates may lead to cardiorespiratory depression. Muscle relaxants, such as methocarbamol, may also be used to diminish muscle rigidity. Frequent turning and soft bedding are necessary to prevent complications such as aspiration pneumonia and decubital ulcers. Additionally reported complications secondary to tetanus include hiatal hernias, coxofemoral luxation, cardiac arrhythmias, and hyperthermia due to severe muscle spasms. Laryngospasm may be seen, necessitating supplementary oxygen in severe cases.

Many severe tetanus patients need to be closely monitored and require intensive nursing care. If avoidable, however, they should not be placed in noisy, busy areas, such as a high-volume intensive care unit. A dark, quiet environment is recommended in order to minimize the potential for reflex muscle spasms. With appropriate care, complete recovery from tetanus is possible in dogs and cats. Survival rates ranging from 50 to 92% have been reported in dogs, with worse prognoses for recovery seen in younger dogs and those with more severe clinical signs and/or autonomic storms. No difference in prognosis was found in two recent reports between dogs that did or did not receive tetanus antitoxin. The median length of hospitalization cited in retrospective studies ranges between 13 and 17 days. Overall, dogs often recover within a month of therapeutic intervention, but cats may require several months to return to normal. Frequently, the earliest indication of improvement is decreased muscle rigidity in the pelvic limbs.

D. Ischemic: Ischemic neuromyopathy[19, 32, 37, 50, 128, 158, 173, 204, 269, 317, 339]

1. Most commonly reported in cats with cardiomyopathy, this syndrome is due to the interruption of blood supply to the pelvic limbs (less commonly a thoracic limb) by a thromboembolism at the trifurcation of the distal aorta. The release of inflammatory mediators (e.g. serotonin, thromboxane A_2) coincident with the thromboembolic event is thought to severely impair collateral circulation to the pelvic limbs. Ischemic damage to pelvic limb nerves and muscles, primarily distal to the stifle area, accounts for the characteristic clinical signs. Ischemic neuromyopathy has also been characterized in dogs. In comparison with cats, a wider variety of conditions can cause aortic thromboemboli in dogs (see below). Also, the clinical signs are often different in dogs, compared with cats. Although an ischemic neuromyopathy may manifest acutely, dogs will frequently present with milder signs initially, such as a chronic lameness, collapse, and/or knuckling of the affected limb(s).
2. Cats of any age, breed, or sex can be affected, but males tend to predominate. Persians and domestic shorthaired cats may also be overrepresented. Typically, there is an acute or peracute onset of pelvic limb dysfunction (Fig. 18.28) and signs of pain, commonly including tachypnea. Rectal thermometers may reveal a relative hypothermia, due to decreased perfusion. While the severity of dysfunction may vary, most cats are either nonambulatory paraparetic or paraplegic. The signs may or may not be symmetric. The gastrocnemius and cranial tibial muscles are usually firm and painful to palpation, the nail beds of the pelvic limbs are cyanotic, and the distal aspects of the pelvic limbs are cool to the touch, compared to the thoracic limbs. There is usually an inability to flex or extend the tarsal joint, although the ability to flex and extend the hip and stifle joints is usually preserved. Femoral pulses are characteristically difficult or impossible to palpate. In most cases, there is also analgesia of the digits and tarsal area. Although involvement of one or

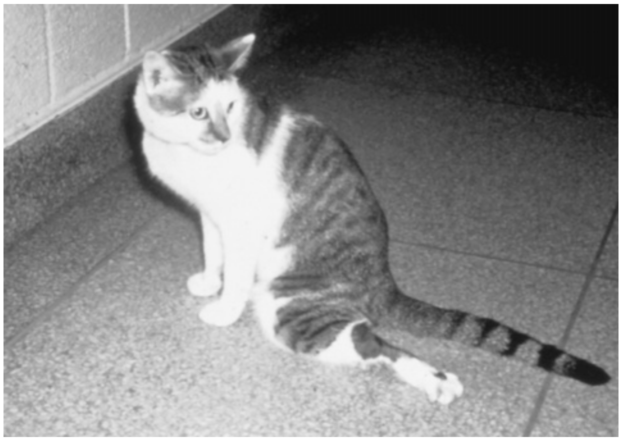


Figure 18.28 Bilateral pelvic limb dysfunction in a cat with ischemic neuromyopathy. (Dr. G Kortz, 2014. Reproduced with permission from Dr. G Kortz.)

both rear limbs is most common, front limb(s) may also be affected in a small subset of cases.

Clinical signs in dogs are more variable than in cats. In general, dogs tend to have more protracted clinical signs, varying from subacute to chronic. Some patients may even display intermittent clinical signs referable to the pelvic limbs. In general, pelvic limb lameness, paresis, and paralysis occur in dogs with aortic thromboembolism. Abnormal pelvic limb reflexes, cool extremities, evidence of pain, and decreased digital sensation are also observed in dogs with this disorder.

3. A tentative diagnosis is based primarily upon signalment, history, and characteristic clinical findings. Cats, and some dogs, will have evidence of cardiomyopathy on thoracic radiographs and/or echocardiography. Embolization of the distal aorta by an airgun pellet has been reported in one cat. Additionally, feline arterial obstruction may be caused by neoplastic emboli, traveling in circulation as intravascular metastases. A variety of disease conditions have been associated with canine aortic thromboembolism and include cardiac disease, neoplasia (neoplastic emboli), renal dysfunction, immune-mediated hemolytic anemia, sepsis, and endocrine disorders (e.g. hypothyroidism, hyperadrenocorticism). Serum CK levels are markedly elevated. Some patients are also acidotic and hyperkalemic. Evidence of disseminated intravascular coagulation (DIC) may also be elucidated (low platelet count, prolonged activated clotting time, etc.). While not commonly performed, electrodiagnostic tests will support the diagnosis of a neuromyopathy. Histopathology of nerve and muscle, if performed, will reveal axonal loss and myofiber necrosis, respectively. In both dogs and cats, ultrasonography and arteriography may be helpful in confirming the presence of thromboembolic disease. MRI has also been reportedly useful in diagnosing ischemic neuromyopathies.
4. No single treatment has been proven to be effective in improving the outcome of these patients. Suggested therapies directed specifically at the thromboembolic problem have included aspirin therapy, administration of plasminogen activators (streptokinase, urokinase), administration of anticoagulants (e.g. heparin, coumadin), administration of vasodilatory agents (e.g. acepromazine), and catheter or surgical (not currently recommended, especially in dilated cardiomyopathy) embolectomy. Attendant conditions, such as acidosis, hyperkalemia, and DIC, should be addressed. Specific treatment for cardiomyopathy is also recommended in cats, and in those dogs presenting with cardiac disease. In dogs, the treatment and prognosis are variable, largely dependent upon the underlying disease. In cats, although many will recover pelvic limb function within 6 wks to 6 mos, the prognosis is poor, primarily due to an inability to control or prevent congestive heart failure episodes. Reported prognostic values for cats with aortic thromboemboli include survival rates to discharge ranging from 0 to 45% of cases, with subsequent median survival times of 77 days or 223 days, for cats presenting with and without congestive heart failure, respectively, in one report. Additional median survival times for cats ranging from 51 to 184 days have been reported. Longer survival times are seen overall in cats in which a single limb was affected, those presenting with motor function in the affected limb(s), and those that were not hypothermic on presentation. Reported recurrence rates vary, ranging from 9 to 75% of cases. These values are likely affected by the presence of underlying disease and by the use of preventative therapies. Prophylactic aspirin therapy (25 mg/kg, every third day) has been recommended for recovering and recovered cats, but there is no evidence of efficacy.

E. Traumatic

1. Infraspinatus contracture[24, 51, 60, 89, 137, 179, 312, 320]
   a. This is an uncommon injury encountered mainly in hunting and working dogs, which can manifest in acute or chronic stages. The acute stage may be observed during or shortly after physical exertion, secondary to trauma or sprain of the infraspinatus muscle. As this muscle swells, due to edema and/or hematoma formation, it does so within the confines of surrounding fascia and bony structures. This increased tissue pressure within a confined space, if sufficiently high, may lead to decreased perfusion, with subsequent ischemic damage of the muscle and/or nerves locally (defined as compartment syndrome). Frequently the acute phase may not be witnessed, and the animal may present in the chronic phase of the injury. The presumed initial damage results in subsequent contracture and fibrosis of the infraspinatus muscle, causing a characteristic thoracic limb gait abnormality. Development of periarticular

connective tissue contributes to clinical signs of lameness. A similar disorder has been reported associated with injury to the teres minor muscle. Additionally, compartment syndrome has been reported within the caudal thigh muscles (caudal femoral compartment) in a dog, occurring secondary to a muscular hemangiosarcoma.

b. Hunting and working dog breeds are most commonly affected by this myopathy; there is no age or sex predilection. Bilateral involvement has been reported, but is very uncommon. In acute presentations, with suspected compartment syndrome, a sudden-onset severe lameness is seen, usually during exercise. The shoulder muscles appear swollen and are painful and tense on palpation. In chronic cases, the typical gait abnormality often develops 2–6 wks after the initial shoulder injury. In these cases there is usually a history of an acute thoracic limb lameness that improved or resolved with rest and anti-inflammatory drugs. The typical gait of dogs with infraspinatus contracture is characterized by elbow adduction, with excessive lateral or outward rotation (abduction) of the humerus. Affected dogs may hold the thoracic limb in this position while stationary (Fig. 18.29). When walking, these dogs often exhibit a compensatory "flip" of the carpus on the affected limb. A limited range of motion of the shoulder joint may also be appreciated. Atrophy of scapular musculature associated with the affected limb is often evident.

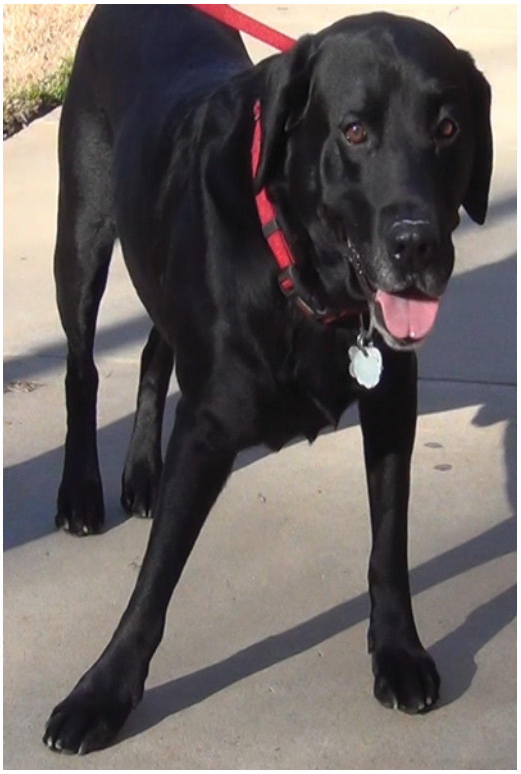


Figure 18.29 Typical thoracic limb carriage in a dog with infraspinatus contracture.

c. Diagnosis is based primarily upon historical and clinical features. Ultrasonography of the shoulder region may allow identification of the abnormal infraspinatus muscle. EMG abnormalities are often present, but the damaged muscle may be electrically silent (e.g. if virtually replaced by fibrous connective tissue). Muscle biopsy confirms fibrous connective tissue replacement of muscle fibers in chronic cases. In acute presentations, biopsy may reveal necrosis, and swelling of the muscle through the facial incision may be seen. Increased intracompartmental pressure may also be confirmed using various specialized catheters (wick catheter, slit catheter, solid-state transducer intracompartmental catheter). Normal intrafascial pressure ranges between −2 and +8 mmHg.

d. In acute cases, when compartment syndrome is suspected, surgical decompression via a fasciotomy should be performed as soon as possible, to decrease intracompartmental pressure and prevent continued ischemic muscle/nerve damage. Treatment for chronic presentations consists of surgical tenomyectomy of the abnormal infraspinatus, with removal of all visible periarticular fibrous tissue. Prognosis for recovery is excellent following surgery.

2. Iliopsoas muscle injury[48, 278, 322]

   a. Pelvic limb lameness due to a suspected strain injury to the iliopsoas musculature has been reported in four adult dogs and a 12-wk-old puppy. In many of these cases, an inciting traumatic event was suspected but not witnessed. A concurrent femoral neuropathy, presumed secondary to iliopsoas muscle pathology, was reported in two of these cases.

   b. Two dogs experienced an acute onset of pelvic limb lameness; the other three dogs exhibited chronic lameness. One of the affected dogs exhibited bilateral pelvic limb involvement. When standing, this dog showed external rotation of the pelvic limbs ("cow-hocked stance"). All dogs displayed signs of discomfort upon extension of the associated coxofemoral joint. A painful (hyperesthetic) response was also appreciated upon palpation of the affected iliopsoas muscle(s), at the lesser trochanter, ventromedial to the ilium, and/or per rectum. Also, simultaneous internal rotation and extension of the affected coxofemoral joint elicited pain in all dogs. The affected limb showed a decreased patellar reflex, indicating femoral nerve involvement, in two of these cases. Additionally, absent sensation to the medial aspect of the thigh, leg, and pes was noted in the puppy, suggesting saphenous nerve involvement.

   c. Diagnosis was based upon finding pain associated with the iliopsoas muscle on clinical examination, as well as demonstrating abnormal iliopsoas musculature on ultrasonography (e.g. hypoechoic, swollen musculature) in three dogs. CT was used to initially identify iliopsoas muscle injury (multifocally hypoattenuating and contrast enhancing, enlarged musculature) in one dog. Muscle abnormalities could not be seen on ultrasound or on CT evaluation in one case, but could be detected with MRI (focal area of hyperintensity on T2-W images with mild hyperintensity on T1-W images, and no contrast enhancement).
   d. Most dogs responded well to rest and treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). Lameness recurred or did not respond to conservative management in two dogs, despite rest and NSAID therapy. Both of these dogs responded well to tenomyectomy of the iliopsoas muscle.
3. Quadriceps contracture (stiff stifle syndrome)[39, 45, 179]
   a. This is a phenomenon most commonly associated with inadequate fracture repair and/or prolonged immobilization of distal femoral fractures in young dogs, especially of large breeds. Other conditions, such as osteomyelitis of the femur, may also lead to this sequela. Inflammation and fibrous tissue proliferation cause adhesions between the quadriceps muscle group and the femur. With prolonged disuse of the limb, periarticular fibrosis of the stifle develops.
   b. Clinical signs typically include progressive pelvic limb extension and lameness following an orthopedic injury. Muscle contracture and disuse atrophy often progress to the point that the limb is nonfunctional. The affected limb is usually abducted, and there is severe limitation of the range of motion in the stifle joint.
   c. Diagnosis is based on characteristic historical and clinical features. Muscle fiber size variability, fibrosis, and necrosis are characteristic muscle biopsy features. Extensive muscle fiber atrophy, predominantly affecting type I fibers, is also typical.
   d. Proposed treatments for quadriceps contracture include surgical breakdown of fibrous tissue, Z-plasty of the quadriceps muscle group, and stifle arthrodesis in a functional walking angle. In general, the prognosis for a functional limb once contracture has developed is guarded to poor. Efforts should be focused on preventing this condition.
4. Gastrocnemius muscle avulsion[271, 273, 275, 327]
   a. Avulsion or rupture of the proximal attachment of the gastrocnemius muscle has been reported sporadically in dogs. There is usually a known traumatic event associated with this injury, but atraumatic avulsion of this muscle has also been described.
   b. Clinical signs include either a unilateral or bilateral pelvic limb lameness, often of chronic duration. A plantigrade stance with excessive hock flexion and a crouched gait is characteristic. Other clinical features may include flexion of the digits and pelvic limb muscle atrophy.
   c. In addition to clinical features, radiographic abnormalities such as distal displacement of the fabellae, and osteophyte formation in the region of the gastrocnemius muscle origin, contribute to a tentative diagnosis. Confirmation of muscle avulsion may be confirmed at surgery, if reattachment is attempted.
   d. Some dogs have responded to external support and NSAID therapy, whereas others have responded to surgical reattachment of the avulsed muscles. The prognosis for functional recovery appears to be generally favorable but may require several months to occur.
5. Coccygeal muscle injury (limber tail, cold tail, frozen tail)[319–321]
   a. A transient flaccidity of the tail occurs in hunting dogs, primarily pointers and Labrador Retrievers. Other reported breeds include setters and foxhounds. The condition is believed to be traumatic, and is theorized to involve a compartment syndrome phenomenon (see Chapter 17) in some cases. Common factors that appear to predispose dogs to developing this disorder include strenuous exercise following a period of underconditioning, prolonged cage transport, and cold weather.
   b. Affected animals are typically adult hunting dogs. A sudden onset of tail flaccidity is characteristic, with the tail either hanging from the tail base or projecting horizontally from the tail base for a short distance (e.g. 8 cm), then hanging downward. The hair on the proximal tail may be raised early in the disease course. Some dogs exhibit discomfort associated with palpation of the tail, often most apparent approximately 8 cm distal to the base. During the recovery phase of this disorder, the tail may hang to one side.
   c. Diagnosis is based primarily on signalment, history, and characteristic clinical signs. An extensive diagnostic investigation is not often pursued, owing to the self-limiting nature of the disease. Serum CK levels may be mildly elevated, and EMG examination typically reveals abnormal spontaneous muscle activity (e.g. fibrillation potentials, positive sharp waves). Thermography and scintigraphy of the tail region in affected dogs have been reported to reveal abnormalities. Muscle biopsy has confirmed pathologic changes in tail musculature (e.g. fiber splitting, atrophy, necrosis), particularly in the laterally situated intertransversarius ventralis caudalis muscles. Intramuscular nerve fibers were normal. Muscle biopsy is not recommended, due to the potential for further injury to

the tail and the high likelihood of recovery with no intervention.

d. Complete recovery occurs most often within several days but may take several weeks in some cases. There is anecdotal evidence that administering anti-inflammatory drugs may speed recovery if given early on in the disease course. In dogs exhibiting discomfort associated with the tail, administration of analgesic drugs is recommended. Minimizing prolonged cage transport and ensuring a regular training schedule are suggested preventive measures.

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Video Resources

Video resources are available on the companion website: www.wiley.com/go/dewey/neurology

See videos 38 and 39.

CHAPTER 19

Junctionopathies: Disorders of the Neuromuscular Junction

Jacques Penderis & Paula Martin-Vaquero

Introduction

By its very name, the "neuromuscular junction" (NMJ) describes the junction between an efferent nerve (in the context of the diseases discussed in this chapter, usually a somatic efferent nerve) and the muscle innervated by that nerve. Pathological processes that affect the NMJ are commonly referred to as "junctionopathies."

Normal anatomy and physiology of the neuromuscular junction[64, 140, 159, 163, 248, 261, 264, 279, 304]

The NMJ can be subdivided into three basic components: the presynaptic membrane, the synaptic cleft, and the postsynaptic membrane in the endplate region of a skeletal muscle fiber. The NMJ is part of the acetylcholine (ACh) group of neurotransmitter systems. ACh neurotransmitter systems are also found in autonomic ganglia and parasympathetic effector junctions in the peripheral nervous system, in the spinal cord, and in the brain (particularly as a major component of the ascending reticular activating system). Each motor neuron innervates a number of muscle fibers (myofibers); combined, these are termed a motor unit. For successful NMJ transmission to occur, the action potential traveling down a motor neuron to a myofiber must be successfully propagated to the endplate region of the innervated muscle fiber. The arriving action potential at the level of the nerve terminal results in depolarization of this region and the consequent opening of calcium (Ca^{2+}) channels on the axolemmal surface. The increased cytosolic concentration of Ca^{2+} triggers exocytosis of ACh by causing ACh-containing vesicles to dock and fuse with the plasmalemma at the synaptic cleft region. Three classes of proteins are involved in the process of ACh exocytosis and all three are vulnerable to toxins and disease processes:

- synapsin I (controls the availability of synaptic vesicles) and synaptotagmin (associated with N-type Ca^{2+} channels)
- synaptobrevin (vesicle-associated membrane protein), syntaxin, and synaptosome-associated protein 25, which are all essential components of the exocytosis process
- N-ethylmaleimide-sensitive fusion protein (NSF) and soluble NSF-attachment proteins, which are all involved in neurotransmitter release.

The released ACh molecules cross the synaptic cleft to reach the ACh receptors, located on the endplate region of the skeletal muscle fiber. The ACh receptor molecules are integral membrane proteins consisting of five subunits and function as sodium (Na^+) channels. The five subunits are arranged in a circular shape around the central Na^+ channel (Fig. 19.1). Located on the extracellular portion of the alpha (a)-subunit (of which there are two per receptor molecule) are the ACh binding sites. Binding of ACh to the ACh binding sites results in the opening of the Na^+ channel and Na^+ influx into the muscle cell. This influx of Na^+ results in depolarization of the endplate region, termed the endplate potential (EPP). The EPP has to reach a threshold to result in the sufficient spread of the depolarization along the muscle fiber to cause release of the intracellular Ca^{2+} stores and result in muscle contraction.

The magnitude of the EPP depends on the number of ACh receptors activated. In the normal situation, there is an overabundance of both available ACh and ACh receptors and the EPP produced by nerve depolarization therefore usually far exceeds the requirement for muscle contraction; this excess is termed the safety factor of neuromuscular transmission. During repetitive depolarization of the nerve terminal following repeated firing of a motor nerve, there is a decrease in the amount of ACh released into the synaptic cleft with each depolarizing event, a phenomenon termed rundown. In normal

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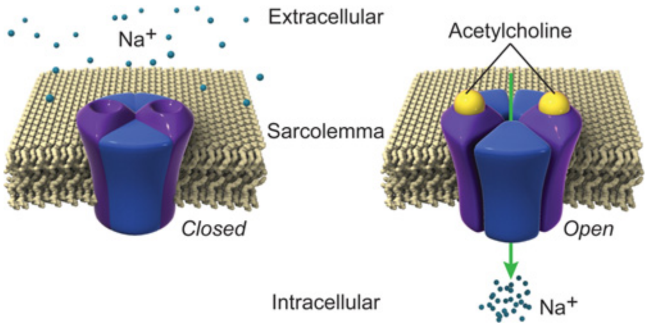


Figure 19.1 The ACh receptor consists of five subunits arranged in a circular shape around the central Na^+ channel. The ACh binding sites are located on the extracellular portion of the two (a)-subunits. Binding of ACh to the ACh binding sites results in opening of the Na^+ channel and Na^+ influx into the muscle cell. (The Ohio State University. Reproduced with permission.)

individuals, however, the degree of rundown is insignificant due to the large safety factor of neuromuscular transmission. Following successful NMJ transmission, several processes prevent excessive stimulation of muscle fibers. First, the Na^+ channels that open following activation of ACh receptors do so only transiently before closing and becoming refractory for a few seconds. Second, shortly after its release into the synaptic cleft, the ACh is rapidly eliminated by both diffusion away from the cleft region and by hydrolysis by ACh esterase (AChE) in the cleft region.

Vulnerability of the neuromuscular junction

Disorders affecting neuromuscular transmission are usually classified as pre- or postsynaptic, although some disease processes may affect both. Processes affecting neuromuscular transmission may either increase or decrease the activity of this system and do so by:

- increasing or decreasing presynaptic ACh release, as a result of altering ACh synthesis, transport, reuptake, or presynaptic release
- altering the concentration or duration of ACh effect in the synaptic cleft, as a result of altered removal of ACh from the synaptic cleft
- acting as an ACh agonist or antagonist at the NMJ by affecting the interaction between ACh and the postsynaptic receptor.

Botulism toxin and α-latrotoxin (a toxin elaborated by the black widow spider) can be used as examples of diseases affecting the same component of neuromuscular transmission in opposite manners but with the same result: the failure of neuromuscular transmission. Botulism light-chain toxin (the entry of which through the plasmalemma is facilitated by the heavy-chain toxin) blocks synaptic transmission by cleaving synaptic vesicle fusion proteins required for the process of exocytosis. In contrast, α-latrotoxin causes massive ACh release at the NMJ by apparently increasing the probability of vesicle fusion with the plasmalemma and inhibiting vesicle recycling.

A. Vulnerability of the axonal transport system

Although not specifically disorders of the NMJ, substances may interfere with normal neuronal and axonal functions, resulting in disruption of the normal anterograde transport of material essential for neurotransmitter synthesis (including ACh at the NMJ). An example would be vincristine, which nonspecifically blocks axonal transport.

B. Vulnerability of the presynaptic functions

The functions within the presynaptic region are involved in the reuptake of choline from the synaptic cleft, the synthesis of ACh, and the storage thereof in synaptic vesicles, with a large number of substances and disease processes known to target these processes.

Examples of substances affecting these pathways include:

1. The Na^+-dependent high-affinity choline transport system is specifically targeted by hemicholiniuum, which competes with choline for uptake by the choline-carrier and inhibiting choline uptake, thereby resulting in NMJ blockade.
2. The enzyme choline acetyltransferase, involved in ACh synthesis, is targeted by a number of substances including the naphthoquinones and halogenated cholines, which have been shown to be effective enzyme inhibitors in vitro. Choline acetyltransferase is also targeted by false cholinergic neurotransmitters, including triethylcholine and diethylaminoethanol, which are acetylated by the enzyme, stored in synaptic vesicles, but on synaptic release display cholinergic agonist activity below that of ACh (cholinergic hypofunction).
3. Vesamicol (an experimental substance) is one of a number of substances shown to induce neuromuscular blockade by blocking the transport of ACh into synaptic vesicles.

C. Vulnerability of presynaptic release of ACh

Numerous toxins target the presynaptic release of ACh. Botulinum toxin and certain snake toxins (including Mojave toxin and β-bungarotoxin, among others) block the release of ACh from motor axon terminals. As previously discussed, α-latrotoxin (from the black widow spider) causes NMJ blockade by targeting the same part of the system, but instead by causing massive ACh release.

D. Vulnerability of AChE

Numerous naturally occurring and synthetic substances target the AChE system, resulting in increased synaptic residence of ACh and therefore excessive stimulation following ACh release. Some of the substances bind to the AChE active site for varying times (including edrophonium, physostigmine, and neostigmine) while others interact with the active center to form stable complexes (e.g. organophosphorus compounds).

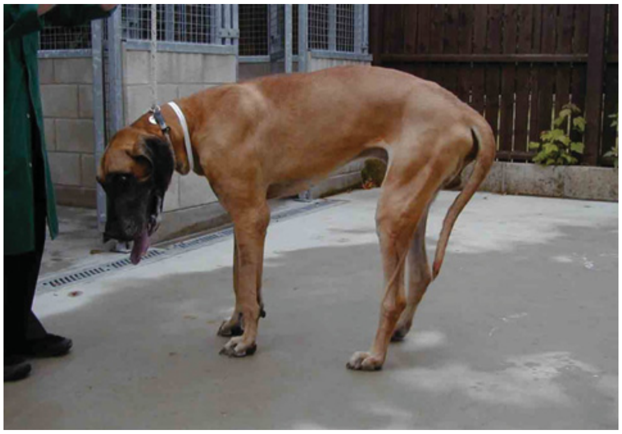
E. Vulnerability of nicotinic muscle receptors
A wide variety of compounds target the nicotinic receptors, either throughout the nervous system or specific to only the nicotinic receptors of muscle. For example, the snake toxin α-bungarotoxin (from the many-banded krait, *Bungarus multicinctus*) blocks the nicotinic muscle receptors, but those in peripheral autonomic ganglia appear resistant. The compounds affecting the nicotinic muscle receptors include, among others, strychnine (the indole alkaloid from the *Strychnos* spp.), many snake toxins, anatoxin-a from blue-green algae, and curare-like substances.

Clinical presentation of neuromuscular transmission syndromes[16, 205, 264, 279, 304]

NMJ transmission disorders are frequently classified as either pre- or postsynaptic. Irrespective of the cause of failure of neuromuscular transmission, the presenting clinical signs may often be very similar in character. Junctionopathies usually present as symmetric, progressive muscle weakness of both the thoracic and pelvic limbs (Fig. 19.2). Tendon reflexes are often intact in the early stages of the disease, which is a useful method to distinguish these diseases from peripheral neuropathies. The NMJ transmission syndrome frequently demonstrates a predilection for certain muscle groups, particularly the small, rapid-movement muscle groups. For this reason, failure of certain cranial nerve muscles may be apparent, including the failure of the extraocular muscles and muscles to control the palpebral reflex and alterations in the voice (dysphonia) and swallowing. Sensory function and level of consciousness are typically unaffected. In botulism, a combination of skeletal muscle weakness and autonomic nervous system dysfunction (e.g. urinary retention, alterations of heart rate, mydriasis with depressed pupillary light reflexes) is often seen, secondary to the action of the botulinum toxin blocking the release of ACh from both the NMJ and the cholinergic autonomic synapses. In some postsynaptic disorders (e.g. organophosphorus compound poisoning), there may be additional cholinergic signs, including lacrimation, miosis, and bradycardia.

In most cases, removal of the source of NMJ blockade will result in a rapid resolution of the clinical signs, but in some cases there is tight binding of the agent to the NMJ (e.g. botulism) and recovery may take a prolonged period of time.

Based on the classification of NMJ transmission disorders, examples of mainly presynaptic agents include: botulinum toxin, tick saliva, and black widow spider venom. Examples of postsynaptic agents include: anticholinesterase agents, tetracycline antibiotics, and interferon-a. Most of the toxic NMJ transmission disorders include a combination of both pre- and postsynaptic blockades and include: snake envenomation, aminoglycoside antibiotics, and polymyxin antibiotics.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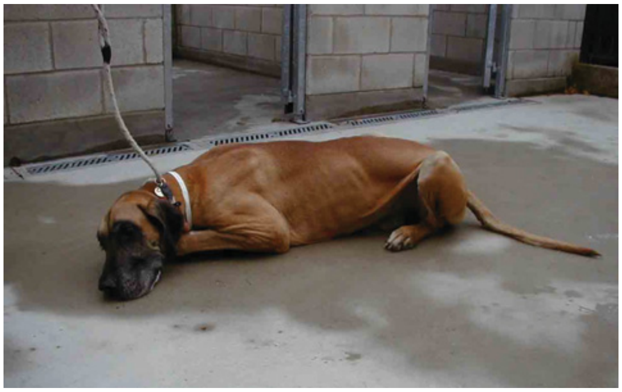

(b)

Figure 19.2 Great Dane with acquired exercise intolerance demonstrating (A) exercise-induced weakness with cervical ventroflexion and respiratory distress, followed by (B) collapse into ventral recumbency.

Myasthenia gravis (MG)

A. Congenital myasthenia gravis[34, 62, 83, 84, 93, 129, 132, 133, 178, 187, 188, 205, 213, 228, 257, 300] (Video 40)

1. Congenital MG is due to an abnormal reduction in the number of ACh receptors on the muscular endplate, resulting in clinical signs of exercise-induced weakness.
2. The disorder has been described in a number of breeds, including Springer Spaniels, Jack Russell Terriers, Smooth-haired Fox Terriers, Samoyeds, and Miniature Dachshunds. Although reported, congenital MG is rare in cats. Clinical signs of recurrent and progressive muscle fatigue usually become apparent between 6 and 9 wks of age. Multiple pups in a litter are usually affected. In both the terrier breeds, autosomal recessive inheritance has been demonstrated. A myasthenic syndrome, inherited as an autosomal recessive disorder, has been described in the Gammel Dansk Honsehund (Old Danish pointing dog), where a presynaptic disorder interferes with ACh synthesis. A missense mutation in exon 6 causing a single-base G to A substitution in the *CHAT* gene, which encodes the enzyme choline acetyltransferase, has

been identified in affected dogs of this Danish breed. This enzyme is involved in the resynthesis of ACh, and mutations in this gene have been associated with human myasthenic syndromes. Affected Danish dogs are homozygous for the mutation, while unaffected dogs are either homozygous for the normal allele or heterozygous carriers. A DNA test has been developed and is now available to screen Gammel Dansk Honsehunds for this mutation. In breeds other than the Gammel Dansk Honsehund and Miniature Dachshund, congenital MG is characteristically a progressive disorder, and affected dogs are often unable to walk. All breeds may be predisposed to developing aspiration pneumonia, although megaesophagus is typically demonstrable only in the Smooth-haired Fox Terrier.

3. Due to the absence of antibodies to ACh receptors in congenital MG, diagnosis is by signalment, history, and a suitable response to anticholinesterase drugs. Ultrastructural demonstration of decreased ACh receptors in the motor endplates of fresh-frozen biopsy specimens from the external intercostal muscles may help to confirm the postsynaptic disorder (Fig. 19.3).
4. Although the extent of clinical responsiveness is often incomplete and unpredictable, anticholinesterase therapy (e.g. pyridostigmine) is recommended for dogs with congenital MG. Remission of clinical disease is unlikely in most of these cases and lifelong management is therefore required. However, in Miniature Dachshunds the disease appears to resolve spontaneously by 6 mos of age.

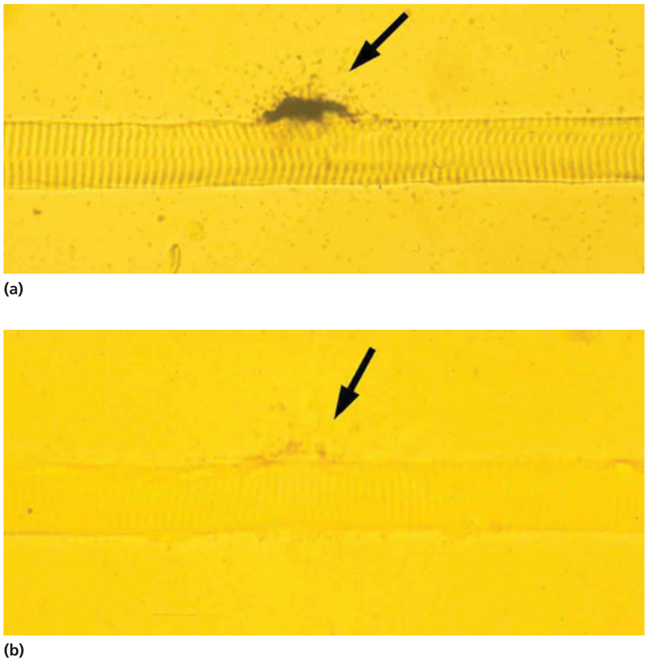


Figure 19.3 Normal ACh receptor concentration in a control 4-mo-old Jack Russell Terrier (arrow) (A) and dramatically decreased ACh receptor numbers in a Jack Russell puppy affected by congenital MG (arrow) (B).

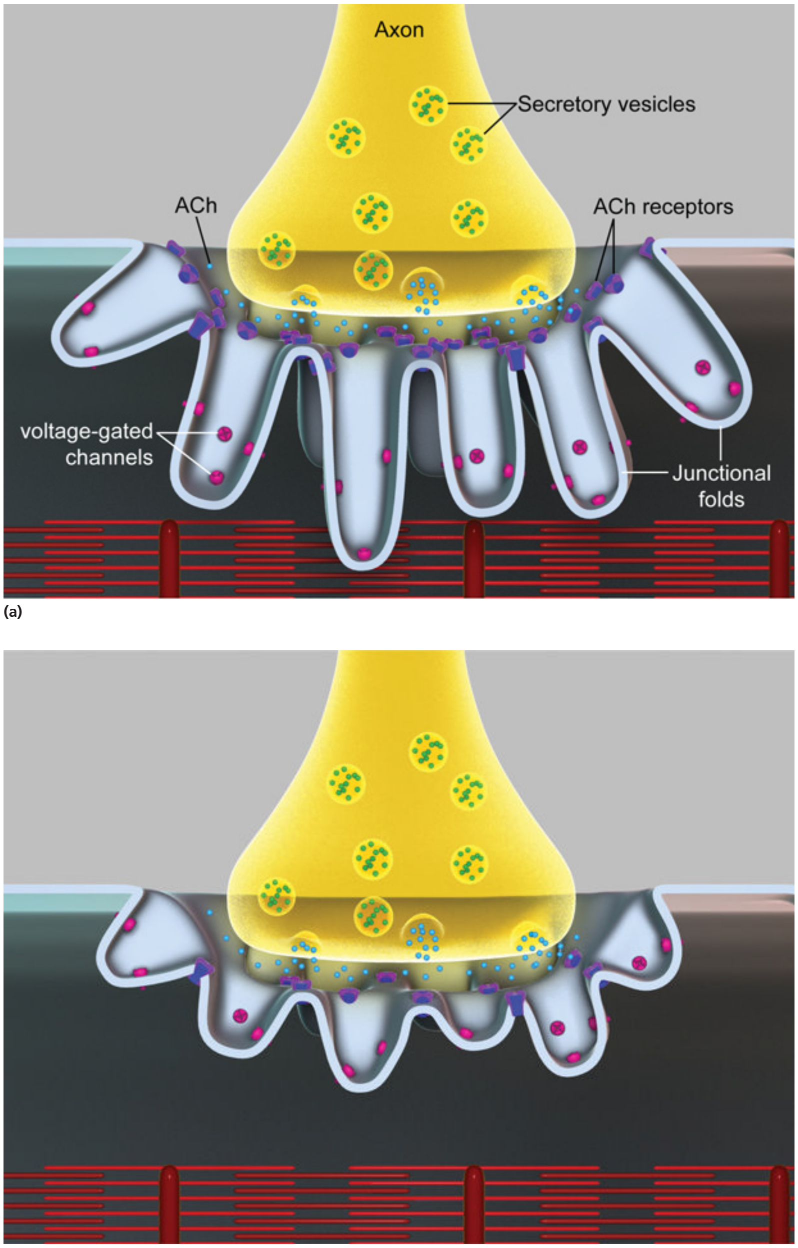
In the remainder breeds, the prognosis of congenital MG is guarded to poor due to the progressive nature of the disorder. Affected dogs may also develop recurrent or severe aspiration pneumonia.

B. Acquired myasthenia gravis[2,5,9–11,15,18,20,22,23,25,26,28,34,36,39,45–47,51,56–61,64,65,68,69,78,87–89,91,92,94,98,108–110,115,121,123,127,129,133,138,140–144,148,151,152,159,160,163,165,174,180,181,184,193,195,196,201–203,205,211,224–226,234,236,238,242,244,248,249,255–270,272,277,279–281,287,288,292,295,296,301,304,305,309]

1. Acquired MG is an autoimmune disease in which antibodies (in most cases IgG) are formed against the nicotinic ACh receptors, resulting in decreased numbers of receptors on the postsynaptic sarcolemmal surface (Fig. 19.4). In the majority of both human and canine cases, these antibodies have been shown to recognize the same epitopes on the ACh receptor. These epitopes are primarily located in the main immunogenic region of the two alpha subunits, on the extracellular surface. The main immunogenic region is in close proximity to (although distinct from) the ACh binding site. These autoantibodies alter the receptor function by one of three mechanisms:
   - Antibodies may bind directly to the ACh receptor, resulting in a blockade of ion channel opening.
   - Antibodies may increase the degradation rate of ACh receptors by cross-linkage, resulting in a decreased concentration of receptors at the postsynaptic membrane.
   - Complement-mediated lysis of the muscle endplate may take place.

   The consequence of this decrease in normal NMJ transmission is skeletal muscle weakness.

   In humans, dogs, and cats, a bimodal age of onset has been identified. Cats are typically affected between 2 and 3 yrs of age or between the ages of 9 and 10 yrs. In dogs, this bimodal age of onset occurs in young dogs between 4 mos and 4 yrs (average, 3 yrs) and in older dogs between 9 yrs and 13 yrs of age (average, 10 yrs). Acquired MG occurs much less commonly in the cat as compared to the dog. Purebred cats tend to develop MG more often than mixed-breed cats, with the Abyssinian and Somali breeds appearing to be overrepresented. In dogs, a high risk for the disease exists in several breeds, including Akitas, several terrier breeds, German Shorthaired Pointers, and Chihuahuas. The German Shepherd dog and Golden Retriever demonstrate the highest absolute morbidity. Sexually intact dogs may be slightly less likely to develop MG than spayed or neutered dogs. A group of young adult Newfoundlands from two distinct lineages with acquired MG were reported. Similarly, three young adult Great Dane littermates were reported to develop clinical signs of acquired MG over a 4-mo period. These two reports suggest that a familial and possibly genetic predisposition to acquired MG may exist in the Newfoundland and Great Dane breeds.



(a)

(b)

Figure 19.4 Schematic representation of a normal neuromuscular junction (A) and one from a patient affected by myasthenia gravis (B). The axon terminal contains the ACh molecules within secretory vesicles, which are released into the synaptic cleft. In myasthenia gravis, the ACh receptor concentration may be reduced and there may be abnormal folding of the muscle endplate. (The Ohio State University. Reproduced with permission.)

Acquired MG can present in the dog and cat as one of three different clinical syndromes: focal MG, generalized MG, and acute fulminating MG. Acquired MG has been associated with other diseases and these should be taken into consideration when planning the diagnostic evaluation of a case and determining the prognosis. These include:

- hypothyroidism
- thymomas
- thymic cysts
- nonepitheliotropic cutaneous lymphoma
- cholangiocellular carcinoma
- anal sac adenocarcinoma
- osteogenic sarcoma
- oral sarcoma
- methimazole therapy in cats
- masticatory muscle myositis
- dysautonomia.

The association of thymomas and acquired MG has been demonstrated in human patients, dogs, and cats. The incidence of cranial mediastinal masses in dogs with acquired MG is low at around 3%, but this figure is considerably higher in cats (15–26%). A recent retrospective study including 116 dogs with thymoma reported that 20/116 (17%) dogs showed clinical signs consistent with MG.

Table 19.1 Clinical findings in cats and dogs with acquired MG.

Clinical findings	Cats (%)	Cats (*n* +20)	Dogs (%)	Dogs (*n* +25)
Generalized weakness	70	14	64	16
Decreased palpebral reflex	60	12	36	9
Decreased menace response	50	10	—	—
Decreased gag reflex	—	—	32	8
Laryngeal weakness	—	—	24	6
Megaesophagus	40	8	84	21
Aspiration pneumonia	20	4	84	21
Cranial mediastinal mass	15	3	8	2
Muscle fasciculations	15	3	—	—
Decreased flexor reflexes	10	2	—	—
Polymyositis	5	1	8	2
Cardiomegaly	5	1	—	—
Muscle atrophy	5	1	—	—

Source: Adapted from Dewey CW, Bailey CS, Shelton GD, *et al.* Clinical forms of acquired myasthenia gravis in dogs: 25 cases (1988–1995). *J Vet Intern Med.* 1997;11:50–57; and Ducoté JM, Dewey CW, Coates JR, Clinical forms of acquired myasthenia gravis in cats. *Compend Contin Educ Pract Vet.* 1999;21:440–448, with permission.

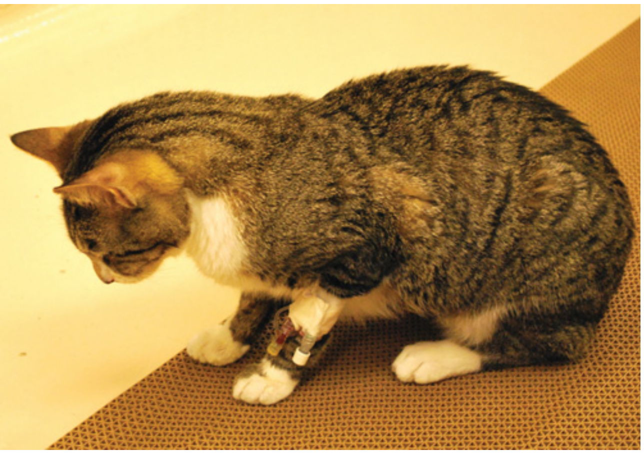
2. In MG cases, the neurologic examination is usually normal when performed prior to the induction of exercise-induced weakness; however, some cases will demonstrate depressed to absent palpebral reflexes in the absence of generalized muscle weakness. Loss of the palpebral reflex is particularly noticeable in cats. Tendon reflexes are usually normal. Clinical findings in canine- and feline-acquired MG are summarized in Table 19.1. Focal, generalized, and acute fulminating forms of MG have been described in dogs and cats. Focal MG presents as weakness of isolated muscle groups, particularly the esophageal, pharyngeal, laryngeal, and facial muscles. Weakness of these muscle groups occurs in the absence of generalized appendicular muscle weakness. The main presenting clinical signs in these cases include:
   - regurgitation secondary to megaesophagus
   - dysphagia due to pharyngeal muscle weakness
   - dropped jaw
   - diminished or absent palpebral reflexes
   - voice changes (dysphonia) due to laryngeal and/or palatal muscle weakness.

   In retrospective studies, 36–43% of dogs presenting with acquired MG demonstrated focal signs, compared to only 15% of cats. These focal signs were mostly secondary to the presence of megaesophagus and dysphagia. The differences in the prevalence of focal signs between both species may be ascribed partially to the larger proportion of smooth muscle in the feline esophagus as compared to the predominantly striated muscle of the canine esophagus.

   The generalized form of MG is characterized by appendicular muscle weakness that may be induced or exacerbated by exercise. Retrospective studies reported that generalized weakness with or without megaesophagus was present in 57–64% of dogs and 80% of cats with MG. Typically, severe exercise intolerance develops after only a few minutes of exercise, but following rest the animal regains muscle strength and can return to activity for a short period before a relapse of the muscular weakness. Regurgitation, especially in dogs, may occur secondary to either megaesophagus or a thymic mass. Muscle tremors and decrementing or absent palpebral reflexes may be present as a feature of the muscle weakness. Pharyngeal and laryngeal muscle weakness is evidenced by the presence of excessive drooling, a moist and productive cough (secondary to aspiration pneumonia), and dysphonia. Appendicular muscle weakness tends to be more severe in the pelvic limbs of dogs, whereas this has not been reported in cats. Cats may frequently demonstrate cervical ventroflexion as a clinical sign of generalized weakness; in some cases, such cats may prefer to remain in thoracic recumbency with their heads supported on their thoracic limbs (Fig. 19.5). Generalized MG has been associated with polymyositis in one cat. Third-degree atrioventricular block has been reported to occur concurrently with MG in dogs. Cardiac involvement in MG is well documented in human medicine and may be the result of autoantibodies directed against the conducting tissue of the heart, or as a result of secondary focal myocarditis.

   Acute fulminating MG is a severe and rapidly progressing form of generalized MG. Affected animals demonstrate regurgitation secondary to megaesophagus and a rapid progression of appendicular muscle weakness, which usually renders the dog nonambulatory. Weakness of the skeletal muscles eventually affects the intercostal muscles and/or diaphragm, at which stage affected animals demonstrate severe respiratory distress. Due to the concurrent pharyngeal and laryngeal muscle weakness, aspiration pneumonia is a frequent complication. It is not uncommon for dogs with fulminating MG to also have concurrent thymomas. The prognosis for fulminating MG is poor. For successful treatment, these cases require rapid recognition and intensive care, including respiratory supportive care, and possibly plasmapheresis.

3. Disorders that may mimic MG include other disorders of the NMJ as well as diseases presenting with generalized or focal weakness of striated muscle. The most important differential diagnoses to consider include:
   - other disorders of the NMJ, in particular botulism, snake envenomation, tick paralysis, and cholinesterase toxicity
   - neuropathies and myopathies (particularly inflammatory and breed-related myopathies).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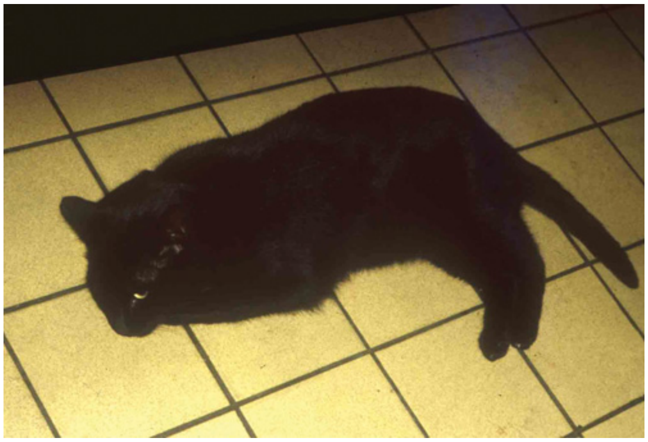
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Figure 19.5 (A) Cats with weakness secondary to acquired myasthenia gravis may demonstrate cervical ventroflexion as a sign of generalized weakness. (B) Affected cats may also show a preference to remain in thoracic recumbency with their heads supported on their thoracic limbs. (Dr. Andrew Sparkes, Animal Health Trust, UK, 2014. Reproduced with permission from Dr. Andrew Sparkes.)

The diagnostic approach to the MG case is challenging, as historical and clinical signs of dysfunction may be caused by a variety of other diseases, including diseases of the peripheral nervous system, NMJ, and muscle. Some of the tests for MG are supportive but not diagnostic, while others may require general anesthesia. The clinician needs to be aware of the limitations of the available tests in order to make a diagnosis as quickly as possible without detriment to the patient.

a. Minimum database

In every patient presenting with clinical signs of suspected MG, a minimum database—including a complete blood count, biochemistry panel, and urinalysis—should be performed to rule out other causes of generalized or focal weakness. Additionally, problems might be identified on the minimum data base that require intervention, particularly in animals demonstrating dysphagia or megaesophagus who may have complications secondary to compromised fluid or nutritional intake. Further endocrine testing, particularly of thyroid and adrenal function, may be indicated based on the presenting clinical signs and findings on the minimum database. Although myopathies are one of the most important differential diagnoses for MG, care must be taken when interpreting muscle enzyme levels, particularly in animals that have been recumbent for a prolonged length of time; recumbency and mild to moderate muscle damage (e.g. an intramuscular injection, falling down) may result in moderate elevations of the creatine kinase (CK) level in the absence of substantial muscle damage.

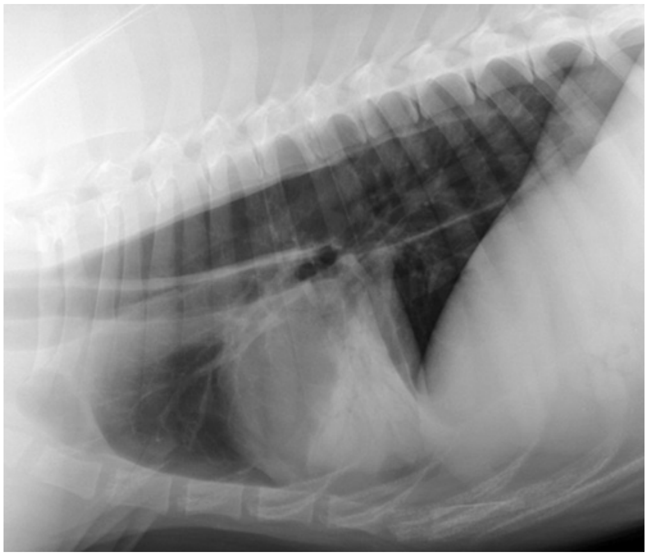

Figure 19.6 Lateral thoracic radiograph demonstrating megaesophagus in a dog with evidence of secondary aspiration pneumonia (Dr. P Scrivani, Cornell University, 2014. Reproduced with permission from Dr. P Scrivani.)

b. Imaging studies

Thoracic radiographs should be obtained to evaluate for the presence of megaesophagus (preferably unsedated, as both sedation and anesthesia can induce an apparent megaesophagus in normal animals). Megaesophagus is a frequent finding in dogs with MG and is often associated with the presence of aspiration pneumonia (Fig. 19.6). In cats, megaesophagus is less common, but its presence may indicate a more guarded prognosis. In cases with a historical suggestion of megaesophagus, for which there is no evidence on thoracic radiographs, esophagography with liquid barium and fluoroscopy has been suggested. However, MG patients with poor pharyngeal and esophageal function are at a greater risk of aspiration pneumonia, and

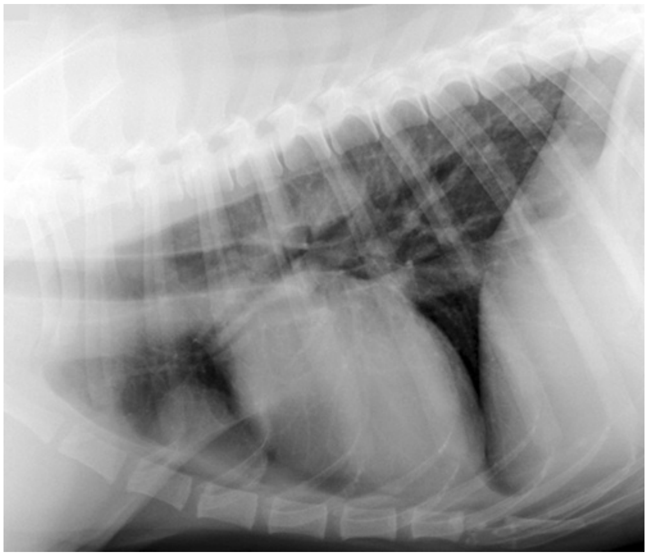

Figure 19.7 Lateral thoracic radiograph of a dog with MG demonstrating a large cranial mediastinal mass (thymoma) and megaesophagus. (Dr. P Scrivani, Cornell University, 2014. Reproduced with permission from Dr. P Scrivani.)

the aspiration of barium could dramatically exacerbate aspiration pneumonia. A safer alternative to a barium esophagram is esophageal scintigraphy. Esophageal scintigraphy is safe and easily performed; this procedure also provides objective information pertaining to esophageal function.

Thymoma has been associated with acquired MG in human, canine, and feline patients. The presence or absence of a cranial mediastinal mass should therefore be assessed with radiography (and ultrasonography if indicated). Such masses are only occasionally present (3.4%, in one study) in canine patients with acquired MG (Fig. 19.7). In feline-acquired MG, however, the incidence of a cranial mediastinal mass has been reported to be between 15 and 25.7%. The absence of a radiographically demonstrable cranial mediastinal mass does not rule out the possibility of a thymoma. Further imaging, including computed tomography and magnetic resonance imaging, is often helpful in human medicine to evaluate the anterior mediastinum.

An ECG should be performed (particularly if bradycardia is present) to rule out third-degree heart block.

c. Edrophonium chloride challenge (Tensilon response) test

To support the presumptive diagnosis of MG, an edrophonium chloride challenge test can be performed in animals demonstrating muscular weakness. Edrophonium chloride is an ultrashort-acting anticholinesterase agent, prolonging the residence time of ACh in the synaptic cleft and thereby improving muscle strength where NMJ blockade is present. A positive response to an intravenous injection of edrophonium chloride is supportive of a presumptive diagnosis of MG. An intravenous catheter is placed prior to the challenge test. In dogs, 0.1–0.2 mg/kg is administered intravenously immediately after exercise-induced weakness. In cats demonstrating muscular weakness, a dose of 0.25–0.50 mg per cat is administered intravenously, after which the patient is observed for evidence of increased muscular activity. A positive response is one in which there is a dramatic increase in muscle strength; this improvement is usually maintained for only a few minutes.

Although edrophonium chloride is relatively safe as a diagnostic agent (due to its short duration of action), atropine should still be available in case a cholinergic crisis is induced. The disadvantages of using edrophonium chloride are primarily the possibility of both false-positive and negative results, and this test is therefore only used as a guide to revealing the presence of MG. Other disorders causing NMJ block may also demonstrate a partial response to edrophonium chloride, while in those MG patients with insufficient available ACh receptors, an inapparent or small response may be evident, despite prolonging the residence time of the ACh. The results of the test are also subjective and depend on the assessment and interpretation of the examiner.

In focal MG, particularly in cats, there is often no detectable improvement in muscular strength and the test is of little use. An exception to this would be a focal MG case with a decremental palpebral response. Such patients often demonstrate an improvement in the palpebral response following edrophonium administration. The short-acting properties of edrophonium chloride, which make it a safe and suitable diagnostic tool, may also make it unsuitable in those cases that either have very brief collapse episodes or are difficult to administer intravenous agents to during a collapse episode. In these cases the use of a longer-acting anticholinesterase agent, neostigmine, would be indicated and following administration the animal exercised to see whether the weakness episodes can be abolished or improved. Due to the long-acting nature of neostigmine, prior administration of atropine is recommended to prevent a cholinergic crisis. The main risk during the administration of any anticholinesterase agent is that of inducing a cholinergic crisis. Overstimulation of muscarinic ACh receptors can result in adverse side effects, including bronchoconstriction and bradycardia. These can be prevented by pretreatment with antimuscarinic agents, either SC or IM atropine (at 0.02–0.04 mg/kg) or glycopyrrolate (at 0.01–0.02 mg/kg). Overstimulation of

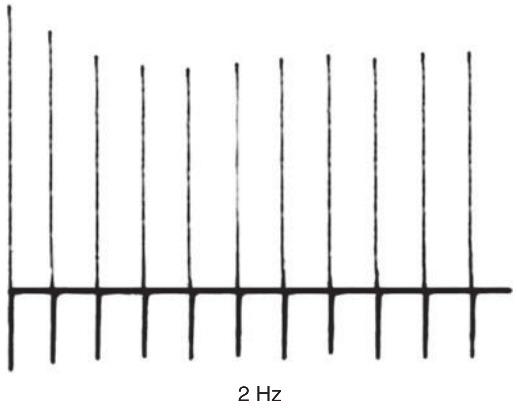

Figure 19.8 Repetitive nerve stimulation in a Jack Russell Terrier with congenital myasthenia gravis, demonstrating progressive decrement of the compound muscle action potential. Normal animals would not demonstrate decrement at stimulation rates less than 5 Hz.

nicotinic ACh receptors can induce a depolarizing blockade and exacerbate muscular weakness. The clinician should therefore be ready to provide respiratory support in rare cases in which respiratory paralysis occurs.

d. Electrodiagnostic assessment
Electrodiagnostic assessment is often useful in the diagnosis of MG, but is limited by the availability of the equipment and the requirement for generalized anesthesia (which may be contraindicated in cases with respiratory impairment due to muscular weakness or aspiration pneumonia).

e. Repetitive nerve stimulation
The repetitive nerve stimulation test utilizes the area or amplitude of successive compound muscle action potentials (CMAP) obtained by repetitively stimulating the nerve supplying that muscle. The tibial, peroneal, or ulnar nerves are usually utilized, with the recording electrodes placed in the digit innervated by that particular nerve. In the normal animal, the amplitude should remain constant at stimulation rates of 5 Hz or less. A decremental response to repetitive nerve stimulation at a stimulation rate of 5 Hz or less is supportive of a diagnosis of MG (Fig. 19.8). A decrease in the compound muscle action potential of 10% or more is considered abnormal. At higher stimulation rates, normal animals will often demonstrate a decremental response. The test is highly sensitive for MG in human patients, although the test is more likely to yield a positive response in cases with generalized MG than focal MG. Repetitive nerve stimulation in focal MG is still more sensitive than determining serum ACh receptor antibody concentrations in human cases with focal MG. Some other NMJ disorders (e.g. organophosphate toxicity) may also demonstrate a decremental response.

f. Single-fiber electromyography (SF-EMG)
A more specific test for NMJ blockade induced by MG, in both dogs and humans, is single-fiber electromyography. The use of SF-EMG is limited at present due to the availability and cost of the recording needles, as well as the expertise required to perform the test. SF-EMG is based on obtaining recordings of the evoked action potential from single muscle fibers using a special recording needle with a very small recording surface. This is in contrast to the conventional recording needles that record motor unit action potentials, which represent the synchronous depolarization of many adjacent muscle fibers. Based on the recording of the evoked action potential from one muscle fiber, the time variation in neuromuscular transmission for that fiber (jitter) can be determined. The test is based on the fact that the time variation for neuromuscular transmission (or latency from stimulus to action potential) is virtually constant for that muscle fiber with repeated measurements. Any alteration in NMJ transmission is likely to result in an increased variation in the time of NMJ transmission. The test can be performed by one of two methods:

a. The latency from the time of stimulus to the peak of an action potential for a single muscle fiber can be recorded repeatedly. The jitter value is then calculated by determining the mean value of the consecutive differences in latency (Fig. 19.9). In normal patients the latency is virtually constant.

b. The interval between the evoked action potentials for two different muscle fibers from the same

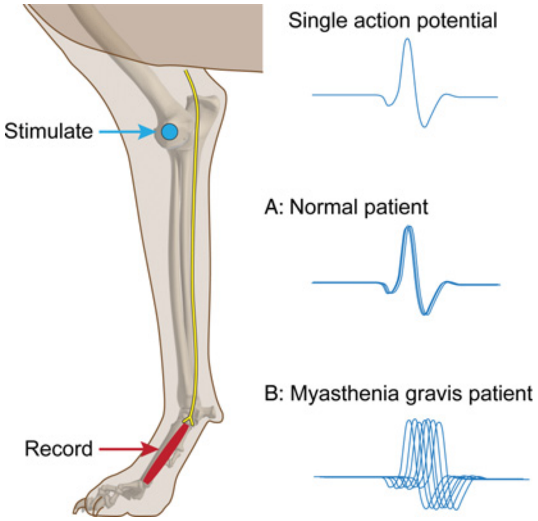

Figure 19.9 Single fiber electromyography from a normal (A) and myasthenic (B) patient illustrating the increased variation in latency (jitter) occurring with MG. (The Ohio State University. Reproduced with permission.)

motor unit (interposital latency) can be measured repeatedly. The jitter value is the mean value of the consecutive differences in interposital latency.

The test is not specific for MG as any disorder of NMJ transmission may result in an abnormal jitter result. However, the main contribution to jitter is impulse conduction at the synaptic cleft-endplate region of the NMJ. In human MG, SF-EMG is considered the most sensitive test for diagnosing all forms of MG, with 92–100% of myasthenic patients demonstrating abnormal jitter values. A method for determining jitter has been reported in dogs, but use of the test in the diagnosis of MG has not been reported in veterinary practice to date.

g. Demonstration of elevated anti-ACh receptor antibody concentrations

The definitive diagnosis for acquired MG is made by demonstrating circulating antibodies directed against nicotinic ACh receptors of skeletal muscle, with the highest antibody concentrations generally occurring in cases with acute fulminating MG. Congenital MG will have a negative antibody concentration. The test is an immunoprecipitation radioimmunoassay using ^{125}I α-bungarotoxin-labeled ACh receptors. In the canine test, the ACh receptors are obtained from near-term fetal canine muscle. The test is available for dogs and cats at the Comparative Neuromuscular Laboratory, University of California, San Diego (vetneuromuscular.ucsd.edu). There appears to be some cross-reactivity in antibody recognition of the ACh receptors between species, but the assay is relatively species-specific, and a canine- or feline-specific assay system should be used. An ACh receptor antibody concentration of greater than 0.30 nmol/L is positive for acquired MG in cats, while greater than 0.6 nmol/L is positive in dogs. False-positive tests are extremely rare and a positive result is therefore virtually confirmatory for a diagnosis of acquired MG. The test is performed on a serum sample and is relatively inexpensive. The serum ACh receptor antibody concentration is usually lowest in cases with focal MG and highest in cases with acute fulminating MG. Within an individual, ACh receptor antibody concentrations seem to correlate well with the disease severity. However, antibody concentrations between patients are highly variable, and do not correlate well with severity and/or degree of weakness.

In human MG, the immunoprecipitation radioimmunoassay fails to detect 10 to 15% of generalized MG cases and 30 to 50% of focal MG cases, with these patients being referred to as seronegative myasthenics. There is evidence that this situation also occurs in canine patients with acquired MG. Approximately 2% of dogs with generalized MG are seronegative. The percentage of seronegative dogs with focal MG is not currently known. The proposed reasons for the failure of this technique to detect some cases include:

- In some cases, the affinity of the antibody is such that all of the available antibody is bound to the muscle endplate region with undetectable levels of circulating antibody.
- During solubilization of the ACh receptors for the test probe, damage to certain antigenic epitopes of the ACh receptor may occur and the test probe may therefore fail to recognize some antigenic variations of the ACh receptor antibodies.
- Some of the antibodies in acquired MG may be directed against antigenic proteins of the endplate region other than the ACh receptors (autoantibodies against non-ACh skeletal muscle proteins, such as titin and ryanodine receptor), and these would therefore not be identified by the test. In dogs, MG has been associated with autoantibodies against skeletal muscle striations and ryanodine receptors in dogs with thymoma, and against titin in older-onset MG.
- Immunosuppressive therapy for longer than 7–10 days will lower antibody titers, so the use of a pretreatment blood sample is strongly recommended.

Criteria used to classify dogs as having seronegative MG include:

1. clinical signs consistent with MG
2. consistent pharmacologic response (positive edrophonium test) and electrophysiologic findings (decremental response of CMAP during repetitive nerve stimulation)
3. normalization of appendicular muscle weakness following acetylcholinesterase therapy with neostigmine or pyridostigmine
4. at least two negative serum ACh receptor antibody titers as determined by immunoprecipitation radioimmunoassay.

h. Demonstration of immunoglobulin localized to the endplate region of muscle

Supportive of the diagnosis (but not specific for acquired MG), immune complexes may be demonstrated at the level of the NMJ by immunocytochemistry of fresh muscle biopsy specimens or by incubating the patient's serum with stored normal canine muscle samples. The test is relatively inexpensive and easy to perform, but the staphylococcal protein A-horseradish peroxidase conjugate is not specific to antibodies against the ACh receptors; the test is therefore not specific for acquired MG. The test is, however, a useful screening tool, as a negative result generally rules out the possibility of acquired MG. Pretreatment with immunosuppressive drugs may decrease the chance of a positive test.

4. Treatment of MG can be subdivided into supportive treatment, which is similar for all cases with neuromuscular blockade, and specific therapy, aimed at relieving the NMJ blockade and controlling the underlying autoimmune process in acquired MG.
   a. Supportive treatment
      1. Aspiration pneumonia
         Prevention and/or treatment of aspiration pneumonia are/is important due to the increased morbidity and mortality associated with its development. Recumbent patients should be turned frequently (every 2–4 hrs) to prevent hypostatic lung edema and exacerbation of any existing pneumonia. If aspiration pneumonia is present, or the development thereof is thought to be likely, antibiotic therapy should be implemented. Ideally, the choice of antibiotic should be based on culture and sensitivity results from tracheal wash fluid and should be tailored to avoid using antibiotics associated with NMJ blockade (see "Antibiotics" section below). Frequent nebulization and coupage are useful in the treatment of pneumonia.
      2. Fluid requirements
         The maintenance of hydration in the face of significant regurgitation can be a challenge, especially as some animals tend to regurgitate liquids more readily than solids. Maintenance of fluid requirements with intravenous fluid therapy should be initiated if required.
      3. Nutritional support
         Maintenance of dietary intake is important in recumbent patients and particularly those with dysphagia or regurgitation. Elevated feeding may help in some cases with megaesophagus, but maintaining head elevation is difficult in cats. In dogs, a specially designed feeding chair can be used, such as the "Bailey chair" (Fig. 19.10). This type of feeding chair allows for the dog to sit in an upright position for feedings. Ideally, the dog should sit in the upright position for 10–15 min after feedings to allow the food to move into the stomach, which decreases the risk of aspiration pneumonia in myasthenic dogs with megaesophagus. In those patients in which elevated feeding is undertaken, determining the ideal food consistency for that individual case is a matter of trial and error. Solid food stimulates pharyngeal and esophageal peristalsis more effectively in the normal dog, but some dogs with pharyngeal and esophageal dysfunction tolerate semisolid food better. The head should be maintained elevated throughout feeding and for 10 to 15 min following feeding. In those cases with unmanageable regurgitation, a nasogastric, esophageal, or, ideally, a gastrostomy tube can be placed. Due to poor esophageal function, regurgitation can still occur with a nasogastric or esophageal tube, and a gastrostomy tube would be better suited to MG patients. The advantages of gastrostomy tube placement include that head elevation during feeding is no longer required, the risk of aspiration pneumonia is reduced, and proper delivery of oral medication can be guaranteed (versus variable delivery and passage time with megaesophagus and dysphagia). The disadvantages of gastrostomy tube placement are that only semiliquid and liquid foods can be administered and tube placement requires a short general anesthetic that may be deleterious to some myasthenic patients.
      4. Respiratory support
         Intensive care and specifically respiratory support with intermittent positive pressure ventilation may be required in animals demonstrating severe weakness.
      5. Drugs to modify gastrointestinal tract function
         The main consideration in the manipulation of gastrointestinal tract (GIT) function in MG is the management of megaesophagus and dysphagia, with the resultant complications of regurgitation, esophagitis, and aspiration pneumonia.
         a. Improving esophageal motility
            Drugs with prokinetic effects on GIT smooth muscle include metoclopramide and cisapride.

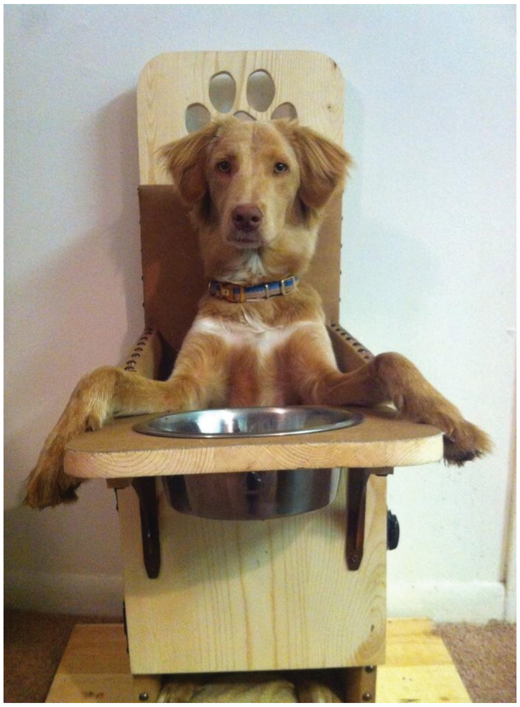

Figure 19.10 Myasthenic dog sitting in a specifically designed feeding chair ("Bailey chair"). (Susan Sanchez, 2014. Reproduced with permission from Susan Sanchez.)

Both of these drugs are believed to mediate their prokinetic effect by stimulating enteric cholinergic neurons, which in turn leads to ACh release and resultant smooth-muscle contraction. There is, however, no evidence that either of these two drugs stimulates increased esophageal motility in either the normal or MG-affected canine esophagus. Cisapride has actually been demonstrated to increase esophageal transit time in the normal dog. The dose of metoclopramide in the dog is 0.2–0.5 mg/kg given orally, intramuscularly, or subcutaneously every 8 hrs and that of cisapride is 0.1–0.5 mg/kg given orally every 8 hrs.

b. Increasing lower esophageal sphincter tone

Where elevated oral feeding is being used, drugs that increase lower esophageal tone should be avoided as this would result in resistance to the passage of food into the stomach. Increased lower esophageal tone would be beneficial where feeding is being performed via a gastrostomy tube by decreasing gastroesophageal reflux and consequently reducing or limiting esophagitis. Both metoclopramide and cisapride increase lower esophageal tone, with cisapride having the more potent action.

c. Prevention and management of esophagitis

Animals with megaesophagus and gastric reflux into the esophagus are at risk of developing esophagitis, which may in itself perpetuate esophageal dilation. The risk of esophagitis (or management thereof where esophagitis is already present) can be decreased by feeding via a gastrostomy tube (combined with drugs to increase lower esophageal sphincter resistance) and by increasing the pH of GIT content.

d. Increasing the pH of GIT content

The acidity of aspirated material is a major determinant of the degree of pulmonary damage in aspiration pneumonia as well as contributing to the severity of esophagitis. A frequent component of aspirated material in MG is refluxed gastric content; increasing the gastric content pH is therefore advisable in MG cases at risk of aspiration pneumonia. Famotidine is a histamine-2 receptor antagonist that increases gastric content pH. Famotidine is administered at 0.5–1 mg/kg every 12–24 hrs (orally or intravenously). Omeprazole and pantoprazole are proton pump inhibitors that also increase gastric content pH. The recommended dose of oral omeprazole is 0.7–1 mg/kg every 24 hrs. The same dose applies to pantoprazole but is administered intravenously. Overall, proton pump inhibitors appear to provide superior gastric acid suppression than famotidine.

b. Specific therapy

The mainstay of specific therapy in MG is the use of anticholinesterase agents, although an attempt should also be made to address the underlying disease process by immunomodulatory therapy and addressing any contributory disease processes.

1. Anticholinesterase therapy

Anticholinesterase drugs prolong the availability of ACh for binding to ACh receptors by inhibiting degradation by AChE. Pyridostigmine bromide is administered orally every 8 to 12 hrs at a dose of 0.5–3.0 mg/kg in dogs and 0.25 mg/kg in cats. Pyridostigmine bromide is available in both tablet and syrup forms. A slow-release tablet form is available but the gastrointestinal absorption may be erratic. Cats are more sensitive than dogs to anticholinesterase drugs; the starting dose is therefore lower than in dogs. Care should also be taken when altering the dose in cats. The dose should be started at the lower end of the scale and slowly titrated to achieve the best clinical response while avoiding cholinergic side effects. Cholinergic signs include hypersalivation, vomiting, diarrhea, and muscle fasciculations. Should these signs develop, the dose should be decreased.

If oral medication cannot be tolerated due to pharyngeal weakness or aspiration pneumonia, then either administration of pyridostigmine by gastrostomy tube (if one has been placed), administration of pyridostigmine bromide as a constant rate infusion (0.01–0.03 mg/kg/hr), or parenteral neostigmine may be considered until oral pyridostigmine administration can be tolerated. The onset of effect for parenteral neostigmine is more rapid, but of shorter duration than pyridostigmine; it therefore needs to be administered every 6 hrs. In dogs it can be administered at a dose of 0.04 mg/kg.

There is some variability in the response to anticholinesterase therapy, and the reason for this variability is poorly understood. Certainly, in human patients with acquired MG, most cases are not satisfactorily controlled with anticholinesterase therapy alone and these drugs are often ineffective in controlling the ocular form of the disease. Some dogs appear to respond well to therapy, while others respond poorly. To some extent, the variability in the severity of the autoimmune response against the ACh receptors may explain the variability to anticholinesterase therapy, as anticholinesterase therapy does not address the underlying autoimmune process. The effect of anticholinesterase therapy on improving esophageal function in dogs with megaesophagus is thought to be less than the effect on appendicular muscle weakness. Although myasthenic cats can be treated successfully with anticholinesterase drugs, it has been suggested that cats with MG may respond better to immunosuppression than to anticholinesterase therapy.

2. Immunosuppressive therapy
   The use of immunosuppressive therapy in acquired MG is based on the underlying pathophysiology, an autoimmune destruction of functional ACh receptors. If an optimal response to therapy is not obtained with supportive care and anticholinesterase drugs alone, immunosuppressive therapy may be considered. There is, however, some controversy about the use of immunosuppressive therapy in MG, with the main reasons being the high incidence of aspiration pneumonia in MG (especially in canine patients) with the potential for immunosuppressive therapy to exacerbate that, as well as the potential for glucocorticoid therapy to worsen neuromuscular weakness.
3. Glucocorticoid therapy
   The potential for glucocorticoid therapy to exacerbate muscular weakness has been demonstrated in both dogs and cats, especially in cases with marked muscular weakness and respiratory distress. However, myasthenic cats appear to be more resistant than dogs to the development of weakness associated with glucocorticoid therapy. Increased muscle weakness associated with glucocorticoid therapy has been observed in 50% of human MG patients. In cases responsive to edrophonium chloride, a conservative treatment regime would be to start pyridostigmine bromide therapy, combined with alternate-day low-dose (anti-inflammatory dose) prednisone therapy. Increasing (or in naive cases introducing) corticosteroid therapy should be considered if the response to anticholinesterase therapy is suboptimal or if the animal is demonstrating resistance to the drug therapy. An initial dosage of 0.5 mg/kg every 12 hrs is suggested in these cases, as higher doses may result in the exacerbation of neuromuscular weakness. In cats, prednisone doses of 1–2 mg/kg/day have been used and dexamethasone at 0.25–1.0 mg/kg/day. Dexamethasone is associated with more gastrointestinal side effects and a higher myopathic potential than prednisone, and its use should therefore be avoided in MG. The exact mechanism whereby prednisone results in improvement of the clinical signs of MG is not fully understood, but may be related to the inhibitory effects of prednisone on the formation and release of inflammatory agents, lymphocyte division, lymphocyte reactivity to ACh receptors, and leukocyte chemotaxis.
   a. Azathioprine
      Azathioprine is a cytotoxic antimetabolite that interferes with DNA synthesis, with its beneficial effect in acquired MG probably being mediated through reducing lymphocyte numbers and consequently immunoglobulin production, as well as specifically inhibiting T-cell production. The use of azathioprine alone or combined with prednisone has been demonstrated to be highly effective in resolving clinical signs in human MG. The potential side effects of azathioprine therapy include the development of bone marrow suppression and, less often, hepatotoxicity, pancreatitis, and GIT irritation. Bone marrow suppression is much more common in cats; azathioprine use is therefore not advised in this species.

      In dogs with evidence of bone marrow suppression (leukopenia with or without anemia and thrombocytopenia), azathioprine therapy should be discontinued (or reduced in cases with mild bone marrow suppression). It is recommended that azathioprine be discontinued if the patient's white blood cell count is less than 4000 cells/mL, and/or if the neutrophil count is below 1000 cells/mL. The onset of the clinical effect of azathioprine is delayed in both human and canine cases. A complete immune response to this medication may take up to 6 wks, but in many cases clinical response is seen within 2 wks. Therefore, its use should be combined with prednisone if an early effect is required. A conservative prednisone dose should be used initially, as discussed earlier. The clinical signs should abate rapidly with prednisone therapy. After 2–4–mos, the prednisone therapy can be tapered to a minimum alternate-day dosage or in some cases stopped entirely. This protocol should minimize side effects with a rapid and sustained control of the clinical signs in many patients. In stable MG dogs, azathioprine may be considered as a sole immunosuppressive agent. It may take several weeks before an obvious clinical benefit is realized in such patients. The dose of azathioprine in dogs is 1–2 mg/kg once a day or every other day. Bone marrow function should be monitored by assessing for suppression on a hemogram every 1–2 wks during the initial 1–2 mos of therapy and every 1–2 mos thereafter.

b. Cyclosporine
Cyclosporine has been demonstrated to have some efficacy in human cases of acquired MG, and it is particularly used in those cases that cannot tolerate or are nonresponsive to other immunosuppressive drugs. Cyclosporine blocks the transcription of genes required for T-cell activation, notably those encoding immunoregulatory cytokines including interleukin-2. The dose is 3–6 mg/kg twice a day orally or intravenously. In one report, cyclosporine was successful in the treatment of two dogs with acquired MG, at a dosage of 4 mg/kg every 12 hrs. Although its specificity for lymphocytes is an attractive feature, cyclosporine can become cost prohibitive for large-sized dogs. The most common side effects in dogs include mild gastrointestinal signs, which are often transient or responsive to dose reduction. Other less common but more serious side effects include gingival hyperplasia, opportunistic infections, hepatotoxicity, allergic reactions, and lymphoproliferative disorders.

c. Mycophenolate mofetil (MMF)
MMF is an inhibitor of purine synthesis in both T- and B-lymphocytes. As a consequence, MMF interferes with lymphocyte proliferation, differentiation of T_c cells, and antibody responses. MMF is commonly used in people to prevent renal allograft rejection, and it has also been used to treat various autoimmune diseases (including MG). In dogs, controversial results exist about the efficacy of MMF to treat acquired MG. A case series of three dogs with severe generalized MG treated with intravenous MMF demonstrated clinical remission in 48 hrs with no adverse effects. Successful treatment of MG in a dog with oral MMF has been reported. The institution of MMF therapy resulted in a rapid resolution of clinical signs (within the first week of therapy) and the return of the ACh receptor antibody concentration to within the normal range. However, a retrospective case series including 27 dogs with acquired MG that were treated with a combination of MMF and pyridostigmine compared with those treated with pyridostigmine alone did not show any significant benefit of MMF over the long term. The recommended oral (or gastrostomy tube) dose of MMF is 7–20 mg/kg every 12 hrs. The intravenous dose of MMF is 15–20 mg/kg, diluted in 500 mL of 0.45% NaCl and 2.5% dextrose and administered over 4 hrs. The side effects of MMF described in dogs are primarily gastrointestinal (e.g. vomiting, bloody diarrhea). It is recommended that the MMF dose be reduced by half, once clinical signs of MG improve substantially or resolve, in order to minimize adverse side effects. Since side effects are typically evident by 3–4 wks of therapy with MMF, reducing the dose prior to this time is recommended, especially if a positive clinical response has already been achieved.

d. Leflunomide and cyclophosphamide
Leflunomide inhibits T- and B-cell proliferation, suppresses immunoglobulin production, and interferes with cell adhesion. It has been used in dogs to treat immune-mediated diseases such as immune-mediated polyarthritis, nonsuppurative encephalitis/meningomyelitis, and Evans syndrome. Leflunomide prevented the development of experimental MG in rats. There is no available information on the treatment of MG in dogs or cats.

Cyclophosphamide is a cytotoxic alkylating agent that cross-links DNA, disrupting nucleic acid function and inhibiting cell proliferation. It has been used in people with refractory MG. Serious adverse effects can be seen with its use, including myelosuppression and hemorrhagic cystitis. There is no well-documented use of cyclophosphamide in veterinary patients with MG.

4. Intravenous immunoglobulin (IVIg) and plasmapheresis
Both intravenous immunoglobulin and plasmapheresis (plasma exchange) therapy have been used to treat human-acquired MG. However, reports on the efficacy of these treatments in human-acquired MG have been variable. It appears that their main value may be in the treatment of acute fulminating MG, where rapid improvement in the clinical signs is required. These techniques are limited in veterinary medicine due to the cost limitations and equipment requirements, but may be of benefit in the management of acute fulminating MG.

The mode of action of IVIg is poorly understood but may be related to the binding of circulating autoantibodies, blocking macrophage and lymphocyte Fc receptors, enhanced suppressor T-cell activity, and inhibition of the complement cascade. A recent meta-analysis investigated the data available on the efficacy of IVIg for treating human MG. It was concluded that in MG acute exacerbations one dose of IVIg was more efficacious than placebo, with the results being borderline significant ($P = 0.055$). No significant difference was identified between the use of IVIg and oral methylprednisolone in the treatment of acute exacerbation of MG. In the case of chronic MG, there was insufficient evidence to determine whether IVIg was efficacious. Two dogs with MG were treated with human IVIg. The dogs received one and four IVIg transfusions each, at a dose of 0.5 g/kg. Both dogs reportedly improved with all weakness resolving within 48 hrs; however, both dogs had recurrence of clinical signs during the subsequent days to weeks. No additional veterinary studies exist evaluating the use of human IVIg in MG.

Plasmapheresis involves removing the plasma and plasma constituents (including immunoglobulins) from the whole blood of patients and returning the blood elements with either stored plasma or plasma substitutes to the patients. Immunoadsorption therapy is a form of plasmapheresis in which a patient's plasma is returned after being passed through a filter that adsorbs immunoglobulins. Plasmapheresis results in the removal of ACh receptor antibodies from circulation. Plasmapheresis and human IVIg have been of equal benefit in the treatment of human MG patients. Although there are reports of plasmapheresis being effective in the treatment of human MG, a recent meta-analysis concluded that the current evidence available is insufficient to support or refute the use of plasmapheresis for the treatment of human-acquired MG. A case report documented clinical remission in one dog with acquired MG who received two treatments of plasmapheresis in combination with prednisone therapy.

5. Therapeutic vaccines

Peptides that mimic antigen receptors of T and B cells necessary for the generation and maintenance of the autoimmune response in acquired MG have been evaluated as therapeutic vaccines in both a rat model and naturally occurring canine-acquired MG. These peptides lead to the production of anergizing antibodies against ACh-specific receptors on these immune cells, blunting the autoimmune response. Although the data are preliminary, this approach appears to be have been effective in a small number of dogs (10) evaluated. These 10 vaccinated dogs experienced a higher rate and shorter time to clinical and serologic remission when compared with historical controls.

c. Management of concurrent neoplasia

If a concurrent thymic mass or other neoplasia is present, surgery (with or without radiation therapy) should be considered. In humans, pathological alterations of the thymus (either thymic hyperplasia or thymoma) are present in approximately 80% of cases with generalized acquired MG showing autoantibodies against ACh receptor. The removal of thymic hyperplasia has been demonstrated to improve remission rates in human patients with acquired MG. In contrast to the removal of thymic hyperplasia, thymoma removal in human patients with acquired MG is usually not associated with an improvement in clinical signs. Occasionally, a myasthenic person will worsen following thymoma removal. An acute onset of clinical signs consistent with acquired MG following thymectomy has also been documented in dogs and cats. The improvement documented in human cases with thymic hyperplasia is probably related to the removal of a source of continued antigenic stimulation, while the worsening of the clinical signs occasionally seen in acquired MG following thymoma removal may be related to the loss of an immunosuppressive effect of the thymus.

The beneficial effect of thymic removal in the absence of a thymoma has not been demonstrated in dogs and cats. Thymic hyperplasia has also not been described in dogs and cats with MG, and thymectomy in the absence of a demonstrable thymic mass would not be recommended, owing to the detrimental and stressful effects of surgery and anesthesia. In the few documented cases in which thymectomy was performed in dogs with acquired MG, the outcome was generally poor, particularly in those cases presenting concurrent megaesophagus, with the majority dying of aspiration pneumonia shortly after surgery. The successful management of thymoma with radiation therapy has been reported in dogs.

5. Treatment of acute fulminating myasthenia gravis

The mortality associated with MG is highest with the fulminating form, although luckily this is the most uncommon form of the disease. Cases present with rapidly progressive generalized weakness with concurrent megaesophagus. Rapid diagnosis and treatment (combining anticholinesterase therapy and ventilatory support) are therefore essential. The main cause of death in these cases is respiratory failure secondary to muscular weakness, and this may be further complicated by aspiration pneumonia. Care should be taken when initiating immunosuppressive therapy with corticosteroids, owing to the potential to exacerbate the muscular weakness. In human cases with acute fulminating MG, plasmapheresis and intravenous immunoglobulin have been used, but their use in veterinary medicine is limited by cost and availability.

6. Contraindications

Drugs that adversely affect NMJ transmission should be avoided, including ampicillin, aminoglycoside antibiotics, anti-arrhythmic agents, phenothiazines, anesthetics, narcotics, and muscle relaxants. Organophosphates may act in an additive manner with pyridostigmine; their concurrent use should therefore be avoided.

7. Prognosis

The overall prognosis for acquired MG in dogs is guarded due to this species' propensity to develop megaesophagus and aspiration pneumonia. The prognosis for recovery from acquired MG in dogs is good if severe aspiration pneumonia or pharyngeal weakness is not present. In humans, the prognosis with uncomplicated acquired MG is considered good to excellent. However, the incidence of aspiration pneumonia in canine patients is significantly higher than in human medicine and the overall survival rate is therefore lower than human patients. The overall 1-yr mortality rate for canine acquired MG has been reported to be between 40 and 60%. The reason for death or euthanasia of myasthenic dogs is almost always severe or recurrent aspiration pneumonia. In order to maximize the chance of a favorable outcome in canine MG patients, aggressive prevention and/or treatment of aspiration pneumonia is essential. Anecdotally, the survival rate of dogs with acquired MG appears to have improved in recent years, perhaps due to the increased recognition and prompt diagnosis of the disorder, improved treatment options, or some combination of these two. In addition, there is evidence that the spontaneous remission of acquired MG in dogs is more common than previously thought. Some dogs (especially in the young age group) may go into spontaneous remission, even without immunosuppressive therapy. A retrospective study reported that 47/53 dogs treated with anticholinesterase therapy alone went into remission within an average of 6.4 mos.

Information on documented cases of acquired MG in cats suggests that the prognosis for focal and generalized MG may be better than that reported for dogs. This is likely due to the lower incidence of megaesophagus and associated aspiration pneumonia in cats. In one series of acquired MG in 20 cats, only three of the cats died and all three of these presented with acute fulminating MG with death due to respiratory failure. Of the remaining cats, 11 of 20 demonstrated improvement of clinical signs at 2 mos after diagnosis, with six remaining unchanged. One-year follow-up was available for five cats, at which time two were still alive, while the other three cats had died or were euthanized for unrelated illnesses. At 1.5 yrs, two cats were found to be free of clinical signs of disease.

Clinical remission of MG is associated with a return of serum ACh receptor antibody concentrations to the normal range. These concentrations should therefore be evaluated every 6–8 wks to monitor the clinical course of the disease.

Drugs and toxins associated with junctionopathies (Box 19.1 and Fig. 19.11)

Box 19.1 Drugs and toxins associated with NMJ blockade syndromes.

- Algae
  - **Blue-green algae (anatoxins)**[a]
  - Green algae (charatoxin)
- Antibiotics:
  - **Aminoglycosides**
  - Lincomycin
  - Penicillamine (penicillin degradation product)
  - **Polymyxins**
  - Tetracyclines
  - **Ionophores (Lasalocid)**
- Antiprotozoal agents:
  - Chloroquine
  - Quinine
- **Black widow spider venom**
- **Botulinum toxin**
- Gila monster venom
- Hornet mandaratoxin (*Vespa mandarinia*)
- Interferon-α and interferon-β
- Lithium
- Marine toxins
- Methoxyflurane
- Neuromuscular blocking agents:
  - Hexamethonium
  - Succinylcholine
  - Trimethaphan camsylate
  - Vecuronium
- Pesticides:
  - **Organophosphorus compounds**
  - Carbamates
- Poisonous plants
  - *Delphinium* spp. (larkspur)
  - Dihydro-b-erythroidine (alkaloid from seeds of the genus *Erythrina*)
  - Hemlock (*Conium maculatum*)
  - Tubocurarine (*Strychnos toxifera*)
- **Snake venoms**
- Tetanus toxin (minor effect)
- **Tick bite paralysis**

The box includes experimental and human drugs and toxins.

[a] Bold type indicates clinically most important agents and syndromes.

A. Algae-derived toxins[7, 14, 21, 38, 42, 122, 128, 171, 172, 199, 229, 230, 286]

1. Blue-green algae (anatoxins)

Cyanobacteria (blue-green algae) are found in freshwater worldwide. Blue-green algae can produce four types of toxins: hepatotoxins, neurotoxins, lipopolysaccharide endotoxins, and cytotoxins. The most common blue-green algal neurotoxin is anatoxin-a. Anatoxin-a is produced by several genera of blue-green algae mainly in the *Anabaena* genus, but also by other genera, such as *Aphanizomenon*, *Oscillatoria*, *Microcystis*,

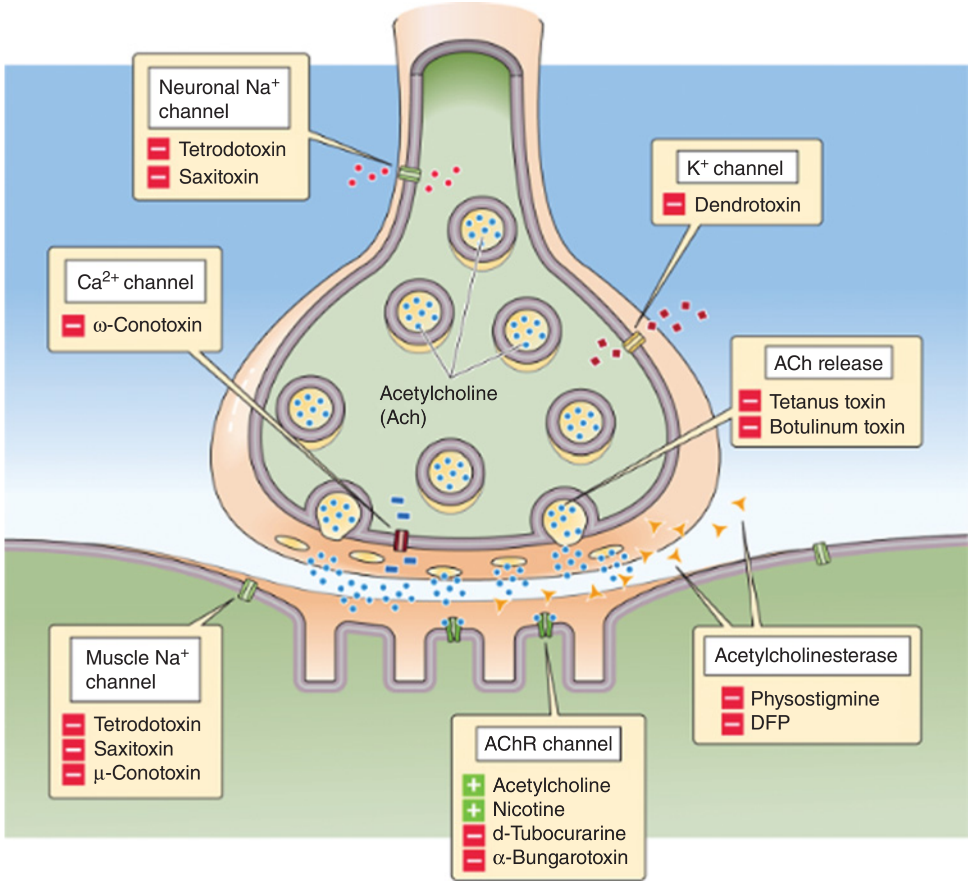
Neuronal Na+ channel
− Tetrodotoxin
− Saxitoxin
K+ channel
− Dendrotoxin
Ca2+ channel
− ω-Conotoxin
Acetylcholine (Ach)
ACh release
− Tetanus toxin
− Botulinum toxin
Muscle Na+ channel
− Tetrodotoxin
− Saxitoxin
− μ-Conotoxin
Acetylcholinesterase
− Physostigmine
− DFP
AChR channel
+ Acetylcholine
+ Nicotine
− d-Tubocurarine
− α-Bungarotoxin

Figure 19.11 Schematic representation of the pharmacology of the vertebrate neuromuscular junction. Many of the proteins that are involved in synaptic transmission at the mammalian neuromuscular junction are the targets of naturally occurring or synthetic drugs. The antagonists are shown as minus signs highlighted in *red*. The agonists are shown as plus signs highlighted in *green*. (Moczydlowski, 2011.[192] Reprinted with permission.)

Planktothrix, *Woronichinia*, *Cylindrospermum*, *Lyngbya*, and *Phormidium*. Anatoxin-a is a potent cholinergic agonist at nicotinic ACh receptors in neurons and at the NMJ. Dogs are particularly vulnerable to blue-green algae intoxication because of their tendency to swim in and drink water containing algae and/or ingest algal mats. The clinical signs of anatoxin-a poisoning include muscle fasciculations, muscle rigidity, incoordination, recumbency, seizures, collapse, respiratory depression, cyanosis, and death. Clinical signs occur within 1 hr of exposure, and can begin as early as 5–10 min after exposure. Diagnosis is often presumptive based on history of exposure to freshwater and/or algae material followed by a rapid onset of clinical signs. A definitive diagnosis of anatoxin-a intoxication is based on the identification of anatoxin-a in biological specimens (e.g. water, gastric contents) by liquid chromatography and mass spectrometry. No antidote exists, and treatment is mainly based on early decontamination and supportive care. Unfortunately, prognosis is poor to grave.

Anatoxin-a(s), another potent neurotoxin, has been isolated from *Anabaena flos-aquae*, which is distinct from the *Anabaena* strains that produce anatoxin-a. Anatoxin-a(s) is a naturally produced organophosphate. Anatoxin-a(s) has been demonstrated to be a potent irreversible inhibitor of ACh in experimental studies and certainly the inhibitory kinetics of anatoxin-a(s) are supportive of an in vivo anticholinesterase action. Anatoxin-a(s) toxicity can be reversed by treatment as for cholinesterase toxicity, including the use of oxime reactivators, carbamates, and atropine.

2. Green algae (charatoxin)

   Charatoxin is produced by the alga *Chara globularis*, which has been shown to be an insecticidal agent. In high concentrations it is a competitive antagonist at the nicotinic ACh receptor, while at lower concentrations it enhances ACh binding.

B. Antibiotics[4, 24, 27, 32, 33, 37, 40, 42, 54, 77, 80, 81, 85, 114, 118–120, 125, 131, 136, 137, 139, 146, 149, 153, 156–158, 176, 205, 210, 212, 233, 239, 240, 245, 247, 250, 252, 254, 273, 275, 276, 278, 293, 294, 299, 306]

1. Antibiotics causing NMJ blockade are unusual in veterinary medicine, but the understanding of the few reported cases is augmented by the large amount of experimental data. One of the most important areas of concern is the

concurrent use of these antibiotics and anesthesia incorporating NMJ blocking agents or in animals with concurrent MG. Certainly, gentamycin has been shown to augment the neuromuscular blockade of atracurium in anesthetized horses and dogs. Antibiotics with demonstrated NMJ blocking effects include:

- aminoglycosides
- lincomycin
- penicillamine
- polymyxins
- tetracyclines.

Of these, the aminoglycoside antibiotics are clinically the most important.

a. Aminoglycoside antibiotics

The aminoglycoside family of antibiotics is primarily used to treat infections from aerobic gram-negative bacteria. These drugs act in a bactericidal manner by interfering with protein synthesis. The family includes Gentamycin, Neomycin, Streptomycin, Kanamycin, Tobramycin, Amikacin, and Netilmicin. The primary limitations for the use of aminoglycoside antibiotics are the development of ototoxicity and nephrotoxicity, but acute neuromuscular blockade has been reported, particularly when aminoglycoside antibiotics are used in conjunction with general anesthesia.

The toxic mechanism for the acute, reversible NMJ blockade induced by aminoglycoside antibiotics appears to be mediated via calcium antagonism at the external cell membrane channel sites on both the pre- and postsynaptic cell membrane. The NMJ blockade induced by aminoglycoside antibiotics is transient and experimentally is virtually completely antagonized by calcium and partially antagonized by neostigmine. All members of the aminoglycoside family can cause NMJ blockade, but both the degree of NMJ blockade and the balance between pre- and postsynaptic effects vary between the different agents. In order of decreasing effect of NMJ blockade are neomycin, kanamycin, amikacin, gentamycin, and tobramycin.

The presynaptic inhibition of NMJ transmission, by the inhibition of ACh release, is a feature of all aminoglycoside antibiotics. With gentamycin, the presynaptic NMJ blockade has been demonstrated to be as a result of the extracellular blockade of calcium influx. Neomycin has been demonstrated to be the aminoglycoside antibiotic with the most potent presynaptic NMJ blocking effect; this presynaptic block of ACh release by neomycin is so predictable that it has been used experimentally to reverse organophosphorus anticholinesterase-induced NMJ blockade.

The difference between members of the aminoglycoside family lies in the varying degree of effect on postsynaptic NMJ blockade and this may in part be due to the effect being mediated via two different mechanisms. Neomycin displays significant postsynaptic NMJ blockade by apparently interacting with the ion channel receptor in the open configuration and is partially reversible by neostigmine. The effect of streptomycin on the postsynaptic NMJ is minimal and is mediated by blocking the receptor, and neostigmine causes minimal reversal.

Reports of aminoglycoside toxicity causing NMJ blockade are limited in veterinary medicine and mainly made up of experimental studies, particularly in cats. One animal was reported to have developed severe muscle weakness and hyporeflexia following 5 days of gentamycin therapy for deep pyoderma in which the clinical signs resolved 48 hrs after the antibiotic was withdrawn. The onset of NMJ blockade is rapid, and in severe cases may progress from weakness to tetraplegia with respiratory paralysis within 4–6 hrs. Reported aminoglycoside NMJ blockade in humans is most common in the presence of concomitant disease of the NMJ (e.g. MG) or concomitant administration of NMJ blocking agents (e.g. succinylcholine), but occasional cases do occur in the absence of predisposing factors. In human medicine, it appears that a high dose of aminoglycoside antibiotic is not always required and that the duration of medication prior to the development of clinical signs is variable. Certain predisposing factors that have been recognized include:

- The intravenous, intraperitoneal, and intrapleural routes of administration are more risk-prone, as are high doses rates.
- The impairment of renal excretion through renal disease or dehydration increases the risk.
- Some other disease states increase the risk, particularly gram-negative septicemia.

Treatment of aminoglycoside-induced NMJ blockade is by withdrawal of the antibiotic therapy, which is usually followed by rapid recovery as the plasma aminoglycoside levels decline. In patients with impaired renal function, fluid therapy may be required. In human patients, calcium chloride and neostigmine have been administered, with variable success, usually in an attempt to reverse NMJ blockade in emergency postanesthetic situations.

b. Lincomycin

Lincomycin is produced by an actinomycete, *Streptomyces lincolnensis*, but has largely been supplanted by clindamycin, which is more active and has fewer side effects. The mechanism of lincomycin action on the NMJ probably involves both pre- and postsynaptic mechanisms. There are no veterinary reports of lincomycin-induced NMJ blockade and the reports in human medicine are largely confined to the potentiation of the effects of d-tubocurarine and pancuronium.

c. Penicillamine
Penicillamine is a degradation product of penicillin and the D-isomer is an effective chelator of copper, zinc, mercury, and lead. It is used in human medicine as a chelating agent for the treatment of cysteinuria (by forming a soluble disulphide compound with cysteine) and for the suppression of rheumatoid arthritis. Penicillamine is not routinely used in veterinary medicine; however, in human medicine the neurotoxic effects include the induction of MG and polymyositis/dermatomyositis.

Penicillamine induces MG in up to 7% of human patients and appears to act by altering the antigenic structure of the ACh receptor and subsequently initiating a new autoimmune response.

d. Polymyxins
The polymyxin antibiotics, comprising polymyxin B and polymyxin E, are microorganism-derived polypeptides that disrupt the structure of cell membranes and are affective against gram-negative bacteria. There is no absorption through mucous membranes and enteral administration does therefore not result in systemic effects. Following parenteral administration, polymyxins remain largely unmetabolized with intact excretion occurring in the urine. Patients with renal compromise are therefore particularly susceptible to toxic effects. In human medicine, the parenteral administration of polymyxin at conventional dose rates is associated with renal dysfunction in approximately 20% of patients. The most significant neurologic toxic effect of polymyxin is NMJ blockade. In contrast to the aminoglycoside antibiotics, the primary effect is on the postsynaptic membrane in a nondepolarizing and noncompetitive manner. The postsynaptic NMJ-blocking effect of polymyxin is also more potent than that induced by the aminoglycoside antibiotics and is not reversed by either neostigmine or calcium chloride.

In an experimental study in cats, the effects of neomycin and polymyxin B were found to be additive in neuromuscular effects, in both potency and duration of effect. The slight presynaptic inhibition of transmitter release is partially reversible by calcium chloride. In human patients, the primary clinical sign of polymyxin-induced NMJ blockade is the sudden manifestation of apnea after only a day or two on medication. This may be accompanied by other clinical signs of NMJ blockade, including weakness, ptosis, and diplopia. The use of parenteral polymyxin is contraindicated in patients with concomitant MG. In veterinary medicine, polymyxin-induced NMJ blockade is restricted to experimental studies, primarily in cats. Administration of 4-aminopyridine at 0.6 mg/kg bodyweight has been reported to reverse the NMJ blocking effects of polymyxin in both acute and chronic toxicity studies in cats.

e. Tetracyclines
The tetracycline antibiotics were first isolated in 1948 from soil samples containing the antibiotic-producing microbes. Since then, semisynthetic and synthetic forms have been developed. Tetracycline antibiotics are active against a large variety of organisms, including gram-positive and gram-negative bacteria, chlamydia, and rickettsiae. The NMJ-blocking effects of oxytetracycline and pyrrolidine-methyl-tetracycline have been demonstrated experimentally in the cat, in which intravenous injection into the femoral vein leads to NMJ-blocking effects in the ipsilateral pelvic limb. The NMJ blockade could be reversed with prostigmine and partially reversed with calcium. In human MG patients, transient weakness has been reported following the intravenous administration of tetracyclines. Proposed mechanisms for the NMJ blocking effect of tetracyclines include:

- chelation of serum calcium by tetracycline
- calcium antagonizing effects of the magnesium in the diluent
- post-NMJ depression of muscle to the effect of Ach.

Tetracycline antibiotic therapy should therefore be avoided in myasthenic patients.

2. Ionophore antibiotics (lasalocid, monensin, salinomycin)
Ionophores are broad-spectrum antibiotics used as anticoccidials in poultry and as growth promoters in ruminants. They are by-products of fungal fermentation (*Streptomyces* spp.). Ionophores are lipid-soluble and their mechanisms of action reside in their ability to bind and transport ions across biologic membranes. Ionophore toxicosis has been documented in most domestic species, including dogs and cats. Most of the toxic effects of ionophores are thought to be mediated by disrupting the normal ionic gradients of cells.

Lasalocid poisoning leading to an acute onset of diffuse lower motor neuron (LMN) signs has been described in 30 dogs. The mechanism by which lasalocid can lead to neurologic deficits is unclear. Unlike monensin or salinomycin, lasalocid is unique in its ability to complex with equal affinity both monovalent (K^+, Na^+) and divalent cations (Ca^{2+}). It has been suggested that lasalocid may induce changes in the membrane potential by influencing the permeability of nerve cell membranes to cations. Experimentally, lasalocid caused membrane depolarization in rat myofiber membranes, induced spontaneous release of ACh in phrenic nerve–diaphragm muscle junction, and increased ACh release from rat brain in vitro. Lasalocid also inhibited fast axonal transport and decreased axonal microtubules with a concurrent increase in total Ca^{2+} content in sciatic nerves from frogs. Clinical signs of lasalocid poisoning in dogs appeared less than 12 hrs after the animals were fed from newly opened bags of commercial dog food or ate dead broilers from a nearby farm. Clinical signs included progressive, bilaterally symmetrical, ascending muscle weakness, which progressed from the pelvic limbs to the thoracic limbs, leading to tetraparesis or tetraplegia. Dogs showed hyporeflexia and hypotonia. Hypersalivation and dyspnea were occasionally noted. Mental status, cranial nerve function, and pain perception were reportedly normal, and the dogs preserved the ability to wag their tails. Marked hyperthermia, tongue laxity, and anisocoria were reported in one severely affected dog. The severity of signs appeared to correlate with the amount of contaminated food ingested. Bloodwork often revealed mild hemoconcentration, and mild to moderate elevations of CK, lactate dehydrogenase, and aspartate aminotransferase. There was no response to edrophonium hydrochloride. High-performance liquid chromatography demonstrated high concentrations of lasalocid in the dog food (166 to 200 mg/kg of food), which was accidentally introduced into the food during the manufacturing process. The LD_{50} in dogs was estimated at 10–15 mg/kg, making dogs highly susceptible to lasalocid toxicity compared to other species. There is no specific antidote for ionophore toxicity. The vast majority of the dogs that received in-hospital supportive treatment survived and fully recovered within a period of two to 50 days.

Two other ionophore antibiotics have been associated with the development of profound neuromuscular weakness in dogs and cats. Contamination of dog food with monensin resulted in myopathy with markedly elevated serum CK and myoglobinuria in dogs. In cats, an acute onset of diffuse neuromuscular signs secondary to a salinomycin-induced sensory and motor distal polyneuropathy has been described (see Chapter 17).

C. Antiprotozoal agents[66, 96, 117, 150, 155, 170, 185, 237]

1. Chloroquine

Chloroquine is primarily used as an antimalarial agent, being effective against *Plasmodium vivax* and *P. falciparum*; however, at high doses its use in human medicine includes the treatment of rheumatoid arthritis and discoid lupus arthritis. In human medicine, chloroquine has been reported to impair NMJ transmission and is contraindicated in patients with concurrent MG. In experimental studies in animals, including cats, the primary toxic effect of chloroquine is the development of a retinopathy, while in rats a vacuolar myopathy has been demonstrated.

2. Quinine

Quinine is derived from the bark of the cinchona tree and in human medicine is primarily used in the treatment of chloroquine-resistant malaria, to relieve the symptoms of congenital myotonia, and in the treatment of nocturnal leg cramps. Quinine has been shown to disrupt normal NMJ transmission and may cause an exacerbation of the clinical signs in patients with MG. In experimental studies in the cat, sublethal doses were associated with generalized loss of retinal ganglion cells and related structural changes in the eye, but not with any evidence of NMJ blockade.

D. Black widow spider venom[30, 67, 86, 99–101, 164, 189, 209, 218, 222, 227, 291]

The black widow spider (*Latrodectus* spp.) is widespread around the world and among others includes:

- *L. tredecimguttatus*: temperate areas of Europe and North Africa
- *L. mactans*: warm areas of North, Central, and South America
- *L. geometricus*: tropical Americas.

Male black widow spiders are of little medical importance. Female black widow spiders can be 20 times larger than the males, and are capable of life-threatening envenomations. Female spiders can be identified by the hourglass pattern, red or orange in color, on the ventral aspect of their shiny, globose black abdomen. The venom of the black widow spider has been shown to consist of a number of proteins with potent neurotoxic effects. Purified fraction B (purified to a single peak: B5) or a-latrotoxin has been shown to be the probable source of the majority of the clinical neurotoxic effects in vertebrates. A-Latrotoxin does not cross the blood–brain barrier and therefore exerts its effects on peripheral NMJ and autonomic synapses. The toxin acts by causing potent activation of neurotransmitter release and loss of synaptic vesicles, followed by depletion of neurotransmitter and conduction block. The primary mechanism behind this process appears to be by the promotion of the docking and fusion of synaptic vesicles with the plasma membrane and furthermore by inhibiting membrane recycling and blocking the production of new synaptic vesicles. Black widow spider venom reverses the botulinum toxin-induced blockade of synaptic transmission. Additionally, intramuscular injection of black widow spider toxin results in the degeneration of botulinum-blocked presynaptic axons. This results in the subsequent regeneration and restoration of functional NMJs within 3–5 days.

Clinical signs of black widow spider envenomation in human medicine usually occur within the first 8 hrs after the bite, and they are a reflection of the hyperactivation of motor, sensory, and autonomic sympathetic systems. The motor clinical signs include tremor, spasmodic leg movements, and clonic muscle contractions. This is followed by the development of flaccid paralysis. Sensory clinical signs include the development of intense generalized pain, hyperesthesia, abdominal pain, and rigidity. Salivation, lacrimation, sweating, and tachycardia frequently accompany these clinical signs. Reports of veterinary black widow spider envenomation are rare, but have been recognized for a number of years. It has been reported that cats appear more susceptible to black widow spider envenomation. In one report of apparent envenomation in a cat, the presenting clinical signs were very similar to those seen in human medicine. The affected cat demonstrated progression from fine-muscle tremors, muscular spasticity, abdominal pain with a rigid abdomen, and an increased respiratory rate to profound muscle weakness and flaccidity. Electrolyte disturbances in the case included a profound hypocalcemia and hypokalemia. Within 2 hrs of antivenom administration, a clinical improvement characterized by an improvement in respiratory function and a return to sternal recumbency was evident. In dogs, initial regional numbness often precedes the development of hyperesthesia, progressive muscle pain, and fasciculations of the affected region. Muscle cramping, restlessness, and abdominal rigidity often occur.

Treatment of black widow spider envenomation is based on the administration of antivenom and the correction of electrolyte disturbances, particularly any existing hypocalcemia. Benzodiazepines may be used to help with muscle relaxation. As the antivenom is equine derived, sensitivity testing by administering a small intradermal test dose prior to administering the parenteral dose is essential. Pretreatment with diphenhydramine, dilution of the antivenom with saline solution, and administration of the diluted antivenom over 30 min may decrease the risk of allergic reactions. A rapid response, usually within 30 min, is seen following administration of the antivenom. In human medicine, the clinical signs associated with untreated spider bites usually subside after 48–72 hrs. Further supportive treatment, including maintenance of fluid balance and analgesia, should be considered. Due to the reported potential for cardiovascular arrest in young or elderly patients in human medicine, consideration should be given to blood pressure monitoring in veterinary cases.

E. Botulinum toxin (botulism)[16, 17, 31, 34, 35, 53, 63, 74, 105–107, 161, 186, 194, 204, 205, 241, 271, 293]

1. Botulism is the term used to describe the disease caused as a result of ingestion of preformed *Clostridium botulinum exotoxin*. Botulism toxin is one of the most potent known toxins. The usual cause of botulism is ingestion of toxin in uncooked and spoiled food (in dogs, most frequently raw meat) or carrion, but in rare cases botulism may occur as a result of GIT formation of botulism toxin secondary to colonization of the GIT tract with the "toxico-infectious" form of *C. botulinum*. Preferential colonization sites for *C. botulinum* appear to be the GIT and liver wounds (ulcers and abscesses).

   Eight types of botulinum toxin have been identified based on differing antigenic properties, including A, B, C_1, C_2, D, E, F, and G. The majority of human cases are associated with types A, B, and E, while in veterinary medicine most cases are caused by types C and D. In dogs the most common toxin associated with clinical disease is type-C_1, although two cases of type-D intoxication have been reported from Senegal. Type-C_2 botulinum toxin is not considered neurotoxic, although it may alter vascular permeability. Botulism is uncommon in dogs, and there is only one report of natural infection in cats. Type-C botulism has been reported in lions. The botulinum toxins are serologically distinct, but the majority result in similar neurotoxic effects.

   The main effect of botulinum toxin is to block the release of ACh at the level of the NMJ and at cholinergic autonomic synapses. This results in the development of flaccid paralysis and alterations in the autonomic nervous system. The botulinum toxin is absorbed from the stomach and upper small intestine following ingestion of food containing the preformed toxin (or local production in the toxico-infectious form). Type-E toxin appears to be activated and made more potent by the proteolytic enzymes in the upper GIT, although in the other toxin types there is evidence that some of the toxin does get denatured. Toxin passing through to the lower GIT demonstrates lower absorption efficiency. Once absorbed, the toxin passes into the general circulation, where it circulates to cholinergic synapses in the peripheral nervous system, including the NMJ, followed by binding of the toxin to receptor molecules on the external surface of the cell membrane. The receptor is postulated to be sialic acid to which rapid bindings occurs, independent of neural activity and temperature. The toxin is then internalized into the nerve terminal within a vesicle. Internalized toxin is not accessible to neutralization by antitoxin. The toxin inhibits neurotransmitter release by cleaving the proteins required for neurotransmitter exocytosis.

2. Onset and severity of clinical signs are dependent on the total dose of toxin ingested and typically develop rapidly within 12 hrs (up to 6 days) following ingestion. Affected animals develop a progressive and symmetrical paresis, progressing to flaccid paralysis that typically first becomes evident in the pelvic limbs before extending to the thoracic limbs. Consistent with an LMN lesion, reflexes and muscle tone are decreased to absent. In severe cases, death may result from paralysis of the respiratory muscles. Sensory function, including pain perception, and level of consciousness are unaffected. Distinct from other causes of diffuse LMN signs, with botulism there is frequently additional evidence of cranial nerve deficits (e.g. facial nerve paralysis, depressed gag reflex, decreased jaw tone, megaesophagus) and occasional evidence of dysfunction of the cholinergic neurons of the autonomic nervous system. The cholinergic signs

include alterations of heart rate (elevated or decreased), pupil changes (mydriasis with depressed pupillary light reflexes), keratoconjunctivitis sicca, urinary retention, and constipation.

3. Diagnosis of botulism is primarily based on the history and suggestive clinical presentation. Due to the dietary origin of the toxin, multiple cases may occur in some situations. Routine laboratory analysis is usually unremarkable and the definitive diagnosis is based on the demonstration of botulinum toxin early in the course of the disease, either in blood (10 mL of serum should be collected) or GIT contents (50 g of feces, vomitus, or food sample should be collected). It is essential to discuss the diagnostic sample requirements with the laboratory performing the investigation. The use of an ELISA test to measure serum antibodies against *C. botulinum* type-C has also been used to diagnose canine botulism. Electrodiagnostic evaluation may assist in the diagnosis but is not definitive. Affected cases may demonstrate decreased amplitude of compound evoked muscle action potentials with normal motor nerve conduction velocity. Repetitive nerve stimulation at low frequency rates (e.g. less than 5 Hz) may produce a decrement in compound muscle action potentials; rapid stimulation rates (e.g. 50 Hz) may produce an increment in amplitude of successive compound muscle action potentials. EMG may demonstrate fibrillation potentials and positive sharp waves after 7–10 days of paralysis.
4. Treatment of botulism toxicity is largely supportive as toxin internalized into the nervous system is not accessible to antitoxin. As in any recumbent animal, the prevention of pressure sores by maintaining patients on soft surfaces (padded mattresses or water beds) is important, as is the provision of fluid and dietary requirements (by intravenous fluid administration and nasogastric, pharyngostomy, or gastrostomy tube placement in more severe cases). In the presence of megaesophagus and a decreased gag reflex, special care must be taken to minimize the potential for the development of aspiration pneumonia, in the event of which prompt antibiotic therapy, combined with coupage and nebulization, should be initiated. Antibiotics with the potential to interfere with NMJ transmission should be avoided (e.g. aminoglycosides).

   Due to the potential for autonomic dysfunction, close attention should be paid to bladder and bowel function, with suitable intervention if required. Botulism toxicity is the result of the ingestion of preformed toxin. Covering antibiotic therapy is therefore not indicated in the absence of secondary bacterial infections. Due to the relative inaccessibility of the bound botulinum toxin, administration of antitoxin (if available) should only be considered in severe cases and if toxin exposure occurred relatively recently (within 5 days), and then only following a negative response to an intradermal test dose to avoid anaphylaxis. The polyvalent antitoxin, containing type-C antitoxin, is indicated in dogs. Generally, only extracellular unbound toxin is susceptible to antitoxin. Mild to moderately affected dogs should recover spontaneously in the absence of pneumonia. Affected animals do not usually develop immunity to future episodes as the dose of toxin sufficient to cause clinical signs is not usually sufficient to stimulate a protective immune response. Prevention of repeat episodes (although extremely rare) is based upon preventing access to preformed toxin in the diet by limiting access to carrion and not feeding raw or contaminated meat. Botulism toxin can be neutralized by heating food to 100°C for 10 min or 80°C for 30 min. Since the damage to the synaptic membranes is permanent, complete recovery in affected animals requires the synthesis of new functional membranes at the synaptic cleft.

F. Gila monster venom[168, 222, 243, 290]

The Gila monster (*Heloderma suspectum*) is a nocturnal reptile living in the arid regions of southern North America. Gila monsters may bite following provocation and the painful bite is always associated with the injection of toxin B comprising a variety of toxins. NMJ blockade syndrome is reported as one of the syndromes of Gila envenomation in human medicine, but is more likely to be the consequence of hypotension due to vasoactive effects of a kallikrein-like enzyme and not primary neurotoxin effects on the NMJ. Treatment is supportive, with no specific antivenom being available.

G. Hornet mandaratoxin[1]

Experimental studies on mandaratoxin from the hornet (*Vespa mandarinia*) have shown that it induces irreversible blockade of the excitatory postsynaptic potential of the NMJ.

H. Interferon-α and interferon-β[19, 39, 52, 251, 283, 284]

The potential neurotoxic effects of interferon-α are relevant now that its use is increasing in veterinary medicine. In human medicine, MG secondary to interferon-α therapy has been reported in 15 patients. Similarly, the use of recombinant interferon-β therapy has also been associated with sporadic cases of MG in people. In these patients, the use of either interferon-α or interferon-β therapy triggered a new onset of MG or exacerbated preexisting ocular myasthenia gravis. It appears that interferon-α/β result in induced autoantibodies against the ACh receptors in the postsynaptic membrane. It has also been suggested that interferon-β may trigger overexpression of the α-ACh receptor subunit. Elevated levels of antibodies against ACh receptors commonly persisted even after the discontinuation of interferon therapy, which suggests that these medications may lead to failure of self-tolerance and autoimmunity that is perpetuated by the persistence of memory cells. Most patients required long-term treatment with pyridostigmine therapy, and some also required plasmapheresis and/or IVIg therapy.

I. Lithium[232, 307]

In experimental studies on dogs, lithium has been demonstrated to significantly prolong NMJ blockade with both pancuronium bromide and succinylcholine. Although the NMJ-blocking effects of lithium are well documented, the exact toxic mechanism is unclear.

J. Marine toxins[6, 41, 43, 183, 191, 198, 200]

Marine toxins with demonstrated NMJ blocking effects include:

- Greenland shark meat (*Somniosus microcephalus*): a-Glycerotoxins—toxin from polychaete annelid worms *Glycera dibranchiata* and *G. convoluta*
- Holothurians and holotoxins—saponin toxins from sea cucumbers (*Holothurioidea*)
- Lophotoxin—toxin from Pacific soft (gorgonian) corals (sea fans and whips of the *Lophogorgia* spp.)
- Marine cone snails (conotoxins)
- Nereistoxin and related toxins (marine worm—*Lumbriconereis heteropoda*)
- Sea snakes
- Stonefish (*Synanceia horrida*) venom
- Tetrodotoxin—toxin found in multiple aquatic organisms (e.g. puffer fish, sea slugs, starfish, toads), as well as various types of bacteria (e.g. *Vibrio* spp., *Pseudomonas* spp., *Bacillus* spp.)

Considering the environment these organisms normally inhabit, dog and cat envenomation would be extremely unusual. For example, human envenomation by the fish-hunting marine cone snails is almost exclusively restricted to sponge divers. Reported veterinary exposure is confined to sea snakes, Greenland shark meat, and tetrodotoxin (TTX) from sea slugs.

Ingestion of meat of the Greenland shark, particularly fresh meat, has been demonstrated to be toxic to both humans and dogs. Toxin analysis has demonstrated high levels of trimethylamine oxide, which is reduced in the GIT to trimethylamine (TMA). TMA toxicity occurs acutely following consumption of Greenland shark meat. In experimental studies, low doses result in increased NMJ contraction, while high doses appear to cause NMJ blockade.

Tetrodotoxin is a potent neurotoxin that selectively blocks the voltage-gated Na^+ conductance mechanism common to both nerve and muscle, and thus inhibits propagation of action potentials. In people, TTX is most notorious as the toxin that causes puffer fish poisoning, particularly in Japan. Commonly reported clinical signs in people include neuromuscular (jaw and limb muscle weakness, muscle cramping, dysphagia) and gastrointestinal symptoms (salivation, nausea, vomiting, abdominal pain). The ingestion of grey side-gilled sea slug (*Pleurobranchaea maculata*) containing TTX has been associated with neurotoxicosis affecting 15 dogs in New Zealand over a period of 5 mos. All dogs had accessed beaches in the Auckland region and developed a variety of clinical signs (vomiting, diarrhea, lethargy, salivation, muscle fasciculation, ataxia) within 48 hrs of access to a beach. Very high levels of TTX were isolated from the sea slugs, as well as from vomit and gastrointestinal contents in two of the affected dogs.

K. Methoxyflurane[75]

Methoxyflurane has been reported to produce an apparently subclinical MG syndrome in a human anesthetist, but no veterinary or experimental studies are reported.

L. Neuromuscular blocking agents[177, 287]

These agents are categorized as follows:

- membrane stabilizing agents, e.g. vecuronium
- depolarizing agents, e.g. succinylcholine.

The neuromuscular agents, of which d-tubocurarine was the prototype, are used clinically to induce NMJ blockade, usually as an adjunct to general anesthesia.

1. Membrane stabilizing NMJ blocking agents

   The curare class of NMJ blocking agents acts on the postsynaptic membrane, binding to the nicotinic cholinergic receptor and competitively blocking the action of ACh. These agents can be classified according to their duration of action into long-, intermediate-, and short-acting. D-tubocurarine is an example of a long-acting agent (and is also one of the most potent), atracurium and vecuronium are examples of intermediate-acting agents, and mivacurium is an example of a short-acting agent. The development of newer agents allows a more rapid onset of action, as due to the fewer side effects of these newer agents (including histamine release, bronchospasm, hypotension, and excessive secretions) higher doses can be tolerated. Treatment of overdose or reversal of the effects following general anesthesia is, in general, by the administration of anticholinesterase agents (neostigmine, pyridostigmine, or edrophonium), muscarinic antagonists (atropine or glycopyrrolate) to prevent muscarinic stimulation, antihistamines to counter the antihistamine effects and sympathomimetics to maintain blood pressure.

2. Depolarizing NMJ blocking agents

   In contrast to the stabilizing NMJ blocking agents of the curare class, the depolarizing NMJ agents (including succinylcholine and decamethonium) induce depolarization of the postjunctional membrane by opening ion channels, similarly to ACh, but the resultant depolarization in the endplate and adjacent area of the sarcoplasmic reticulum is persistent.

3. Ganglionic-blocking agents

   Muscle relaxants in clinical use that act as ganglionic-blocking agents may have similar clinical signs to the NMJ blocking agents. These substances inhibit synaptic transmission by blocking postsynaptic ion channels and include hexamethonium and trimethaphan camsylate.

M. Pesticides[3, 48, 55, 70–73, 82, 130, 166, 235, 289, 308]

1. Organophosphorus compounds (organophosphates)

   Organophosphorus (OP) compounds comprise around 20,000 different chemical formulations and represent one of the most widely studied groups of toxins. Clinical toxicosis with OP compounds in veterinary medicine is mainly restricted to those substances used as pesticides and usually following inappropriate or accidental dosing and overdosing. The neurotoxic effects of the OP compounds can be divided into a number of clinical categories, including:

- cholinergic syndrome (muscarinic, nicotinic, and central nervous system [CNS] effects)
- OP-induced delayed polyneuropathy
- neuromuscular transmission syndrome (junctional myopathy)
- chronic encephalopathy (cognitive dysfunction in affected humans).

Experimentally, the cholinergic dysfunction and the delayed peripheral neuropathy effects have been extensively studied.

In the cholinergic syndrome, OPs act as competitive and irreversible AChE inhibitors by binding to the enzyme esteric site. After binding, the bonds of some OP compounds strengthen with time in a process known as aging, which renders the enzyme unusable. With AChE bound, ACh accumulates at the nerve junctions in muscles, glands, and CNS. The accumulation of ACh produces a combination of muscarinic (e.g. salivation, lacrimation, urination/urinary incontinence, defecation/diarrhea, gastric cramping, emesis, miosis, bradycardia) nicotinic (muscle fasciculation, tremors, weakness, ataxia, paresis/paralysis, tachycardia, hypertension), and CNS signs (hyperactivity, seizures, coma). AChE activity can be measured in whole blood. OP toxicosis often results in profound AChE inhibition (< 75% of normal AChE activity). Treatment of OP toxicity consists of atropine administration to control the muscarinic signs, and oxime therapy (e.g. Pralidoxime chloride, 2-PAM) to treat the nicotinic signs. If OP toxicity is suspected, oxime therapy should be initiated as soon as possible because it cannot reverse AChE binding once aging has occurred. In addition to atropine and 2-PAM administration, treatment of muscle tremors with either methocarbamol or diazepam may be considered.

A subacute to chronic clinical presentation of organophosphate intoxication associated with chlorpyrifos has been described in cats. This form of the disease may occur if an animal is exposed to minimal toxic concentrations of OP for days or weeks. Clinical signs typically develop 1–2 wks after exposure. Muscle fatigue, weakness progressing to paraparesis, and cervical ventroflexion were often present in affected cats. However, in the cases of subacute toxicity the muscarinic signs typically seen in acute OP toxicity were absent. Affected cats fully recovered within 4–6 days once treatment with 2-PAM and atropine was initiated. This differs from the OP-induced delayed polyneuropathy, in which rapid recovery is not expected, owing to the existing degeneration of axons.

The underlying pathology resulting in the neuromuscular transmission syndrome has been demonstrated for a number of anti-AChE agents, including several OP compounds, given at doses causing muscle fasciculation. The primary feature is the presence of a myopathy in selected skeletal muscles, with myofiber necrosis limited to the region of the NMJ and sparing the endplate-free regions of the muscle. The myopathy is limited to a small proportion of fibers in certain muscle groups. The necrosis in the region of the endplate suggests that the myopathy reflects alterations in the endplate induced by AChE inhibition (Fig. 19.12), but the exact mechanism is not fully understood.

2. Carbamates

The carbamates are either carbamic or dithiocarbamic acids that are widely used as insecticides, fungicides,

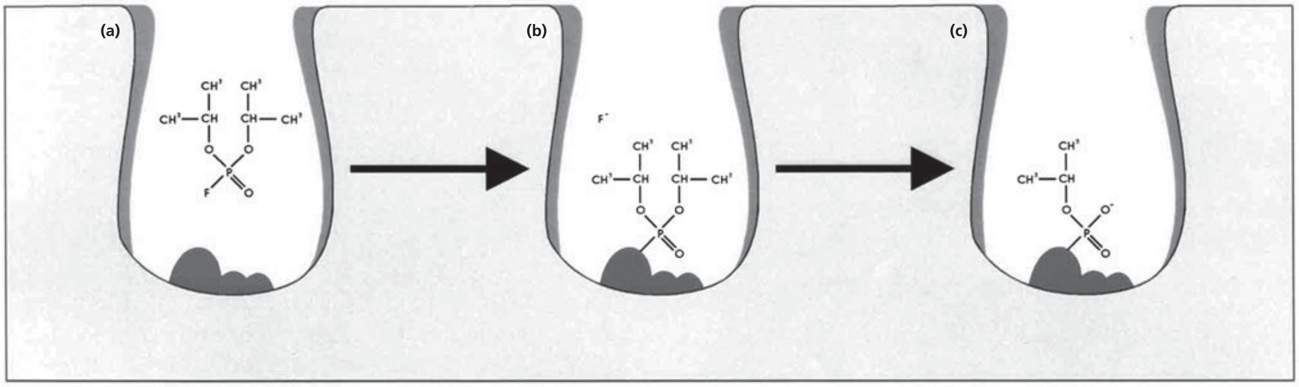

Figure 19.12 Schematic representation of the interaction of organophosphorus compounds with the ACh esterase active center. Phosphorylation of the enzyme active site by organophosphorus compounds is similar to acetylation of ACh, but in contrast to ACh, the phosphorylated enzyme is stable (A and B). When aging occurs the enzyme becomes irreversibly inhibited (C). (Adapted from Lotti, 2000.)[166]

and herbicides. Neurotoxic effects of carbamates can be divided into two categories:

- insecticides that have direct neurotoxic effects
- fungicides that mediate their neurotoxic effects through their breakdown products.

a. Insecticidal carbamates

The insecticidal carbamates are most widely used in veterinary medicine as flea and tick formulations. Toxicity due to insecticidal carbamates usually results in immediate mild to severe signs that rapidly resolve in most cases. In rare cases, neurologic signs may be delayed or prolonged. The carbamate insecticides target AChE at parasympathetic autonomic junctions, all ganglia and NMJs. Contrary to OPs, carbamates reversibly bind AChE, which allows dissociation to occur more readily, facilitating reactivation of AChE activity and a shorter duration of clinical signs. Additionally, carbamate insecticides may inhibit erythrocyte AChE, plasma pseudocholinesterase, and tissue nonspecific carboxylesterase. Short-term exposure of dogs to repeated oral doses of carbamate insecticides does inhibit plasma, erythrocytic, and CNS cholinesterases, with associated typical clinical signs of cholinergic toxicity, but does not result in prolonged nervous system effects.

If carbaryl is used as an example of typical carbamate insecticide toxicity, toxic signs would usually first become apparent after 15–30 min following administration, with peak clinical signs at 90 min to 4 hrs. Clinical improvement should be apparent by 6 hrs, and most of the clinical signs should resolve by 24 hrs. Carbamate esters appear to induce some neurologic and behavioral changes at dose levels with minimal evidence of toxic effects and in the presence of normal nervous tissue AChE activity. The most dramatic evidence of the effect of carbamate toxicity on the NMJ (in addition to other cholinergic effects) was demonstrated in experimental studies in pigs receiving oral carbaryl at 150 mg/kg bodyweight for up to 83 days. These pigs developed progressive MG, ataxia, intention tremor, and clonic muscular contractions leading to paraplegia and recumbency.

Treatment of carbamate insecticidal toxicity is primarily by removing the source and combating the excessive ACh effects via the administration of atropine. The dose of atropine should be carefully titrated to effect, by initial small subcutaneous doses and observing for mydriasis and evaluating for drying of the mucous membranes. In addition to atropine, the use of diazepam as a muscle relaxant (to reduce muscle fasciculations), anxiolytic, and blocker of some of the CNS effects should be considered. Traditionally, the use of oxime reactivators (e.g. 2-PAM, obidoxime, pralidoxime mesylate [P2S]) has not been recommended in carbamate intoxications (especially for carbaryl), because carbamates do not irreversibly inhibit AChE. Oxime reactivators do not appear to be effective antidotes and in the case of carbaryl may actually increase the toxicity. Although controversial, more recent animal studies and human case reports suggest that therapeutic doses of oxime may be synergistic with atropine in the treatment of some types of carbamate toxicosis, including aldicarb. Although uncommon, severe cases of carbamate toxicity may cause ventilatory failure, and require the use of mechanical ventilation. In general, carbamate toxicosis carries a good prognosis for survival and hospital discharge with treatment.

b. Fungicidal carbamates

Only the dithiocarbamate group of antifungal carbamates has been shown to have neurotoxic effects. As these agents are usually administered as powders or creams, most toxicity would be through accidental inhalation or ingestion. In experimental toxicity in the rat, the induced ataxia and pelvic limb paralysis was demonstrated to be secondary to spinal cord ventral horn chromatolysis and axonal degeneration, rather than neuromuscular effects. Whether the demonstrated sensitivity of dogs to ziram results in similar changes as in the rats or affect the NMJ is unclear, but dogs receiving 25 mg/kg/day demonstrated pelvic limb weakness, decreased reflexes, loss of muscle tone, ataxia, tremors, and seizures.

N. Poisonous plants[29, 79, 90, 167, 206–208, 214, 223, 285]

The following plants have the potential to produce NMJ blockade:

- *Delphinium* spp. (Larkspur)
- *Aconitum* spp. (monkswood and aconite)
- dihydro-b-erythroidine (alkaloid from seeds of the genus *Erythrina*)
- hemlock (*Conium maculatum*)
- tubocurarine (*Strychnos toxifera*).

A variety of plants has been demonstrated to contain poisonous agents with the primary effect directed against the NMJ. Intoxication of dogs and cats would be extremely unlikely. Usually, plant intoxication is only clinically significant in livestock.

1. *Delphinium* spp. (Larkspur)

Delphinium spp. intoxication occurs in livestock, and accidental intoxication in cats and dogs has not been reported. The clinical signs of accidental intoxication in livestock and in experimental intoxication in rats, mice, and hamsters is characterized by dose-dependent failure of neuromuscular transmission by diterpenoid alkaloids, although effects on central cholinergic systems and the autonomic nervous system are probably also part of the clinical picture. Livestock intoxication is much more common in North America (*Delphinium barbeyi*, tall larkspur; *D. andersonii*, low larkspur) than in Europe (*D. elatum* and *D. elatum*), where the *Delphinium* spp. appear to be less toxic. A number of factors determine toxicity, including plant species, growth stage, plant parts, soil composition, and climate.

2. *Aconitum* spp. (monkswood and aconite)
   These plant species contain similar toxic alkaloids to those of the *Delphinium* spp.
3. Dihydro-b-erythroidine (from genus *Erythrina*)
   Dihydro-b-erythroidine is an alkaloid derived from the seeds of trees and shrubs of the genus *Erythrina*, which has been demonstrated to be a competitive antagonist at muscle and neuronal nicotinic receptors. The NMJ effects can be partially reversed with neostigmine.
4. Hemlock (*Conium maculatum*)
   The neurotoxic agent of *Conium maculatum* (hemlock, poison hemlock, spotted hemlock, Nebraska or California fern, or fool's parsley) is responsible for occasional accidental livestock and rare human poisoning. The plant is widespread across Europe, Asia, and North and South America. The toxic agent, coniine, results in depression, muscular weakness, and death due to respiratory failure in laboratory animals and domestic herbivores. The exact mechanism of NMJ blockade is poorly understood, but the toxic agent has a curare-like action.
5. Tubocurarine (*Strychnos toxifera*)
   The curare class of NMJ blocking agents was originally derived from the *Strychnos* spp. of plant, which are widespread throughout the world. The main neurotoxic agent, tubocurarine, acts on the postsynaptic membrane, binding to the nicotinic cholinergic receptor and competitively blocking the action of ACh. Following administration, the clinical signs rapidly progress from initial muscle weakness to flaccid paralysis. The first muscles to be affected are the small rapidly moving muscles (e.g. extraocular muscles), followed by the limb muscles, the intercostal muscles, and finally the diaphragm. Recovery occurs in reverse order to the loss of motor function. As tubocurarine (and related compounds) are unable to cross the blood–brain barrier, there are no central effects.

O. Snake envenomation[8, 44, 95, 97, 112, 113, 116, 124, 126, 134, 147, 162, 169, 175, 182, 190, 215, 217, 219–222, 231, 246]

The following snake venoms are capable of causing NMJ blockade:

- *Bungarus* spp. (krait)—α-bungarotoxin, β-bungarotoxin
- cobra venom
- coral snake (*Micrurus fulvius*) and Sonoran coral snake (*Micruroides euryxanthus*)
- *Crotalus durissus terrificus* (southern Brazilian rattlesnake)—crotoxin
- *Crotalus scutulatus scutulatus* (North American rattlesnake)—Mojave toxin
- *Crotalus horridus atricaudatus* (canebrake rattlesnake) *and Crotalus tigris* (tiger rattlesnake)—Mojave-like toxin
- *Dendroaspis angusticeps* (East African or Eastern green mamba)—dendrotoxins, fasciculins, muscarinic toxins
- *Hydrophiidae* toxins (sea snakes)
- *Laticauda semifasciata* (sea snake)—erabutoxin
- *Pelamis platurus* (yellow-bellied sea snake)—pelamitoxin
- *Oxyuranus scutellatus scutellatus* (southern Papua New Guinean and Australian Taipan snake)—taipoxin.

The neurotoxins in snake venom interfere with neuromuscular transmission at the presynaptic level or the postsynaptic level, or (most often) both. Presynaptic neurotoxins are known as β-neurotoxins, and postsynaptic neurotoxins are commonly called α-neurotoxins. Snakebite is a common injury in domestic animals with an annual estimate of at least 150,000 incidents in the United States and 6200 incidents in Australia. NMJ blockade of domestic animals as a result of snakebite envenomation is primarily seen in the Mojave rattlesnake (*Crotalus scutulatus scutulatus*), the South American rattlesnake (*Crotalus durissus terrificus*), and elapids (including the coral snakes).

1. The Mojave and South American rattlesnakes
   In North America, most of the reported envenomations in humans and animals are due to snakes of the family *Crotalinae*, commonly known as pit vipers because of the specialized heat-sensitive pits located between the eyes. Toxins of the pit viper group are usually associated with hemolytic properties causing edema, ecchymosis, tissue necrosis, coagulopathy, and increased vascular permeability. However, the primary toxin action of several rattlesnake species—including the Mojave, South American, canebrake, and tiger rattlesnakes—is that of a neurotoxin. The Mojave rattlesnake venom is described as either venom A (Mojave toxin) or venom B (proteolytic venom). Mojave rattlesnakes can contain venom A, venom B, or both. The proteolytic venom causes local tissue injury and hemorrhagic effects, whereas the Mojave toxin is a potent neurotoxin that acts as a noncompetitive Ca^{2+} channel blocker blocking the release of ACh and causing a presynaptic block. In severely affected nerve endplates, only minimal amounts of neurotransmitter release can be demonstrated, with the nerve impulse apparently unable to invade the motor axon terminal. The effect of the toxin on the diaphragm is greater than that on the skeletal muscle and this is the usual cause of death.

   In comparison to the South American rattlesnake, other clinical signs of neuromuscular blockade (including cranial nerve paresis or paralysis, and myotoxicity) are less common in Mojave rattlesnake envenomation, with hypovolemia and hemotoxicity predominating. Sixty to seventy percent of the volume of the crude venom from the South American rattlesnake is made up of crotoxin.

Crotoxin is itself made up of two components: a nontoxic acidic crotapotin (crotoxin A) and a toxic basic phospholipase A2 (PLA2) component (crotoxin B). Crotoxin A potentiates the toxicity effect of crotoxin B when both are combined. Crotoxin B blocks synaptic transmission by inhibiting the release of ACh. The neurotoxin of the South American rattlesnake therefore results in flaccid paralysis by interfering with depolarization–secretion coupling in the motor axon terminal. Crotoxin can also cause myotoxicity, nephrotoxicity, and cardiotoxicity.

The onset of clinical signs after pit viper bite can be delayed for several hours, and clinical signs appear to be more severe in dogs than cats. Puncture wounds that ooze blood or serum with rapid onset of localized swelling, pain, ecchymosis, edema, and tissue necrosis are characteristic of pit viper envenomation. The incidence of neurotoxicity amongst the general population of dogs and cats treated for rattlesnake envenomation was reported to be 5.4%. Neurologic abnormalities described in dogs and cats with rattlesnake envenomation included altered mentation, nonambulatory tetraparesis or tetraplegia, extensor rigidity, and decreased spinal reflexes.

The only proven therapy specific of pit viper envenomation is antivenom (polyvalent crotalid antivenom). Optimally, the antivenom should be administered within 4 hrs, and up to 24 hrs after envenomation. The early administration of antivenom may reverse hematologic and neurologic abnormalities, but it does not reverse local tissue necrosis. Monitoring for adverse reactions during antivenom administration is necessary. Concurrent hypovolemia, hemotoxicity, and respiratory failure should be managed as deemed appropriate. Reported overall mortality rates in dogs range from 1 to 30%, depending on the type of rattlesnake involved. In particular, the mortality rate in dogs and cats with neurotoxic rattlesnake envenomation was reported at 17.6%.

2. The elapids (including coral snakes and cobras)
The elapids have been documented to produce at least three neurotoxins, including taipoxin, β-bungarotoxin, and notexin (a subunit of crotoxin and β-bungarotoxin). These toxins cause morphologic changes in the ultrastructure of the motor axon terminal, including an increase in the number of coated pits in the axolemma, a depletion of synaptic vesicles, and progressive swelling and vacuolization of the mitochondria in the motor axon terminal. For most elapid toxins, the postsynaptic effect is considered of minor importance; one exception to this is cobra venom, for which the effect is mediated by toxin binding to receptors on the motor endplate.
3. Coral snake envenomation
Coral snakes are nocturnal and elusive in nature. As such, bites by coral snakes are relatively rare compared to pit viper bites. However, due to their aggressive nature, coral snake envenomation has been documented on a number of occasions in the veterinary literature. The severity of a coral snake bite is related to the volume of venom injected and the size of the victim. Coral snake venom is primarily neurotoxic with minimal tissue reaction and pain at the bite site. Several neurotoxins are present in the venom, but the most clinically relevant components are postsynaptic α-neurotoxins. The net effect of the neurotoxins is a curare-like syndrome resulting in blockade of the postsynaptic neuromuscular transmission. Muscle paralysis, CNS depression, and vasomotor instability can occur. Cholinesterase effects have been demonstrated as a component of the toxin activity in elapid venoms, but this effect is not thought to contribute significantly to the NMJ block in the case of the North American coral snakes. The onset of clinical signs is within 24 hrs; this may occur as rapidly as in 30 min or may be delayed for up to 18 hrs, with the median in one retrospective study being 105 min in dogs. Few if any local signs are noted, other than the small puncture wounds. The clinical signs described in dogs include CNS depression, ptyalism, progressive flaccid tetraparesis/tetraplegia with depressed to absent spinal reflexes, vomiting, decreased gag reflex, and respiratory paralysis. Dogs may also exhibit intravascular hemolysis with or without the presence of red blood cell abnormalities (echinocytes, spherocytes), anemia, and hemoglobinuria. Blood-tinged diarrhea may also be present. Death is usually due to failure of respiratory muscles, although cardiac arrhythmias have also been reported in dogs with coral snake envenomation. The clinical signs in envenomated cats are similar to dogs. However, hemolysis and hemoglobinuria have not been reported in cats with coral snake envenomation.

Confirmation of coral snake envenomation is often difficult due to the delay in the onset of clinical signs, the frequent absence of pain at the site of the bite, and the relatively small puncture marks from coral snake fangs. Following a thorough search, small punctures can often be found from which blood can be expressed. If evidence of coral snake envenomation can be demonstrated, the patient should rapidly be transferred to a facility able to offer ventilatory support in case of respiratory failure. If respiratory failure occurs, it can be managed with mechanical ventilation, with respiratory function usually returning within 48–72 hrs. Aspiration pneumonia is the main complication, and if it develops, it will result in a significant increase in morbidity and mortality. The prognosis for recovery in cats is usually good with supportive care, and recovery usually occurs within 10–14 days. If the animal is presented early, administration of antivenom (*M. fulvius*, equine origin) should be considered. The earlier the antivenom is administered, the more effective it is. Skin testing to predict allergic reactions to the antivenom is difficult to evaluate in veterinary patients.

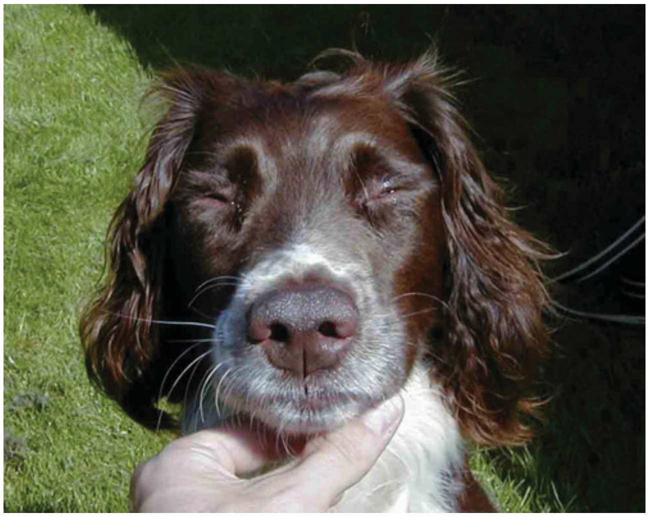

Figure 19.13 English Springer Spaniel demonstrating the classical symptoms of generalized tetanus. In addition to the effect on inhibitory neurons in the CNS, tetanus toxin may also have facilitatory effects at the neuromuscular junction.

The dose of antivenom is based on an estimation of the amount of venom injected into the patient, but this is difficult in practice, and a minimum of one to two vials is usually administered. The venom of the Sonoran coral snake (*Micruroides euryxanthus*) is not inactivated by the *M. fulvius* antivenom, and the treatment in this case is largely supportive. Luckily, this species of coral snake is less aggressive (bites are therefore less common) and no human, dog, or cat fatalities have been ascribed to this snake. In a study assessing the efficacy of antivenom treatment on snakebite incidents in Australia (all types of venom, not just those acting against the NMJ), the administration of antivenom significantly improved the chances of survival in both dogs (from a survival rate of 31 to 75%) and cats (from a survival rate of 66 to 91%). A retrospective study reported an overall 71% survival rate in 16 dogs and four cats with coral snake envenomation. Early diagnosis is crucial as antivenom administration can reduce morbidity.

P. Tetanus toxin (minor effect)[106]

In addition to the effect that tetanus toxin has on the inhibitory neurons in the CNS, resulting in the release of spinal cord and brain-stem motor neurons from inhibition with subsequent hyperexcitability (Fig. 19.13), the toxin may also have a direct effect on the peripheral somatic neurons. It is thought that the toxin has a direct facilitatory effect at the NMJ of these neurons. This effect is believed to be mediated by the affinity for binding of hematogenously spread tetanus toxin to the NMJ, and this effect may be seen prior to the migration of tetanus toxin to the CNS. Canine and feline tetanus are discussed in detail in Chapter 18.

Q. Tick bite paralysis (tick paralysis)[12, 13, 34, 49, 50, 76, 102–104, 111, 135, 145, 154, 173, 179, 197, 205, 216, 253, 274, 282, 297, 298, 302, 303]

1. A flaccid and afebrile ascending motor paralysis has been demonstrated in animals and people after exposure to a neurotoxin generated by engorged female ticks of some strains of certain tick species. Not all infested animals are affected, with cats in the United States appearing resistant. In Australia, infestation with the nymphs and larvae, and not only the adult female tick, may result in clinical signs. Both dogs and cats are affected by tick paralysis in Australia. The ticks release a salivary neurotoxin. The toxin acts by interfering with ACh release at the NMJ and/or propagation of the impulse along motor axon terminals. The toxin may affect both sensory and motor nerve fibers by altering ionic fluxes that mediate the production of the axon potential. Sixty-four tick species have been shown to have the potential to produce paralysis, but the species of clinical significance in the dog and cat population include:
   - *Dermacentor variabilis* (common wood tick)—the most commonly incriminated species in North America
   - *Dermacentor andersoni* (Rocky Mountain wood tick)
   - *Ixodes holocyclus*—the most commonly incriminated species in Australia
   - *Ixodes cornuatus* and *Ixodes hirsti*—occasionally cause paralysis in Australia.

   Tick paralysis affects around 20,000 domestic animals along the east coast of Australia each year. The tick paralysis associated with *Ixodes* spp. ticks appears to result in much more severe clinical signs, frequently leading to death due to CNS effects and respiratory failure within 1–2 days if dogs and/or cats are left untreated. In Australia, tick paralysis is distinctly seasonal, with up to 75% of cases occurring during the southern hemisphere spring season (September–November). A study investigating risk factors for tick paralysis in 2381 affected Australian dogs found that toy-breed dogs and dogs younger than 6 mos of age were at a significantly higher risk of death. Despite the relative frequency of livestock paralysis secondary to tick saliva in Southern Africa, NMJ blockade syndromes in dogs and cats secondary to tick saliva are rare. Paralysis in a dog secondary to the infestation by the hedgehog tick (*Rhipicentor nuttalli*) has been reported in this region. A case of tick paralysis associated with *Ornithodorus lahorensis* was described in a dog in Iran.

   The exact nature of the toxic agent in tick saliva is unknown. Supportive of the toxic principle being in tick saliva are the following observations:
   - The incubation period is constant, with disease progression mirroring the feeding habits of the respective tick species.

- Precise manipulation of the incubation period is possible by applying ticks that have been allowed to feed on other individuals.
- Clinical signs are usually only present when the ticks are fully engorged and rapidly resolve following removal of the ticks.
- Severity of clinical signs is closely correlated to severity of the tick infestation.
- Clinical signs of paralysis can be induced by administering tick saliva or tick homogenate to test animals.
- NMJ blockade can be induced in nerve-muscle explants by the administration of tick salivary gland isolates.
- Inoculation of animals susceptible to tick paralysis with material from affected animals fails to induce paralysis.

2. Affected animals present with an acute, rapidly progressive flaccid paralysis with decreased to absent spinal reflexes. A range of 5–9 days of tick attachment is thought to be required for the development of the clinical disease. Quadriplegia often develops within 12–72 hrs from the onset of clinical signs. Weakness usually first develops in the pelvic limbs and progresses to involve the thoracic limbs. Tendon (stretch) reflexes (e.g. patellar reflex) are typically lost before withdrawal reflexes. Cranial nerves are occasionally involved. Some dogs may exhibit a voice change (weak bark), suggesting laryngeal involvement. Facial and masticatory muscles may also be affected. Sensory function is unaffected. Urethral and anal sphincter function is also typically unaffected. In Australia, cats are reported to show similar clinical signs to dogs, but signs of respiratory distress often appear more marked than gait abnormalities. In severe cases, death may result from respiratory failure or aspiration pneumonia.
3. Diagnosis is based on the history, suggestive clinical presentation, and identification of the offending tick species (in some cases the engorged female may have dropped off, so a negative finding does not exclude tick paralysis). As only one tick may cause the clinical signs, in some cases a careful search of the affected animal is required. Electrophysiological studies in human patients with *Dermacentor*-induced NMJ blockade have demonstrated:
   - motor neuropathy with decreased motor nerve conduction velocity
   - decreased compound motor evoked muscle action potential amplitude in nerves and their corresponding muscles
   - impaired afferent nerve impulse propagation
   - a requirement for higher nerve stimulus current in order to elicit a muscle response.

   Findings of electrophysiological studies in children with *I. holocyclus*-induced NMJ blockade include:
   - decreased evoked compound motor muscle action potential amplitude
   - normal motor nerve conduction velocity, normal sensory conduction, and a normal response to repetitive stimulation.
4. The identification and removal of the offending tick usually results in rapid recovery that may start within hours and continue over several days, although some cases may demonstrate persistent clinical signs for some weeks. In tick paralysis, except in cases due to *I. holocyclus*, full recovery usually occurs within 8–12 hrs after tick removal. More prolonged recoveries are to be expected with paralysis due to *I. holocyclus*. Ticks should be removed with forceps, taking care to remove the mouthparts. Affected dogs and cats should be treated with an acaricide, preferably dipped (thick-coated animals may need to be shaved). Supportive treatment is as for other diseases causing generalized flaccid paralysis, and includes:
   - prevention of pressure sores
   - maintenance of hydration and food intake
   - prevention of hypostatic and aspiration pneumonia
   - mechanical ventilation if respiratory failure ensues.

   A reasonable survival probability (75%) has been reported in dogs and cats with *Ixodes* tick paralysis that required mechanical ventilation. An antiserum is available for *I. holocyclus* that is frequently used in the management of canine and feline tick paralysis cases in Australia. This antiserum is prepared from hyperimmune dogs and can be administered intravenously or intraperitoneally. However, care must be taken to avoid anaphylaxis by first administering an intradermal test dose. A high incidence of acute allergy and serum sickness has been reported in children on whom this has been used. Animals that have previously had tick paralysis do not appear to develop a protective immunity and may be more susceptible to future episodes. Prognosis for recovery varies depending on the tick involved, host factors, and aggressiveness of treatment. In Australia, a 5–6.5% case fatality rate has been reported in dogs. In contrast, mortality rate in cats with *Ixodes* toxicity appears lower. Prevention of tick paralysis in susceptible animals is based on prevention of tick infestation by the use of acaricidal products, preferably products that offer continuous protection. In Australia, efforts are being directed toward the development of a recombinant vaccine based on the *Ixodes* spp. tick neurotoxin peptide sequence.

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Video Resources

Video resources are available on the companion website: www.wiley.com/go/dewey/neurology

See video 40.

CHAPTER 20

Nursing Care and Rehabilitation Therapy for Patients with Neurologic Disease

Mary Tefend Campbell & Janice L. Huntingford

Introduction[4, 34]

Caring for patients with neurologic disease can be extremely challenging, especially if those patients are nonambulatory or only weakly ambulatory. Management of the recumbent dog or cat involves primarily supportive care. A treatment protocol should be implemented at the onset of paresis or paralysis in order to prevent or lessen the severity of complications such as pulmonary atelectasis or pneumonia, poor gastric motility, fecal retention, urinary bladder damage and urinary tract infections, decubital ulcers, muscle atrophy, joint stiffness, pain, inadequate nutritional intake, and patient depression or lethargy. As many of the nursing techniques applied to stable patients require no special equipment or advanced training (e.g. passive physiotherapy, bladder management), clients can become adept at performing basic nursing care for dogs and cats that are expected to be recumbent for long time periods. Successful nursing care of patients with neurologic dysfunction is dependent upon cooperation and communication between clinicians, nurses, and pet owners.

Respiratory care[1, 4, 8–10, 16, 19, 22, 24, 27, 34]

A key factor in the treatment of the recumbent patient is prevention of respiratory dysfunction. It is of utmost importance to assess the respiratory patterns of the patient throughout the course of treatment, to auscultate frequently, and to consistently monitor oxygen saturation via pulse oximetry. Subtle changes in the respiratory system can occur within a very short time period in recumbent patients; such changes can subsequently lead to rapid deterioration of pulmonary function. Although pulse oximetry can be a useful tool in monitoring a patient's oxygenation status, it should never be substituted for a thorough physical examination. Patients must be turned every 4 hrs or kept in a sternal position when at all possible. Management should also include sling therapy if the patient is orthopedically stable (see "Rehabilitation therapy" section below). Respiratory complications in the recumbent patient can be life threatening and must be addressed immediately. Stress should be minimized in the patient in respiratory distress, and oxygen therapy should be administered via the most effective route. Clinicians should also be aware that severe cervical lesions or lower motor neuron (LMN) conditions such as polyradiculoneuritis may compromise respiratory function. Blood gas analysis and capnography are useful in monitoring the efficacy of ventilation, particularly the pressure of carbon dioxide in arterial blood ($PaCO_2$), as poor intercostal muscle movement may impair exhalation. Neck bandages or external splints placed for cervical support (e.g. atlantoaxial instability) may also impair ventilation (Fig. 20.1).

Pain may also cause changes in respiratory patterns. Thoracic radiographs should be included periodically for the recumbent patient to monitor pulmonary health. Treatments for respiratory dysfunction secondary to recumbency include oxygen therapy, nebulization and coupage therapy, positioning techniques, including sling therapy, and mechanical ventilation if respiratory complications are severe. The goals of treatment for respiratory complications include prevention of respiratory secretions and accumulation, expansion of atelectatic lungs, improved oxygenation, elimination of CO_2, and patient comfort.

A. Positioning techniques

Animals that are recumbent for any reason should be turned every 4 hrs from left to right lateral recumbency to prevent atelectasis or accumulation of lung secretions. If atelectasis or pneumonia is present, the patient should be propped sternally or positioned with the most normal functioning lung down to improve ventilation. Postural drainage can also be accomplished by positioning the patient in a head-down posture (20° from horizontal) for 15–30 min every 4 hrs to increase mucus drainage and prevent accumulation of debris within the trachea (tracheal "plugs"). It is important to supervise a patient closely during treatment in

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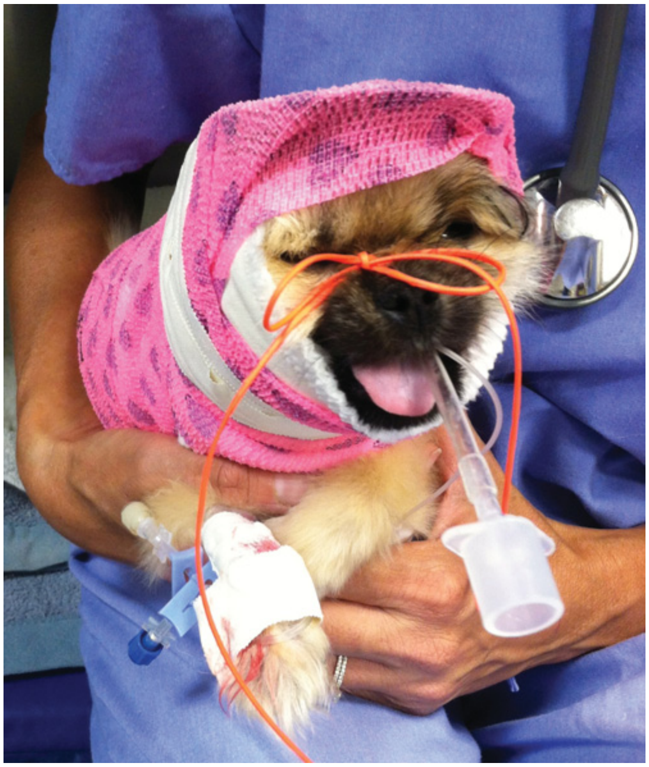


Figure 20.1 In patients requiring a neck bandage or splint, it is important to monitor ventilatory effort by assessing chest expansion and $ETCO_2$ and SpO_2

order to intervene if the patient becomes stressed or if secretions obstruct the airway. Postural techniques are recommended by the authors in conjunction with nebulization and coupage therapy. In the patient with brain injury, preventative measures to control increased intracranial pressure (ICP) include positional techniques to promote venous drainage (elevating the head). Avoiding jugular venipuncture, providing adequate sedation/analgesia, and preventing hyperglycemia and hyperthermia are also beneficial (see Chapter 8). Patients with head injury may also have cervical trauma; careful movement of the head is recommended during triage.

B. Nebulization and coupage therapy

Nebulization and coupage treatment for pneumonia are effective means to move secretions from smaller airways to larger airways and to elicit coughing to remove such secretions. Acetylcysteine may be added to the nebulizer as a mucolytic agent. The recommended dose is 5 mL added to the nebulizer (for a 10% solution) every 12 hrs at 4–6 L/min of oxygen. It is important to practice proper technique and to minimize stress to the patient during therapy. Patients with severe pneumonia may require ventilator therapy with increased positive end-expiratory pressure (PEEP) setting to ensure expansion of collapsed alveoli. Bronchodilators such as theophylline derivatives (e.g. aminophylline) or beta-agonists (terbutaline) can also be used to combat aspiration-induced bronchoconstriction. Nebulizers may be used to deliver bronchodilators (albuterol), antimicrobials (typically aminoglycosides such as gentamicin at a dose of 7 mg/kg with 8 mL saline), or regular saline for supportive therapy (Table 20.1). Aerosolized agents for the treatment of pneumonia are in addition to traditional intravenous antibiotic administration. The nebulizer and nebulizer tubing must be kept clean and not used for multiple patients in order to prevent iatrogenic respiratory infection.

Table 20.1 Inhalation therapy: Nebulized bronchodilators.

Drug	Species	Dosage*	Duration and frequency
Albuterol	Cat, small dog	0.5 mL + 4.0 mL saline	1–3 min sid–qid
Albuterol	Dog (10 kg)	1.0 mL + 4.0 mL saline	1–3 min sid–qid
Albuterol	Dog (20 kg)	2.0 mL + 4.0 mL saline	1–3 min sid–qid
Albuterol	Dog (30 kg)	3.0 mL + 4.0 mL saline	1–3 min sid–qid

*Albuterol supplied as 2.5 mg/3 mL inhalation solution.

1. Materials needed
   - handheld nebulizer
   - oxygen tubing
   - anesthetic/oxygen machine
   - 5–10 mL sterile saline
   - facemask.
2. Technique
   - Place the patient in sternal recumbency in a comfortable position. Sling therapy can be implemented (see “Physical therapy” section below) at the time of nebulization.
   - Instill saline +/− medication into the nebulizer compartment; do not invert the chamber.
   - Connect the oxygen tubing to the oxygen system and nebulizer. Turn the oxygen to 4–5 L/min to ensure proper mist flow.
   - Attach a facemask to the nebulizer and apply to the patient.
   - Nebulize for 5–10 min with saline; medications 1–2 min. If the patient does not tolerate the mask, the nebulizer unit may be held closely to the nose or mouth.
   - Coupage the patient after nebulization by cupping the palms of the hand (or contoured to the curvature of the patient’s thorax) and striking the chest rhythmically by alternating between the right and left sides of the chest (Fig. 20.2).

   Coupage should be forceful enough to elicit a cough but not enough to allow the patient to become stressed. Correct hand positioning and location of coupage are

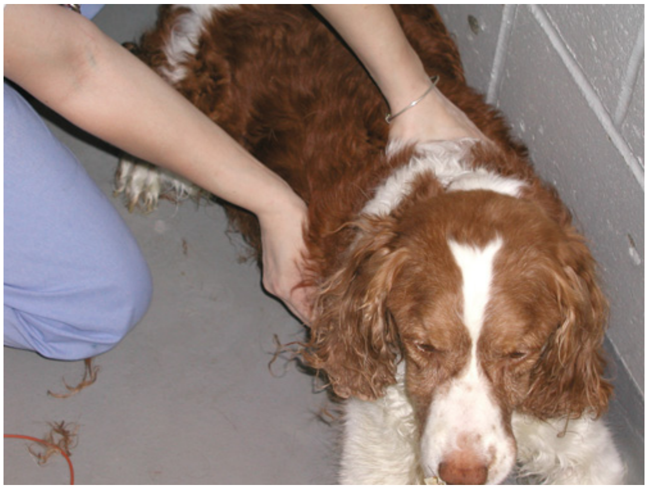


Figure 20.2 Technique for coupage therapy.

more important than the force applied. Coupage should be rhythmic and in a circular motion back and forth over the diseased areas. For puppies, small dogs, and cats, the three middle fingers should be used for coupage rather than the palm of the hand. If stable, deep-chested dogs may be rolled onto their back for coupage, facilitating drainage from ventral lung lobes. It is of the utmost importance to watch respiratory patterns and mucous membrane color during coupage, as it may become necessary to coupage in stages to prevent an increase in respiratory effort. It is also important not to feed a patient shortly before nebulization and coupage therapy, to avoid aspiration of food into the airway. A suctioning device should be readily accessible if the patient has heavy mucus secretions that may clog the airway and compromise ventilation, particularly in the patient with megaesophagus. Contraindications for nebulization and coupage therapy include flail chest, pneumothorax, severe soft tissue trauma to thoracic area, and thoracotomy with chest tube placement. Nebulizing via an oxygen cage is not recommended, as aerosolization is not direct and is usually inadequate. If the patient is oxygen dependent, nasal oxygen can be utilized during therapy, if not already in use. If possible, a short walk immediately after nebulization may help stimulate a cough.

C. Oxygen therapy

Oxygen therapy is critical to the patient exhibiting respiratory dysfunction. Oxygen should be administered in the most effective, least stressful route. Flow-by oxygen supplementation should be provided immediately to postsurgical, postseizure, or head trauma patients in distress while the airway is assessed. It is the opinion of the authors that nasal oxygen is far superior to oxygen cages, although oxygen cages can provide the patient immediate respiratory relief until nasal therapy can be instituted. Transtracheal or nasal-tracheal oxygen can also be administered if the patient has stenotic nares, severe facial trauma, or laryngeal paralysis not responding favorably to nasal oxygen. Nasal prongs (intended for human use) can be used for larger dogs. The prongs are placed in the nares and secured behind the dog's ears. The tubing can be taped or sutured in place. Nasal prongs generally require higher flow rates than nasal catheters.

1. Nasal oxygen tube placement
   a. Materials needed
      - soft, polyvinyl catheter (red rubber)
      - petroleum jelly for lubrication
      - local anesthetic
      - suture material
      - oxygen tubing
      - oxygen canister
      - distilled water.

   For facilitation of catheter placement, the patient should be restrained in a comfortable position. The size of the catheter should be large enough to provide adequate oxygen delivery. The authors recommend using a size 5 French tube for a cat or small dog and a size 8–10 French tube for larger dogs. Transparent feeding tubes are not recommended, as the length is excessive and the tube can be mistaken for an intravenous line.

   b. Technique
      - Instill two to three drops of anesthetic solution into the designated nare (2% lidocaine or proparacaine).
      - Lubricate the end of the red rubber catheter, and slide the catheter into the nasal cavity via the ventral meatus to the level of the medial canthus. In the cat, insert the catheter in a ventromedial direction. In the dog, initially insert the catheter in a dorsomedial direction, then ventromedially.
      - The catheter should be brought up over the head either between the eyes or (preferably in cats) along the mandibular area and anchored in place beginning at the nostril by sutures.
      - Oxygen tubing is connected to the catheter by either an adapter or secured with a Chinese finger lock suture.

   Oxygen tubing (the proximal end) is attached to an infusion bottle filled with distilled water. Oxygen is then delivered through the water and into the tubing connected to the catheter. If in-house oxygen is not available, a portable oxygen machine can be utilized by connecting the tubing to the gas inlet valve. An oxygen flow rate of 100 mL/kg/min will provide an oxygen concentration of approximately 40%. Gastric distension may occur if the conflation rate is too high. Nasal oxygen catheters should be replaced and changed to the opposite nare every 48 hrs due to mucus accumulation. Elizabethan collars should be placed on the patient to keep the catheter from being removed.

2. Transtracheal oxygen catheter placement

   Transtracheal oxygen may be provided if nasal oxygen is not suitable (e.g. nasal occlusion due to hemorrhage). Transtracheal catheters are less irritating than nasal catheters, and lower flow rates can be used to achieve equivalent oxygen concentrations achieved with nasal catheters; however, placement is technically more difficult. Long-term use of transtracheal oxygen should be avoided, as damage to tracheal mucosa may result. Aseptic technique is critical in placing intratracheal oxygen catheters. The bandage should be changed every 24 hrs and the catheter insertion site monitored for inflammation or irritation.

   a. Materials needed
      - a long, flexible, sterile intravenous over-the-needle catheter with a large-gauge needle
      - local anesthetic (2% lidocaine)
      - suture material
      - sterile gloves
      - scalpel blade
      - bandage material
      - oxygen tubing
      - oxygen canister
      - distilled water.

   b. Technique
      - Position the patient in a comfortable, sternal position with the head and neck positioned upward (Fig. 20.3).
      - Shave and prepare the tracheal area using sterile technique.
      - Desensitize the overlying skin area with the local anesthetic agent.
      - Put on surgical gloves and remove the catheter from the sleeve; fenestrate the end with a scalpel blade to minimize tracheal trauma.
      - Insert the needle end of the catheter percutaneously into the trachea at the cricothyroid membrane or between tracheal rings just below the larynx.
      - Slide the catheter into the trachea until the tip of the catheter reaches to approximately the level of the carina.
      - Remove the stylet slowly from the catheter.
      - Pull the needle slowly from the trachea and secure it into the needle guard.
      - Connect the oxygen tubing to the catheter and insufflate oxygen and humidification setup as in nasal oxygen administration.
      - Suture the transtracheal catheter both at the insertion site and around the needle guard.
      - Bandage the neck with loose cotton gauze and veterinary tape, and label oxygen lines appropriately.

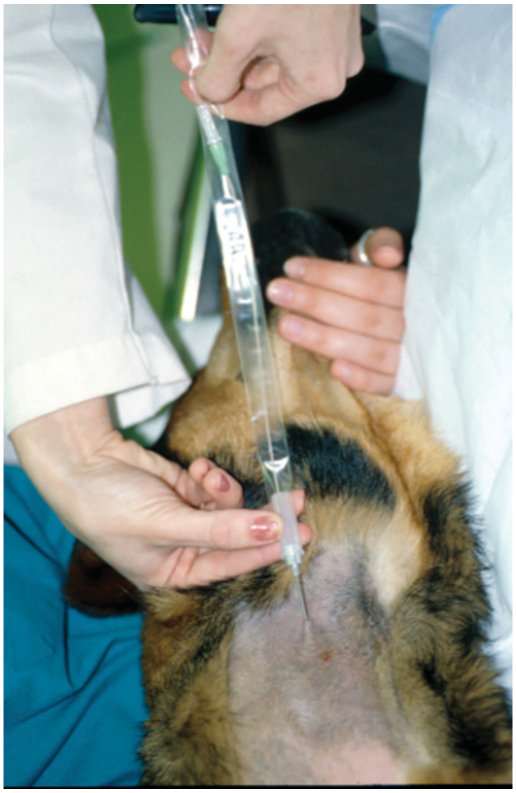


Figure 20.3 Transtracheal oxygen catheter placement.

3. Nasal-tracheal oxygen catheter placement

   Nasal-tracheal oxygen catheter may be used for laryngeal paresis/paralysis, collapsing trachea, or in brachycephalic patients not responding favorably to nasal oxygen.

   a. Materials needed
      - a soft, polyvinyl catheter (red rubber, 3.5–5F for small patients, 5–8 F for medium size dogs, 8–10F tubes for large dogs
      - petroleum jelly for lubrication
      - laryngoscope with long Miller blade
      - tissue or sponge forceps
      - suture material
      - oxygen tubing
      - oxygen canister
      - distilled water
      - note that patient may require mild sedation for catheter placement.

   b. Technique
      - Sedate the patient for visualization of the oral cavity.
      - Premeasure the tube to the fifth intercostal space and mark with a permanent marker; this length is slightly cranial to the tracheal bifurcation.

- Repeat the technique for nasal oxygen placement, keeping the head hyperextended as the catheter reaches the level of the pharynx.
- Open the mouth and visualize the catheter tip, using a laryngoscope with a long Miller blade.
- Using tissue or sponge forceps, grasp the catheter tip and insert it into the trachea.
- Slide the catheter to the predetermined length, and suture it in place.
- Place an Elizabethan collar on the patient.
- Deliver O_2 at 50 mL/kg/min (always humidify).
- Radiographs may be required to confirm location.

4. Mechanical ventilation
Mechanical ventilation is a challenging and labor-intensive therapy in any critical care setting. Indicated for patients who cannot effectively ventilate on their own, mechanical ventilation improves gas exchange, decreases the work of breathing, and assists in the recruitment of alveoli. Neurologic diseases for which mechanical ventilation may be beneficial include secondary pneumonia, severe neurogenic pulmonary edema, ARDS (acute respiratory distress syndrome), thromboembolic disease, head trauma, post-cardiopulmonary arrest, and LMN disease. Modes of mechanical ventilation therapy include controlled ventilation, assisted ventilation, and intermittent mandatory ventilation (IMV). Mechanical ventilators themselves operate as either pressure-limited, volume-limited, or time-limited systems. Depending on the ventilator employed, respiration is controlled by some combination of inspiratory pressure, tidal volume, inspiratory time, respiratory rate, and minute ventilation. Most patients require continuous or intermittent sedation. In some cases, sedative therapy is used in conjunction with paralytic agents. Complications of positive pressure ventilation (PPV) include oxygen toxicity, barotrauma, decreased cardiac output, and pneumonia. Protocols for ventilated patients should be well established and communication between all team members kept active.

Because positive pressure ventilators achieve lung inflation by applying either continuous or intermittent positive pressure to the airway, airtight seals between the patient and the ventilator must be maintained either by a cuffed tracheal or endotracheal tube. Ensuring tight seals should always be the first priority when ventilating a patient. Oxygen and compressed air lines should be monitored every hour to ensure proper supply and delivery. Electrical cords and the power source should be anchored securely and not in the flow of traffic. The ventilated patient should be in a sternal position, level with the ventilator, and on comfortable bedding or pads to prevent sores or ulcerations. It is recommended that all ventilated patients have sterile tracheotomy or endotracheal tubes placed on setup, with the endotracheal tube clearly marked with a visible line at the upper canine tooth to prevent tube migration. Patients expected to need ventilatory support for longer periods (or brachycephalic breeds) may benefit from a temporary tracheostomy tube for airway management. Tracheostomy tubes also help to decrease anesthetic drug requirements and may facilitate successful weaning from the ventilator. Whether a tracheostomy tube or an endotracheal tube is used, the cuff needs to be inflated to protect the airway and to allow PEEP and PPV to be delivered.

Also recommended at setup are arterial catheters for serial blood gas sampling and direct blood pressure monitoring, central catheters for central venous pressure monitoring and serial electrolyte analysis, and ECG telemetry for detecting cardiac arrhythmias. Closed urinary catheters are also helpful in calculating fluid output. Body temperature should be monitored frequently, and circulating water heating pads should be available for hypothermia.

Modes of application are generally determined by patient need and clinician experience. Wherein the goals of PPV are to restore oxygenation and correct ventilation (carbon dioxide levels), barotrauma can result if pressure settings are too aggressive. In addition, patients with diseased or noncompliant lung parenchyma are often placed on higher-than-normal pressure settings in order to prevent small airway and alveolar collapse. Clinical signs of barotrauma can include rapid, shallow voluntary respirations, absence of lung sounds, abnormally high trends in the central venous pressure, and abnormal SpO_2 and $ETCO_2$ readings. Pneumothorax is a common complication, occurring more frequently in patients requiring high airway pressures (> 30 cm H_20) or large tidal volumes. The presence of a pneumothorax should be considered in any patient with a sudden decline in oxygen saturation and/or tidal volume, or an elevation in $ETCO_2$. Management of a pneumothorax includes immediate thoracocentesis; the placement of unilateral or bilateral chest tubes may be required if PPV is continued.

Pulse oximetry should be used on every ventilated patient. If pulse oximeter readings are less than 92%, verify data by first ensuring that an adequate supply of oxygen is present and that the tracheal tube has not migrated or is occluded by a kink or mucous plug. Ensure tight connections of all airway tubing. Second, visibly inspect the patient's mucous membrane color, pulse quality, and heart rate; auscultate lung fields for a possible pneumothorax. Ensure that the probe has not migrated, or change location of the probe. Until the problem can be identified, increase the oxygen flow (FiO_2) to 100%. Verify low oxygen content by running an arterial blood gas, and notify the emergency room clinician of possible respiratory deterioration.

Capnography should be used on the ventilated patient. The $ETCO_2$ values generally should be kept between 30–45 mmHg; high CO_2 values should initially prompt a search for tube occlusion, migration, or pneumothorax. Verify high settings with an arterial blood gas analysis; ventilator settings (breaths per minute) or endotracheal tube length may be altered to decrease dead space. Low $ETCO_2$ values should be monitored for tube occlusion, leaking airway tubing, or a nonpatent cuff. Verification is also recommended by analyzing arterial blood gas, as ventilator settings may need to be altered. The ventilated patient should be monitored for leaking airway sounds, such as bubbling or fluid sounds on inspiration, around the cuff or oral area.

Other considerations with patients on PPV include possible blood pressure abnormalities due to impaired intrathoracic blood flow. As PPV increases pleural pressure, venous return can become compromised to both sides of the heart, affecting diastolic filling. Mechanisms to control such impedance include manipulation of inspiratory time (the length of time pressure is applied) and manipulating respiratory rate (increasing the rate could prevent cardiovascular recovery time). Changes in central venous pressure trends, diastolic and systolic blood pressure trends, pulse quality, mucous membrane color, and heart rate may denote compromise of cardiac performance in the ventilated patient. Any abnormal trends following setup on the ventilator warrant changes in mechanical settings. Cardiovascular compromise may also be particularly severe in patients with intravascular volume depletion or pre-existing cardiovascular instability, or when particularly aggressive ventilator settings are required to maintain adequate arterial blood gas results.

Note that it is always recommended to use minimal ventilator settings to prevent barotrauma and altered blood flow. Consequently, monitoring the arterial blood gases on setup and within the first few hours of PPV is critical. Minimal acceptable PaO_2 values should be about 90 mmHg, with maximum $PaCO_2$ values of 60 mmHg, although every patient should be evaluated on an individual basis.

As most patients will not voluntarily be mechanically ventilated, “bucking” the ventilator (patient–ventilator asynchrony) can become problematic. Changing ventilator mode to IMV can improve patient–ventilator synchrony and sedation protocols can be modified to control patient–ventilator asynchrony. Opioids should be used with caution, as abnormal breathing patterns (panting) may surface as a result of their use. Injectable anesthetic agents, such as propofol, should be kept readily available in the event of tube migration or tube lumen occlusion, requiring re-intubation.

Preventing tube occlusion is critical. If an endotracheal tube is used, sterile suctioning after sterile saline administration is recommended every 4 hrs. Note that there are complications of tracheal suctioning, such as hypoxemia, traumatic airway ulceration, cardiac dysrhythmias secondary to hypoxia and pain, and infection from improper technique. High FiO_2 levels (100%) are recommended both immediately before and after suctioning, with strict sterile technique applied. Suctioning should be brief and thorough, with the suction catheter fed to the bifurcation only.

If a tracheotomy tube is used on the ventilated patient, ensure that the tracheotomy tube used has both a cuff and an inner and outer cannula, if at all possible. The inner cannula can be removed for more thorough cleansing, and can be suctioned with the aforementioned technique. If a tracheotomy tube is used without an inner cannula, cleaning must again be accomplished by cautious aseptic technique. Endotracheal tubes should be removed and replaced with a sterile tube every 24 hrs. In addition, nebulizing through the tracheal tube is recommended to maintain hydration of the pulmonary parenchyma, particularly if pneumonia is present.

Patient hydration should be assessed by monitoring urinary output, daily weighing, electrolyte analysis, and central venous pressure monitoring. As multiple organ dysfunction can occur in any critical patient, renal values should be monitored with consistency. PPV and the use of narcotic sedatives can also increase the secretion of antidiuretic hormone, thereby decreasing urine output. As a result, fluid retention and subsequent edema formation may occur. Intermittent diuretic therapy may be required during the period of ventilation. Nutrition should also be addressed either by nasogastric or gastrostomy tube, depending on the length of proposed ventilation. Note that if nutrition is delivered to the ventilated patient gastrointestinal (GI) motility may be impaired; consequently, aspirating stomach tubes is warranted to monitor residual volume. Facilitating colonic emptying may be required by either an enema or rectal palpation.

It is recommended that patients on PPV be kept in sternal recumbency. Passive range of motion, flexion/extension, and massage/effleurage should be performed every 4–6 hrs. In addition, gentle coupage is recommended to prevent lung parenchyma atelectasis and to help mobilize secretions to central areas reached by routine suctioning. Oral care should also be addressed in order to prevent nosocomial pneumonia. The oral cavity should be flushed with dilute chlorhexidine and suctioned every 12 hrs. The tongue can be kept moist by wrapping it with moist gauze and kept inside the oral cavity. Pressure sores on the tongue can be reduced by the use of mouth bridges or gags. The eyes should also be kept moist by saline flushes and eye lube every 4–6 hrs. Fluorescein staining should be performed regularly to check for ulceration and treatment instituted if necessary.

All patients on mechanical ventilation are at a high risk of acquiring nosocomial infections. Minimizing risk by being conscientious, practicing sterility with handling of catheters and tubes, and cleaning circuitry between patients are highly recommended. Development of fever, or inflammatory changes on complete blood count, may be indicative of sepsis. Thoracic radiographs along with culture and susceptibility testing of airway samples from a bronchoalveolar lavage are recommended. In order to limit the development of bacterial resistance, antimicrobial therapy should not be routinely started on mechanically ventilated patients, unless an underlying infectious process was previously identified.

Established protocols for patient setup, maintenance, and recovery are paramount for a successful outcome. Communication between the nursing staff and clinicians should be concise, and team members need to be ready for any emergency situation, such as re-intubation, hand ventilation (from power failure or machine malfunction), or tube occlusion.

Weaning a patient from mechanical ventilation can be difficult. For weaning to be successful, the patient must have a sufficient respiratory drive, as well as adequate neuromuscular function to achieve a sufficient tidal volume. The weaning process typically involves a gradual reduction in mechanical ventilation with a proportional increase in the work performed by the patient. The patient should be closely monitored at every stage of the process for any sign of respiratory insufficiency (hypoxemia, hypercapnia, hypertension, or patient distress). In addition, oxygen supplementation (e.g. nasal oxygen) should be provided in every patient coming off mechanical ventilation. Successful weaning off the ventilator is largely dependent on the primary disease process leading to the initiation of ventilation.

5. Placement of arterial catheters

Arterial catheters are placed in order to check serial blood gas during respiratory difficulty, hypercapnia, hypoxia, and mechanical ventilation. Catheters are also used for direct blood pressure monitoring.

Arterial catheters should not be used in thrombolytic disease or coagulopathic disease patients.

a. Materials needed
   - clippers
   - surgical scrub
   - suture material
   - heparinized saline flush
   - catheter cap
   - arterial catheter kit or cephalic catheter
   - bandage material
   - saline for infusion if continuous blood pressure is monitored.

b. Technique
   - Lay the patient in lateral recumbency.
   - Give the patient oxygen if the body position compromises respiratory effort.
   - Clip and prep dorsal pedal area (down limb).
   - Palpate the pulse with a single digit.
   - Use a stab incision for a "cut down" at a 45° angle and at least 1 inch away from a palpable pulse.
   - Hold the catheter like a dart; insert the catheter with the bevel up through a tunneled area.
   - Use "baby-steps" toward the pulse (superficial); back out and redirect if there is no flash.
   - Once a flash is obtained, be careful not to move the catheter; slide the entire length of wire via the black tab handle.
   - "Pop" the catheter off the wire and into the arterial space.
   - Remove the wire and ensure blood flow (should be fast and in a spurting or jetting motion).
   - Cap and flush the catheter; aspirate back to ensure blood flow and re-flush.
   - Suture the catheter in place.
   - Place a small amount of antibiotic cream over the insertion site.
   - Cover with a sterile gauze square.
   - Place one layer of gauze bandage.
   - Cover the catheter with elasticon and label "ART."

Change the catheter cap, bandage, and sterile gauze daily. Flush the catheter every 2 hrs with heparinized saline, if you are not using it as a continuous rate infusion (CRI) for direct blood pressure monitoring.

Important note: Do not give any medications through the arterial catheter.

6. Pulse oximetry and capnography

a. Pulse oximetry

Patient monitoring using pulse oximetry should be utilized for every patient undergoing anesthesia or as a monitoring tool in the ICU. A noninvasive method of continually measuring hemoglobin oxygen saturation (SpO_2), the pulse oximeter will display an oxygen waveform or an oxygen saturation percentage useful in evaluating lung function. Pulse oximetry does not assess ventilation, and should not take the place of lung auscultation or arterial blood gas analysis. Pulse oximeters commonly use a tongue, earlobe, or toe digit as the cuvette within which SpO_2 is measured. Pulse oximetry must be used in conjunction with other hemodynamic markers and not used solely to determine respiratory stability. Invalid pulse oximetry readings are common occurrences on the poorly perfused, hypothermic, jaundiced, or patients with cardiovascular compromise. Low pulse oximeter values (less than 94%) in conjunction with other abnormal exam findings should result in oxygen therapy (or increased FiO_2 if already receiving oxygen) and an arterial blood gas analysis.

b. Capnography

Capnography is a noninvasive method for the continuous assessment of ventilation by the measurement of $ETCO_2$. Capnography is superior over pulse oximetry for the prompt identification of apnea and airway mishaps, as there are instantaneous changes in $ETCO_2$ as opposed to slower changes in the percentage of hemoglobin saturated with oxygen (SpO_2). Clinical indications for capnography include ensuring correct endotracheal tube placement, detection of apnea, and in monitoring adequacy of ventilation and pulmonary perfusion during cardiopulmonary resuscitation. $ETCO_2$ monitoring can be critical in detecting potentially catastrophic anesthetic complications during common neurodiagnostics such as the collection of CSF fluid during neck flexion, when the endotracheal tube may be inadvertently kinked (Fig. 20.4).

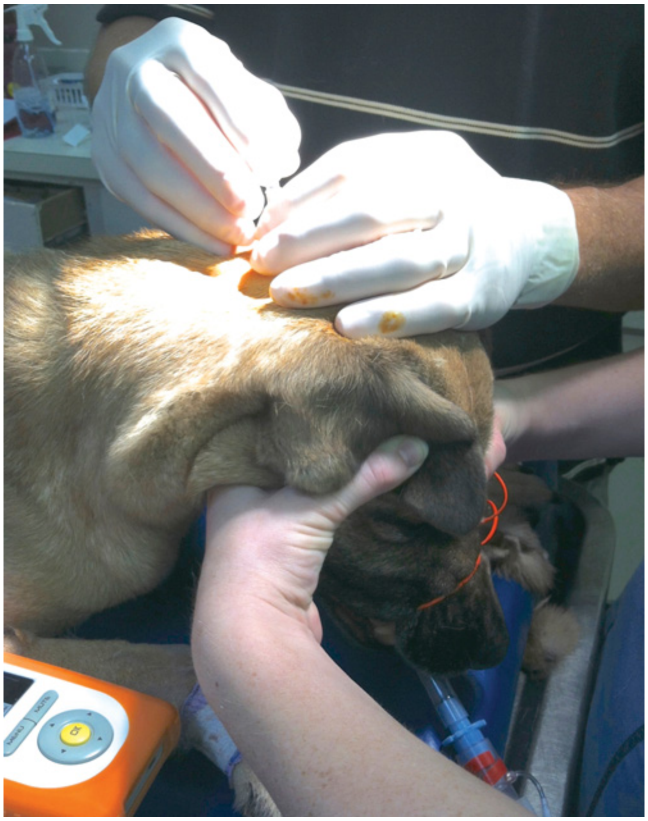


Figure 20.4 Respiratory changes are closely monitored during cervical positioning for CSF collection.

An instrument called the capnograph displays both numerical and waveform imaging. During anesthesia, respiratory depression secondary to drugs and inhalants can be effectively monitored using a capnograph. There are two types of monitors available for assessing end-tidal carbon dioxide: the capnometer or capnograph. Capnometers provide only minimum and maximum $ETCO_2$ values, while capnographs display graphic representation (waveforms) of exhaled carbon dioxide.

Capnometers and capnographs may be categorized as mainstream or sidestream, based on the location of the sensing device. Mainstream (nondiverting) monitors analyze the respiratory gases locally (at the endotracheal tube-breathing system interface), while sidestream (diverting) monitors employ sensing tees placed at the endotracheal tube-breathing system interface and pump respiratory gases for analysis up into the measurement chamber via a length of tubing. Although mainstream monitors provide rapid results and have less mechanical problems caused by condensation, sidestream monitors can be utilized for remote patient monitoring such as during an MRI. In addition, sidestream monitors can detect expired gases in nonintubated patients through nasal tubes, a critical monitoring tool for patients susceptible to hypercapnia (e.g. cervical lesions or LMN conditions).

Normal $ETCO_2$ values are approximately 35–45 mmHg; abnormal $ETCO_2$ trends should be verified by an arterial blood gas sample. Persistently increased $ETCO_2$ values indicate inadequate ventilation, necessitating ventilatory assistance. Prolonged periods of hypercapnia can lead to myocardial depression and respiratory acidosis. Elevated $ETCO_2$ levels may also occur as a result of airway obstruction, pneumothorax, body positioning, or lung parenchymal disease. Hyperventilation (purposefully decreasing $ETCO_2$) during anesthesia for diagnostic or therapeutic procedures can be beneficial to decrease ICP through vasoconstriction of cerebral vasculature.

Recumbency and pressure sores[2, 4, 15, 34, 45]

Other complications of the recumbent animal include development of pressure sores or decubital ulcers. These are local areas of skin necrosis. Pressure sores are often localized to bony prominences; localized pressure over these areas leads to tissue ischemia of variable severity. The extent of tissue damage is often graded from least severe (grade I: darkened area of thickened skin, no exposure of subcutaneous tissue) to most severe (grade IV: deep tissue loss with exposure of bone). Grade II decubital ulcers involve exposure of subcutaneous fat, and grade III ulcers involve tissue defects to the level of deep fascial layers.

Ulcerations on extremities and the pads of the feet can also occur with wheelchair use. Protective boots can prevent damage to paws and help dogs walk on slippery floors. Velcro pads can be applied either onto the bars of the wheelchair or to affected areas to help prevent ulcerations that may form from constant rubbing.

Frequent turning of the patient and appropriate bedding represent the most important preventative measures of a nursing-care protocol. Increased skin moisture and irritation contribute to the development of decubital ulcers; therefore, patients should be kept clean and dry and should be bathed frequently. Since decubital ulcers are primarily caused by pressure, they can be avoided or minimized by using bedding such as sheepskin, foam or air mattresses, trampolines, or bandaging techniques. Sheepskin is advantageous in that it is inexpensive and can be laundered for multiple uses. The sheepskin minimizes friction and can absorb moisture, which is particularly important in preventing urine scalding. Sheepskin may make patients hot, so rectal temperatures should be monitored frequently when this bedding material is used. Air mattresses are also inexpensive and allow pressure distribution to avoid decubital ulceration. Disadvantages associated with air mattresses include puncture holes from the patient's nails and the inability to launder air mattresses for long-term use. Urine scalding can also occur with the use of air mattresses. Trampoline beds are an excellent choice for the recumbent patient. The trampolines are constructed from plastic piping and fiberglass netting, allowing air to circulate underneath. The trampoline also distributes a patient's weight evenly, helping to prevent pressure sores. Urine scalding is also avoided by the fiberglass netting, as the urine falls underneath the patient onto plastic trays. Bandaging techniques in the form of doughnuts (Fig. 20.5) can also be placed over bony prominences to prevent decubital ulcers or over existing decubital ulcers to prevent further pressure damage. Such devices can effectively relieve pressure while allowing for the adequate aeration of tissues.

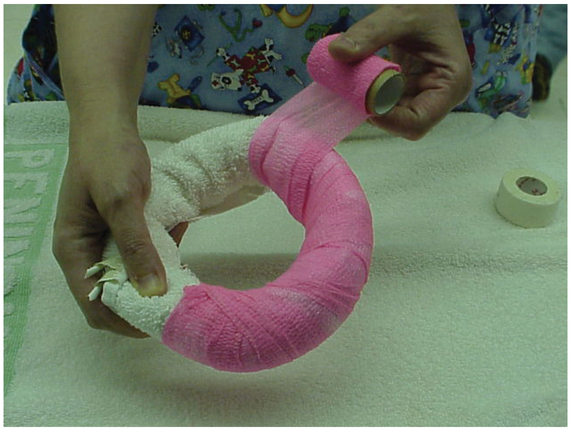


Figure 20.5 Preparing a "doughnut" to place over a decubital ulcer in a dog.

Nonsurgical vertebral fractures and/or spinal luxation involve external splints and strict cage rest for 6–8 wks to allow healing (see Chapter 15); sternal positioning is recommended when at all possible. As splints are held in place using bandage material, bandages should be evaluated daily to ensure there is no respiratory compromise caused by excessive constriction. Bandages should be evaluated daily for evidence of soiling, and limbs examined for decubital ulcer formation or abrasions caused by external splints.

Treatment of decubital ulcers may involve medical and/or surgical therapies. Specific medical therapy depends upon the individual case, but may involve frequent wound lavage, systemic antibiotics, wet-to-dry bandaging, and application of topical drugs. These topical agents include antibacterial preparations (e.g. triple antibiotic, gentamicin, nitrofurazone, silver sulfadiazine ointments), enzymatic debriding agents, and hydrophilic agents (maltodextrin powder wound dressing). Additionally, Preparation H is believed to stimulate wound healing when applied to decubital ulcers. Surgical intervention and wound culture/susceptibility testing may be required for decubital ulcers, especially if they are grade III or IV in severity. Such intervention may include debridement and primary closure, delayed wound closure, or use of cutaneous or myocutaneous flaps.

Bladder management[2–4, 18, 19, 25, 34, 36]

Urinary complications are common in dogs and cats with neurologic dysfunction. Overdistension of the urinary bladder and urinary tract infections are typical sequelae, both of which are avoidable with attentive nursing care. Proper technique in both expressing and catheterizing the bladder is important to prevent urethral and bladder wall trauma, to prevent introduction of bacteria into the urinary tract, and to measure urinary output in the oliguric or anuric patient as a guideline for appropriate fluid therapy. Poor nutrition and decreased water intake can also affect the patient's urinary system and should be corrected. Overdistension of the bladder can result in permanent atony of the detrusor muscle. The bladder should be palpated to estimate size, even if there is urine present in the cage. The presence of urine in the patient's cage is not a reliable indicator of the ability to urinate voluntarily; the patient could have urinary overflow as a result of distension. The bladder should be expressed every 4–6 hrs as a general rule, but the urodynamics of each patient should be assessed on an individual basis (e.g. prednisone use or intravenous fluids could warrant bladder evacuation more frequently). If the bladder cannot be expressed without minimal stress to the patient, a urinary catheter should be placed. Whether placing a closed urinary collection system or intermittently catheterizing the urinary bladder, proper sterile technique must be followed in order to avoid nosocomial urinary tract infections. In the postoperative patient, detrusor dysfunction may occur following systemic (CRI) or epidural use of opiates; therefore, bladder size should be evaluated every 4–6 hrs and expressed or catheterized as necessary.

A. General guidelines for urinary bladder expression

   It is important to distinguish between upper motor neuron (UMN) bladder and LMN bladder dysfunction to best determine which pharmacologic agents will be most efficacious in improving bladder function (see Chapter 16). Before expressing the bladder, it is advisable to first allow the patient to try to urinate voluntarily by walking or carting the animal outside. If the patient does voluntarily urinate, it is still necessary to palpate the bladder after urination to ensure complete evacuation. Catheterization may be necessary in order to determine the amount of residual urine left after urinating if the bladder still palpates as large. Normal residual urine volume in the dog bladder is between 0.2 and 0.4 mL/kg body weight; this is believed to be similar for cats. Normal urine output for the dog and cat is approximately 1–2 mL/kg/hr. Note that the foremost objective in bladder expression is to avoid overdistension and detrusor muscle atony. Stress should be minimized during bladder expression by using proper technique. Diazepam given intravenously or orally can help relax the external sphincter tone, as well as reduce anxiety in dogs requiring frequent bladder expression.

   1. Technique (Fig. 20.6)
      - Place the patient in a comfortable position, either standing or in lateral recumbency.
      - If the patient is in lateral recumbency, gently place one hand on the upper abdominal wall and one hand underneath the position in a symmetrical fashion. If the patient is standing, place one hand on each side of the abdomen. In either case, the hands should be initially placed just caudal to the last rib.
      - Gently palpate the abdomen, slowly advancing the hands medially toward each other. If the urinary bladder is not palpable, simultaneously move both hands caudally until the bladder is contacted. Since the bladder is somewhat mobile within the abdomen, and bladder size is variable, starting cranially and manipulating the bladder caudally will force the bladder into the pelvic inlet region, preventing it from escaping the clinician's grasp.
      - Once the bladder wall is palpable, steady, even pressure is applied with both hands. The direction of the pressure should be medial and caudal. Gently express the bladder until it feels empty. The clinician should be able to feel the bladder "deflate" as urine is expressed.

      It is important to note that with frequent bladder expressions the abdomen may become tense as a result of patient anxiety, consequently making the bladder difficult to express. In addition, as the abdomen tenses, the bladder may become displaced in an otherwise abnormal position (cranially). Evacuation of the bladder should never be

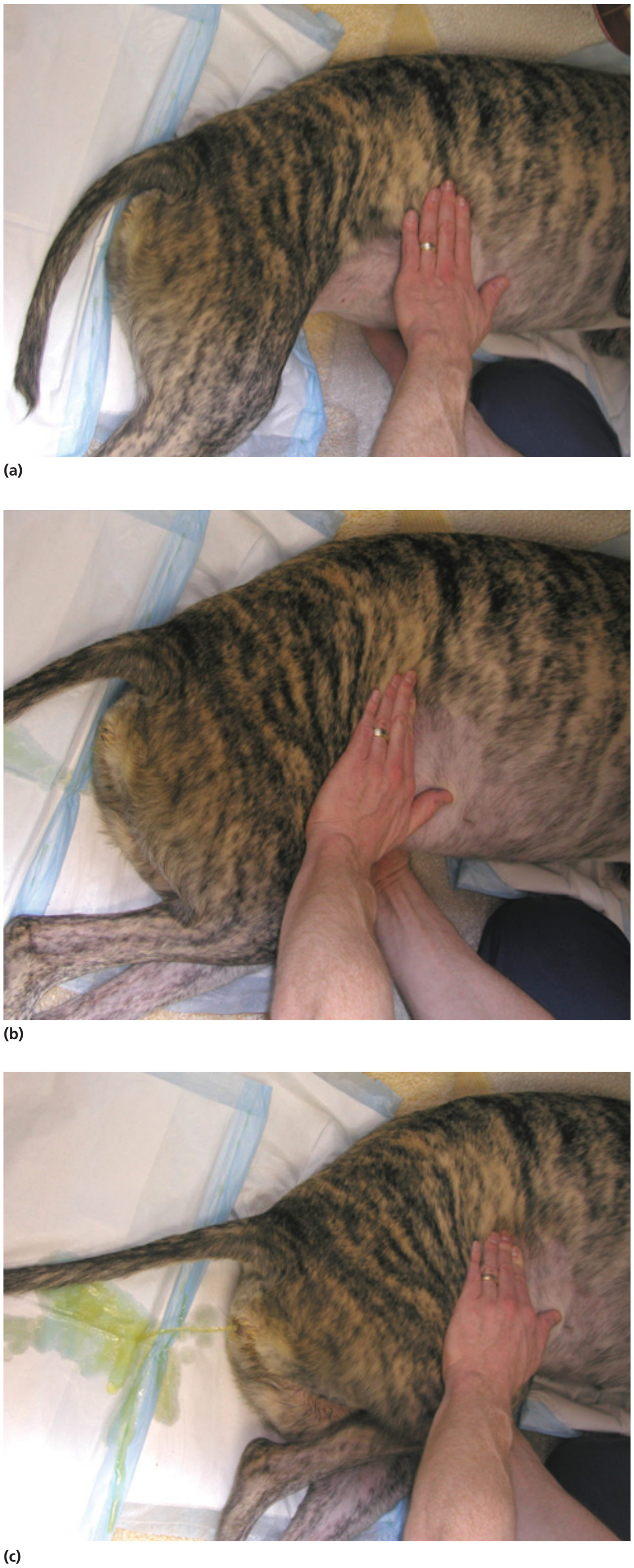


Figure 20.6 Sequential steps (A–C) for bladder expression in the recumbent patient.

forceful or aggressive. Catheterization may become necessary until pharmacologic agents are of benefit.

B. General guidelines for urinary bladder catheterization

Urinary catheterization can introduce microbes into both the bladder and the kidneys, traumatize the urethra, and cause patient discomfort. Catheterization of the neurologic patient should be performed only if attempts at bladder expression are unsuccessful or contraindicated (i.e. entrapped bladder, suspected bladder trauma from automobile trauma), or for recumbent, critical patients with spinal injuries. The type and length of the urinary catheter is important to facilitate efficient bladder evacuation and to measure urinary output. If a closed system for long-term use is desired, a softer, less-irritating catheter with a ballooning device for anchorage should be used, particularly in the female dog. If less frequent catheterization is warranted, bladder decompression can be obtained by intermittent catheterization two to three times daily using a soft, polyvinyl or red rubber catheter or feeding tube. It is of the utmost importance to ensure adequate length of the urinary catheter. The catheter should always reach into the neck of the bladder for either system. The catheter should have a visible marker in order to determine whether it is backing out during patient use. If a Foley catheter is used, adequate dilation of the balloon should be maintained with at least half the amount of air or fluid suggested by the manufacturer (the amount should be indicated on the sleeve of the balloon).

1. Materials needed

- appropriate length and gauge of urinary catheter and stylet
- sterile gloves
- sterile lube
- mild cleansing agent (e.g. dilute chlorhexidine)
- suture material and medical tape (for indwelling catheters)
- sterile closed collection system (for indwelling catheters)
- clippers for sterile preparation (female)
- sterile syringes for urine sample containment
- sterile fluid-filled syringes (saline preferred).

2. Technique

When positioning the patient for placement of a urinary catheter, it should be kept in mind that, while restraint is necessary, the comfort of the patient is of the utmost importance. The patient should be placed in a position that will facilitate both sterile technique and successful catheterization. In the male dog, lateral recumbency is preferred, with the prepuce retracted and the penis aligned parallel with the long axis of the body (Fig. 20.7). A stylet in the catheter for the male patient is usually not required, unless urethral stones are present or suspected. When catheterizing male cats, the penis must be straightened before passing the catheter. This is accomplished by applying caudal traction to the preputial region, directing the penis in a caudal direction, parallel with the long axis of the body. Female patients can be placed either in sternal (usually preferable) or lateral recumbency (whichever is more comfortable for the patient yet optimal for the visualization of the urethral papilla). Due to the curvature and size of the papilla, a stylet in the urinary catheter is often useful when catheterizing the female patient. Mild sedation should be considered for the comfort of the patient and to facilitate catheterization via relaxation of the urethral musculature. Urethral catheterization may be facilitated in some cases by using a syringe attachment and pulsating fluid as the catheter is being advanced.

- Position the patient for catheter placement (lateral for males, sternal for females).

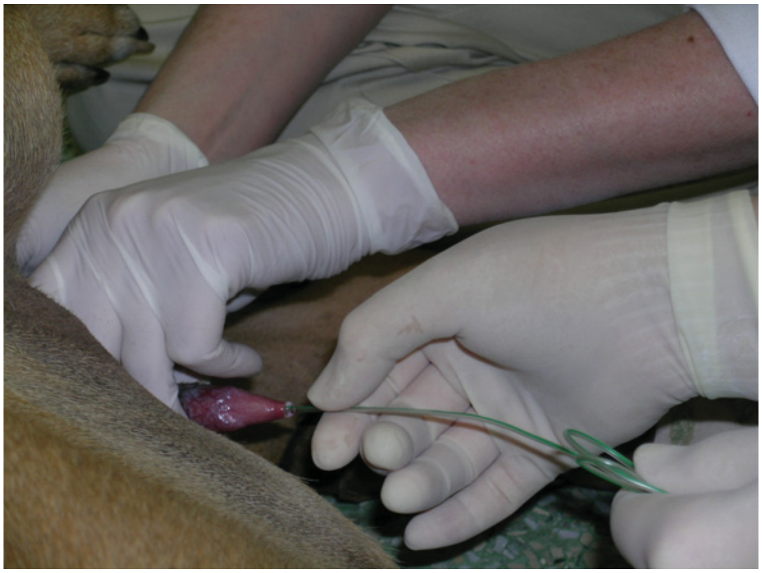


Figure 20.7 Placement of a urinary catheter in the male dog. (Courtesy of Dr. Catherine Langston, The Ohio State University.)

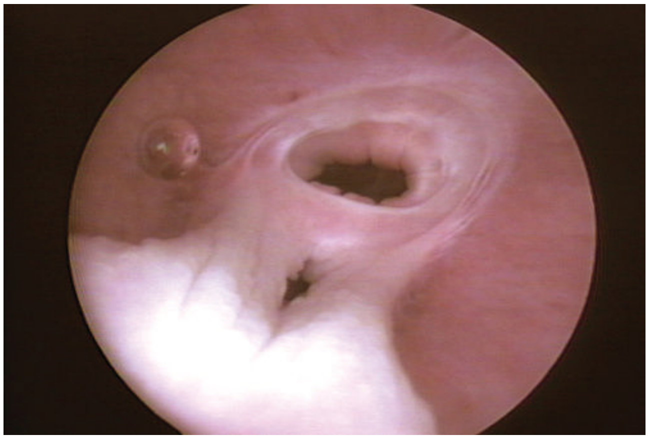


Figure 20.8 Visualization of the urethral papilla in the female dog to facilitate urinary catheter placement. (Courtesy of Dr. Stephen DiBartola, The Ohio State University.)

- Prepare the catheter insertion site with antiseptic solution. Shave the perivulvar area in females prior to skin preparation.
- Wearing sterile gloves, inspect the balloon on the Foley catheter, lubricate the catheter, and measure the estimated length of catheter to be passed by marking the distal end of the catheter with a permanent marker. Insert the stylet into the catheter (females).
- Pass the catheter while an assistant retracts the prepuce or vaginal folds.
- For female patients, visualization of papillae may be best accomplished with a laryngoscope light and/or a vaginal speculum (Fig. 20.8).
- Pass the catheter to the desired measured length.

For closed indwelling systems:

- Inflate the balloon of the Foley catheter with the recommended amount of saline (written on the side of the balloon arm).
- Pull the Foley catheter out of the urethra until the balloon catches on the bladder neck (females only).
- Wipe the catheter dry, and fasten it with tape and suture it in place (Fig. 20.9).
- Obtain a urine sample and attach closed system.

It is recommended to place stay sutures both around the catheter and prepuce/vulva region, with the remainder of the urinary catheter fastened around either the tail or abdominal area to prevent dislodgement. The outer portion of the urinary catheter should be labeled with permanent marker in order to monitor the optimal insertion length for the duration of use. The patient should be observed closely for licking, chewing, or biting at the urinary collection system. An Elizabethan collar should be placed if a patient displays such behavior, to prevent premature catheter removal. Excessive force is contraindicated in the passage of any urinary catheter. Urethral trauma, including tears, can result from aggressive catheterization attempts; such trauma can lead to life-threatening consequences. The type of catheter used is paramount; acceptable indwelling catheters include those made of polyvinyl chloride or silicone Foley catheters. Polypropylene catheters should not be used for indwelling catheters, as they are stiff and uncomfortable to the patient and may cause uroepithelial damage. The length of the catheter is also important. Inserting excessive catheter length may result in the catheter looping around itself and kinking, cutting off the flow of urine. Excessive catheter length may also traumatize the bladder

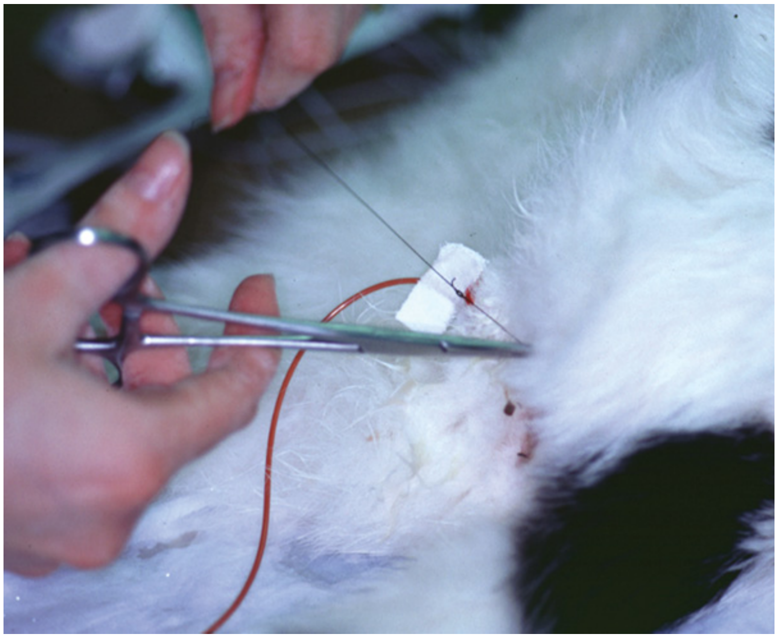


Figure 20.9 Anchoring the urinary catheter. (Courtesy of Dr. Catherine Langston, The Ohio State University.)

wall. Placing the catheter in the urethra and not into the bladder can also hinder bladder evacuation or drainage. The tip of the catheter should ideally be inserted to reach the caudal aspect of the bladder lumen, in the trigone area. Radiographs may be indicated to ensure proper placement if urine production is questionable.

C. Indwelling versus intermittent urinary bladder catheterization and catheter care

Indwelling catheters are advantageous for patients who run the risk of repeat urethral blockage (e.g. feline urolithiasis). Repeated catheterization of such patients may lead to further urethral trauma and tissue inflammation, patient discomfort, and introduction of microbes. Indwelling catheters are also beneficial for patients receiving large volumes of crystalloid fluids as a tool to properly gauge renal function (e.g. “ins and outs” fluid therapy). Indwelling systems are also useful for recumbent patients who cannot be moved outdoors to urinate (e.g. spinal fracture patients) and patients with atonic bladders or historical/clinical evidence of bladder trauma. The importance of aseptic technique cannot be overemphasized; antibiotic therapy to avoid a urinary tract infection is not recommended, as this practice may facilitate antibiotic-resistant urinary tract infections. It is important to maintain a sterile collection system if an indwelling urinary catheter is used. Caution should be exercised when moving either the urine collection bag or the patient to avoid urinary flow from the bag back into the patient. Specialized, anti-reflux urinary collection bags can be utilized to prevent urinary back-flow. If an intravenous drip set is used for the collection device, the roll clamp should be removed to avoid the mistake of restricting urine flow. The urine collection bag should be positioned at a level below the patient to ensure proper urine flow. If the patient is experiencing hematuria or urolithiasis, intermittently flushing the bladder with sterile saline is recommended. The urine collection bag should be emptied every 4 hrs and urine production carefully recorded. If urine production appears inadequate, accurate placement and patency of the urinary catheter should be verified before increasing fluid administration.

In summary, to minimize urinary tract infections from an indwelling catheter, sterile technique should be observed. However, the best way to avoid urinary tract infection is to remove the catheter as soon as it is feasible to do so. Approximately one-half of dogs catheterized for 4 days or longer will develop a urinary tract infection. If a closed urinary system is used, the prepuce or vaginal area around the urinary catheter should be swabbed every 12 hrs with dilute chlorhexidine to minimize bacterial growth. Urinary collection bags should be changed every other day.

Current recommendations for urine culture and susceptibility testing does not include culturing the urinary catheter tip. The urinary catheter should be removed and a urine sample collected via cystocentesis with sterile technique 1–2 hrs after catheter removal. Administration of antibiotics as prophylaxis in patients with an indwelling urinary catheter is not recommended.

Intermittent urinary catheterization must also follow strict aseptic technique. Intermittent catheterization may be used to obtain a urine sample if a diagnosis is dependent on urinalysis and cystocentesis is contraindicated or unsuccessful. Intermittent catheterization may also be used for patients experiencing contractility difficulty; manual expression may be difficult in such patients and may cause discomfort. It should be kept in mind that frequent intermittent catheterization may lead to patient discomfort, urethral trauma, and urinary tract infection. The practice of intermittent catheterization should only be used for the patient who does not need long-term bladder care. Finally, it is very important to keep the patient clean and housed with dry bedding in order to prevent urine scalding if the patient is recumbent and does not have a closed urinary system. As discussed previously, trampolines are available to prevent the patient from lying in urine if 24-hr care is not provided.

Unlike urination, defecation usually proceeds without assistance in animals with neurologic disease. However, constipation may be caused by opioid use, changes in diet, or stress due to hospitalization. Diarrhea may also occur due to medications such as corticosteroids. In addition, dogs with LMN disease may develop urinary and fecal incontinence. Regular expression of feces is recommended to help keep the patient clean. Low-residue diets may be beneficial in patients with fecal incontinence; however, prognosis for functional recovery is often poor. Stools should be evaluated for blood, as glucocorticoids are frequently prescribed for many neurologic disorders. Clinical signs may be diarrhea, black or tarry stools, or pain with defecation. Treatment often includes the administration of gastric protectants.

Rehabilitation therapy[2, 4–7, 11–15, 17, 18, 20, 21, 23, 26, 28, 29, 31–35, 37, 39–44, 46, 47]

Although neurologic rehabilitation is commonplace in humans following neurosurgery or after neurologic emergencies such as strokes, veterinary neurologic rehabilitation is not as widely accepted or applied. The major goals of rehabilitation therapy are to attain or maintain full range of joint motion, minimize muscle atrophy, and prevent or ameliorate patient discomfort. Traditional therapies of hot packing, cold packing, massage, and simple stretching exercises in veterinary medicine have been supplemented by more advanced treatments, such as hydrotherapy, laser therapy, sling therapy, ultrasound, electrical stimulation, sling-supported exercise, and acupuncture. There is an increasing demand for prolonged postoperative care in dogs and cats, reflective of advances in veterinary neurosurgery. Emphasis on such physical therapeutics can result in shorter hospitalization periods and improved patient wellbeing. A plan for rehabilitation therapy should be discussed between veterinarian, technician, and owner, in order to provide the best rehabilitation program. Benefits of rehabilitation therapy include improved circulation, increased production of collagen, decreased inflammation, decreased muscle atrophy, and prevention of joint stiffness. Pain management should always be an important consideration for the patient undergoing rehabilitation therapy. Assessment by the veterinary team and owner includes watching out for pain behaviors, posture, muscle imbalances, and gait impairments before, during, and after rehabilitation therapy.

It is extremely important to have protocols of rehabilitation therapy discussed between veterinarian and technician, as patients with identical diagnoses may require different treatments. For example, animals with intervertebral disc disease (IVDD) may have varying degrees of neurologic impairment and will require differing degrees of rehabilitation therapy. In addition, patients recovering from vertebral fractures may receive varying stabilization techniques and will consequently receive a rehabilitation therapy regime dependent upon the surgical technique. Soft tissue trauma, such as is often encountered in automobile accidents, may be complicated by delayed wound healing if rehabilitation therapy is instituted prematurely.

Rehabilitation therapy emphasizes a return to function rather than treatment of a specific disease or diagnosis.

Managing pain in these patients can be a challenge to any clinician. Anti-inflammatory drugs, analgesics, herbal medications, and alternative modalities such as acupuncture may all be needed to treat painful conditions. Analgesic drugs and alternative therapies are discussed in Chapters 21 and 22, respectively. Therapeutic modalities are used to augment medications and reduce pharmaceutical dosages that are required by the patient. The most common modalities used for pain relief include heat, cryotherapy, as well as manual therapies such as massage, joint mobilizations, and stretching, laser therapy, transcutaneous electrical nerve stimulation (TENS), and therapeutic ultrasound (TUS). Muscle strengthening and re-education is accomplished through the use of neuromuscular electrical stimulation (NMES), therapeutic exercises, hydrotherapy, and proprioceptive neuromuscular facilitation (PNF). Assistive devices, such as harnesses, slings, boots, carts and incontinence aids are often essential to the wellbeing and recovery of the patient.

Therapeutic cold packing, or cryotherapy, is an important nursing technique for the acutely injured or postoperative patient. Cold packing is efficacious in producing local vasoconstriction and in preventing interstitial bleeding and should be the first form of therapy instituted. Owners can be instructed to apply a cold pack to the injured animal en route to the hospital. Benefits of cold therapy include reduction of enzymatic tissue activity (thereby reducing tissue destruction) and a reduction of pain perception (Box 20.1). Typically, cold packing is performed several times a day for 20 min, up to 3 days after injury. Ice packs can also be applied directly over an incision immediately after surgery (e.g. hemilaminectomy) to minimize local swelling and reduce the modulators of pain.

Box 20.1 Beneficial physiological effects of cryotherapy.

- Local vasoconstriction which decreases blood flow thereby decreasing swelling, interstitial hemorrhage and inflammation.
- Reduction of enzymatic tissue activity and damage through inhibition of the release of histamine, protease, hyaluronidase, and collagenase.
- Reduction of cellular metabolism. Decreased tissue oxygen requirements prevent secondary cellular hypoxic injuries.
- Reduction in pain perception. Analgesia and a reduction in muscle spasm occur due to a decrease in nerve conduction velocity.

Cold packs can be made by placing a mixture of ice and rubbing alcohol into plastic bags; alternatively, gel packs can be purchased at packing stores and kept refrigerated. It is usually best not to freeze the cold packs or plastic containers as the packs become difficult to mold around the injured area. Subzero blankets, which circulate cold water, can also be purchased at hospital pharmacies and can be useful in cold-packing procedures. In addition, subzero blankets can be utilized for head-trauma patients by decreasing total body temperature in order to decrease ICP (see Chapter 8). When using cold packs, a thin moist towel should be placed between the patient and the ice pack to avoid damaging the skin and to improve cooling. The length of time to apply the ice pack varies with the size of the patient, the size and depth of the ice pack, and the target tissue. The average-size dog will require 10–15 min of cooling, whereas a large dog may require 15–20 min. A very small dog may only need 5–8 min of icing. Fatter dogs will require more time to cool the target tissue as adipose tissue is a poor conductor of heat. Ice massage can be used for small areas and may be used prior to other manual therapies. Water can be frozen in paper cups and the paper torn away as the ice melts. If a tongue depressor is placed in the center of the cup before freezing, an ice popsicle will result thus giving the therapist a handle for applying the ice. Treatment duration for ice massage is generally 5–10 min (Box 20.2 and Box 20.3).

Box 20.2 Clinical pearls for using ice packs.

- Make your own ice gel packs using three parts water to one part rubbing alcohol and freezing this mixture in zip-lock freezer bags of various sizes. These will stay malleable and can be stored in the freezer.
- Bags of frozen peas can be used as they are malleable but because they contain air spaces they will not cool as well as other methods.
- Duration of ice pack application (for an average-size dog) would be 10–15 min on, then 10–15 min off, twice. Repeat this every 4 hrs for the first 24–48 hrs.
- Use cold packs for 15–20 min prior to laser therapy in large dogs with deep target tissues as this enhances the effect of the laser therapy.

Box 20.3 Precautions and contraindications of cryotherapy.

- Avoid any previous areas of frostbite.
- Apply with caution in very old, very young,or hypertensive patients.
- Avoid superficial wounds, superficial nerves, areas of decreased sensation, and open fractures.
- Check the patient's skin for redness or blanching after the first 5 min to avoid cold injury. Do not apply ice for more than 20 min per session.

Superficial heating or thermal therapy is one of the oldest physical modalities (Box 20.4). It is generally used after icing, before exercise or stretching, or to relieve pain and muscle spasms. Hot packing should follow cold therapy after 72 hrs. Thermal therapy can be delivered by hot packs, hydrotherapy, infrared lamps, heating blankets, and TUS. Moist hot packs are most commonly used. Commercial physical therapy gel packs or oat or beanbags can be heated in the microwave, covered with a thin towel, and used. A hot wet towel covered by a dry towel works well to apply moist heat. Duration of treatment depends on the patient and the condition treated; however, in general heat treatments last 15–30 min and may be applied up to four times daily (Box 20.5). Hot packs work well in conjunction with other forms of therapy such as massage and exercise therapy. Another way of applying thermal therapy is through the use of warm baths. The patient or the affected area can be immersed in a warm bath, a whirlpool, or a hydro treadmill. The advantage of immersion therapy is that the increased hydrostatic pressure of the water decreases edema and improved lymphatic circulation. The water is often circulated with jets and the patient receives the benefit of heat, massage, and increased hydrostatic pressure. Heating pads and infrared lamps have the potential to burn the patient and are not recommended, particularly for patients with neurologic disease who may be unable to move away from the source of heat (Box 20.6).

Human physical therapists have used TUS to treat painful patients for a number of years. The major indication for use of this modality is deep-tissue heating; however, other uses such as enhancement of wound and fracture healing by means of tissue modulation and modification of cellular function have been investigated. Some investigators have demonstrated nonthermal effects of TUS that include increased nerve conduction velocities of both sensory and motor nerves and improved nerve healing. TUS works by the conversion of electricity to sound waves through the piezoelectric effect on the crystal in the transducer head of the machine. It is used to heat tissues from 1–5 cm in depth without superficial heating. The frequency, intensity, and mode of the treatment can be modified by the therapist according to the patient's condition. TUS thermal effects mirror those of superficial heating and include vasodilation, pain relief, increased flexibility of soft tissue, and decreased muscle spasm. TUS requires a coupling medium to be placed between the sound head and the skin as air attenuates the US beam. Generally, a water-soluble US gel is smoothed over the skin and the sound head has direct contact with the gel. TUS requires specialized equipment. Phonophoresis is the delivery of pharmaceutical agents using TUS. It is commonly used in human physiotherapy but not commonly used in veterinary medicine. It has been used to deliver local anesthetics or dexamethasone into painful muscles post surgery or injury (Box 20.7 and Box 20.8).

Box 20.4 Benefits of heat therapy.

- Vasodilation, which increases circulation to tissues. This increases tissue metabolic rate, improves tissue oxygenation, and decreases tissue edema and inflammation.
- Pain relief mediated by an increase in the pain threshold.
- Decreased muscle spasm and relaxed muscle tone. This is thought to occur due to decreased muscle ischemia.
- Increased extensibility of soft tissue. Hot packing before stretching promotes flexibility and increases range of motion. When soft tissue is heated before stretching, the effect of the stretch lasts longer and less force is required to maintain an effective stretch.

Box 20.5 Clinical pearls for use of hot packs.

- If using commercial gel packs or oat bags, be sure to mix the gel or oats well within the bag before applying to the patient to avoid hot areas. Always place a towel between the heat source and the skin.
- To determine whether the hot pack will be comfortable for the patient, apply to the therapist's inner arm or neck to check the temperature. The therapist should put his or her hand between the hot pack and skin at least every 5 min to monitor the temperature.
- If using towels, fold in three and roll (if using around a joint) or accordion fold (if using for a larger area). Immerse in hot water, squeeze the water out, and apply to affected area. Cover with a large dry towel to keep the heat in.
- Always use hot packing before stretching.

Box 20.6 Contraindications and precautions for thermal therapy.

- Protect the patient's skin by wrapping the hot pack in a towel and checking the skin frequently. Discontinue heating if skin has white areas or red mottled areas.
- Do not use heat in areas of impaired sensation or with acute inflammation.
- Use with caution in obese, pregnant, and cardiac patients as well as very young or very old patients.
- Absolute contraindications include active bleeding, malignancy, fever, and open wounds.

Box 20.7 Clinical tips for therapeutic ultrasound.

- Since our patients are hairy, some therapists will shave the area before ultrasound and others will use larger amounts of gel. In the authors' opinion, clipping the hair, whether it is long or short, provides more consistent results with TUS and reduces the amount of heating in the hair coat itself.
- Phonophoresis is used with muscle strain or painful muscles secondary to IVDD surgery or medical therapy. Phonophoresis for these conditions is done using a compounded gel that is dexamethasone 0.4%/lidocaine 0.1%. The settings currently used for phonophoresis treatments is: 0.9 w/cm^2, 1 mHz, 100% duty cycle, and 4 min per probe head that will fit in the area treated (*personal communication*, Dr. HS Steinberg, DACVIM Neurology, VCA Veterinary Referral Associates, Gaithersburg, MD).

TENS is one of two electrical stimulating modalities used in rehabilitation therapy. It is used for pain control and is believed to work via depolarizing the nerve and thereby stopping painful stimuli from traveling the nerve fiber. The other electrical stimulation modality is NMES. TENS works on the sensory nerves to provide pain relief. TENS works by applying high-frequency current to the skin and causing pain relief mediated through the gate theory of pain inhibition (see Chapters 21 and 22). TENS is generally applied immediately post operatively or may be used to provide pain relief during treatment. High-intensity, low-frequency current is another form of therapeutic electrical stimulation called "acupuncture-like" TENS. It is applied to acupuncture points and causes endorphin release. NMES is most frequently used in the rehabilitation of neurologic patients. NMES is used to stimulate motor nerve and muscle fibers. A different piece of equipment is used for TENS versus NMES. NMES is useful for tetraparetic or paraparetic animals. It is used for contracting muscles, reducing edema, and assisting wound healing. In a weight-bearing animal, it can be used to increase the force of contraction. It can also be used to assist gait retraining after surgery or injury. Electrical stimulation is applied from the unit by leads and electrodes. These must be flexible and conform to the skin. The electrodes need to have low resistance, be highly conductive, inexpensive, and reusable (Box 20.9 and Box 20.10).

Box 20.8 Precautions and contraindications for therapeutic ultrasound.

- Avoid TUS over cardiac pacemakers, over the eyes, the gravid uterus, or the testes, over the spinal cord post laminectomy, over open epiphyseal plates, bleeding areas, areas of infection or malignancy.
- Caution should be used over fractures, in areas of decreased circulation, heightened temperature, or pain sensation, in sedated animals, in areas of bony prominences, and over metal implants.

Box 20.9 Parameters and recommendations for NMES.

- Frequency 25–50 Hz.
- Pulse duration 100–400us.
- Ramp up and down 2–4 seconds.
- On/off time ratio 1:3–1:5.
- Treat daily or at least three times weekly.
- Amplitude sufficient to cause contraction.
- Postoperative NMES works best in the first 1–4 wks.
- NMES is of questionable value in cases of LMN disease.

Most TENS and NMES machines come with disposable electrodes meant for human use. They have limited use for veterinary patients due to hair. Nonsticky carbon electrodes which can be gelled and taped to the skin are preferable. Treatment time is generally 15–20 min.

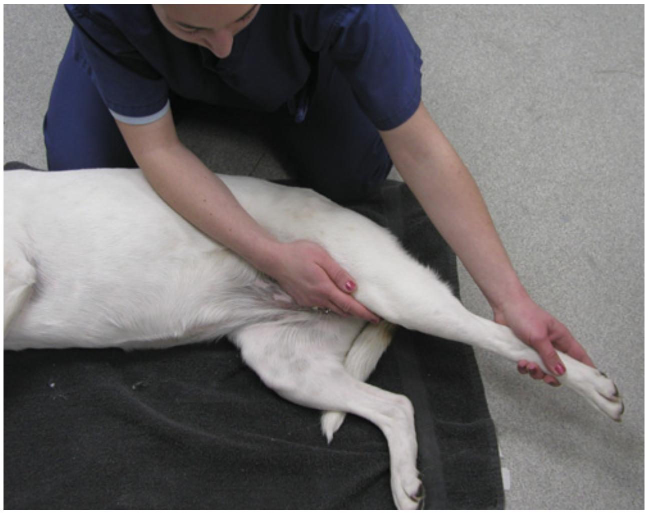
Three common manual therapies used by rehabilitation therapists are joint mobilizations, massage, and passive range of motion (PROM) or stretching. Joint mobilization is used to assess the joint and improve the actions between joint surfaces (joint arthrokinematics) and involves stretching the joint capsule, ligaments, and any fibrous tissue that may be present. Joint mobilizations include glides, oscillations, distractions, and compressions of the joint. Massage or soft tissue mobilization (STM) is another form of manual therapy used in rehabilitation. Manual manipulation of the tissue can increase circulation, loosen stiff muscles, reduce excess interstitial fluid, and minimize muscle atrophy. Massage is particularly important in the neurologic patient who may be recumbent, have some paresis or painful and stiff muscles. Massage can also be beneficial prior to stretching exercises to improve range of motion, relax the patient before more aggressive therapy can be instituted, and provide increased circulation There are a number of massage techniques that can be employed depending on the needs of the patient. Goals of massage must be communicated between veterinarian and technician, and appropriate rhythm, pressure, duration, and frequency established on an individual basis. Techniques such as

Box 20.10 Precautions and contraindications for electrical stimulation.

The following applies to any type of electrical stimulation whether for pain relief or strengthening.
Electrical stimulation is contraindicated:
- over the heart and in animals with pacemakers
- over the pregnant uterus
- over areas of neoplasia or thrombosis
- in animals with seizures
- over the carotid artery.

Caution should be used in areas of skin damage or decreased sensation.

compression, kneading, and stroking (effleurage) are effective therapies, particularly in the recumbent patient. Effleurage is by definition a deep-stroking movement specifically designed to circulate venous blood flow and encourage lymphatic drainage. Typically, massage begins with effleurage in order for the technician to assess the patient's pain response, muscle tone, and detection of any fibrotic areas. Petrissage is short, quick strokes with moderate to deep pressure that is parallel perpendicular, or across the direction of the muscle fibers. Wringing, skin rolling and kneading are all part of petrissage. Tapping on the muscle or tapotement is done with finger tips to stimulate weak muscles. Friction or cross friction massage is moderate pressure applied to scars, tendons and ligaments. It can be perpendicular to the tendon, along the tendon or circularly over the tendon. It is used to break up scar tissue and is usually done for 5–10 min. Trigger point therapy is a technique that applies digital pressure to a trigger point—a firm, tender area of muscle. Trigger points can be treated with pressure, dry needling or injection. The pressure of massage may vary, depending on the goal of massage therapy. Appropriate pressure should be light to moderate in order to relieve tension and to decrease edema. If fibrotic areas are present, pressure of massage should be increased. It is important to monitor response in the patient and to avoid excessive pain. Massage therapy should be implemented three to four times daily, for 10–15 min to each affected area, in conjunction with other forms of therapy mentioned below. Technique of massage or effleurage may vary. The authors prefer to start with the distal aspect of each affected limb and apply light to moderate pressure in smooth movements with the fingertips running lateral and medial before returning distally and removing pressure. Using the palm of the hand, kneading or twisting the skin may also improve circulation and create an effective massage to larger muscular groups. Massage technique should not be applied to areas with soft tissue damage or skin grafts.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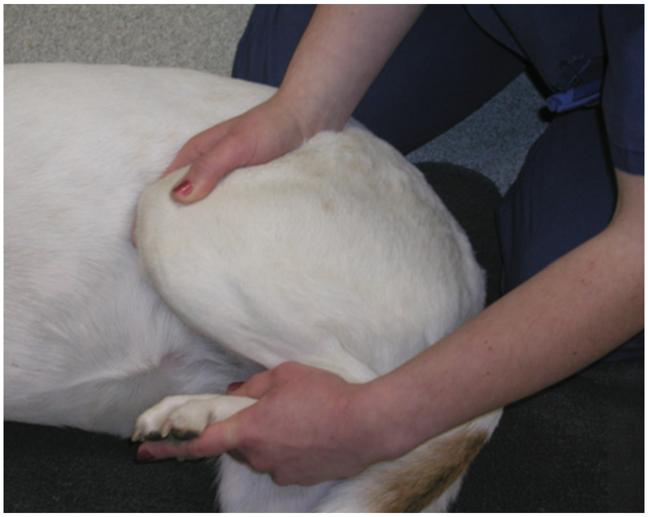
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Figure 20.10 Passive range of motion exercises, extension (A) and flexion (B).

Stretching or PROM exercises are an important form of physical therapy that can be performed by both technician and owner. Benefits of PROM include joint homeostasis, preventing range of motion loss in joints, improved circulation and lymphatic drainage, prevention of muscle atrophy, and prevention of tissue adhesions. Similar to other forms of physical therapy, it is important for effective communication between veterinarian and technician with regard to the goals of physical therapy on an individual basis. Ideally, PROM exercises should begin the day after surgery or injury, unless there is severe soft tissue damage or orthopedic injury. Passive range of motion is accomplished through a series of repetitious motions. It is the authors' opinion that each limb should be cycled individually in order for an adequate assessment of function and range of motion of all limbs to be made. By holding the foot with one hand and grasping the caudal aspect of the stifle or elbow with the other, the limb is pulled forward and then back in a cycling motion (Fig. 20.10). It is recommended to perform 5–10 flexions and extensions first on individual joints before flexing the entire limb. Flexion and extension exercises should be scheduled at least three times a day (Box 20.11). Particular attention should be given to the limb that is injured or surgically repaired and caution used with regard to the patient's pain response. Geriatric patients require careful flexion, as fragility of bone density may be an issue. Patients with sensory nerve impairment must also be flexed with caution, as pain response may be absent. The goal of PROM is to cycle the limbs through a normal range of motion with normal joint motility. Hot packing and massage may be initiated prior to range of motion exercises to facilitate muscle and joint compliance. Combining sling therapy with PROM exercises can also provide added physical benefit to the patient. Providing a more natural sternal position without added limb stress permits gravity to pull the limbs for increased circulation and stimulation. The gravity supplied by the sling will also promote drainage and decrease edema that often develops with recumbent patients.

Box 20.11 Clinical pearls for passive range of motion exercises.

- In neurologic patients, PROM works best after heating the tissue with hot packs to warm up the muscles.
- Neurologic patients are at risk of contractures of tendons and ligaments. PROM mitigates this condition.
- Do each joint of the affected limb in flexion and extension approximately 10 times before entire limb is flexed. This avoids pain and spasm.

After stretching and PROM, it is important to re-educate the muscles that are unresponsive. Generally, these are muscles that are antagonistic to those shortened through contracture or by spasticity. This re-education process takes place through proprioceptive neuromuscular facilitation (PNF) patterning. PNF is used to simulate movement patterns that are ingrained and functional. Common patterns are walking, running, scratching, sit to stand, movement from lateral to sternal recumbency, kicking back, turning, and many others. PNF patterns can be done in any position depending on the disability. One example of PNF patterning is rhythmic stabilization. This involves placing a dog in normal standing position or sternal recumbency and applying a resistance in one direction that is gradually decreased and then applied in the opposite direction. This movement strengthens the patient's isometric contractions. Passive running is another PNF pattern that is easily performed.

Therapeutic exercises are used to reduce pain, strengthen muscles and joints, mitigate muscle atrophy, and improve proprioception and balance. One common exercise used in non-ambulatory patients is assisted standing. An exercise ball may be used to assist standing or to increase weight bearing on the thoracic and/or pelvic limbs (Fig. 20.11). The exercise ball also provides greater lateral support and can relieve stress on the handlers. The size of the ball should allow the patient to touch the ground with all four feet; if the roll is too tall, it may be deflated slightly. Once the patient is secure on the ball, one person should stabilize the front of the patient while another stabilizes the rear. As the patient is supported in a standing position, the technician can generate a very gentle up-and-down "bouncing" motion through the patient and the inflated ball. Such activity will provide proprioceptive input and stimulate contraction of the limb muscles. In addition, rolling the ball forward and backward will provide weight-bearing exercises to the thoracic or pelvic limbs. As the patient's strength increases, these techniques may be performed at faster speeds to challenge balance and neuromuscular function. Exercise ball techniques may require more patient conditioning and technician training than other traditional rehabilitation techniques (Box 20.12). NMES can also be utilized with these techniques to facilitate and increase the force of contraction. Other standing exercises utilizing rocker boards and slings/harnesses may be incorporated into the exercise regime also. Sling therapy is an important aspect of rehabilitation therapy, particularly in the recumbent patient. Slings can be constructed out of plastic piping (Fig. 20.12) or aluminum

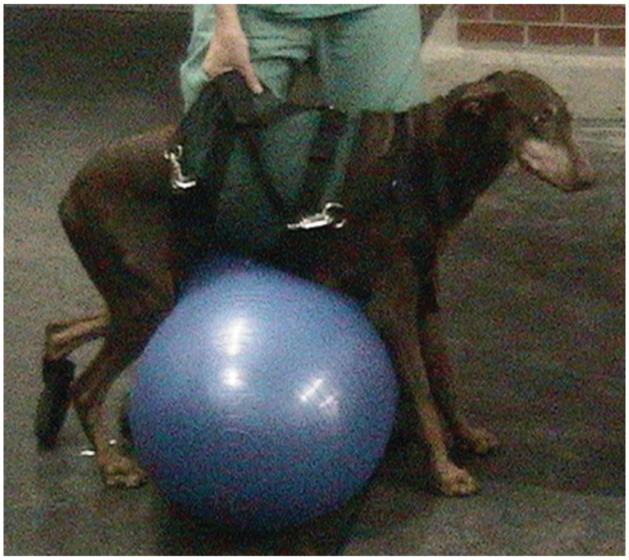


Figure 20.11 Using an exercise ball for physical therapy in a caudal cervical spondylomyelopathy patient.

Box 20.12 Exercise tips.

- Do not start therapeutic exercises in a patient with an unstable spine.
- Mini trampolines are useful for small patients. Have the animal walk on stand on the trampoline while the therapist creates a small bounce.
- Use a glider or rocking chair to improve standing balance. Put the patient on the chair and rock it while holding the patient so he does not jump off.
- Walking forward, backward, or sideways through a ladder helps with proprioceptive training.
- Walking on air mattresses, bubble wrap, or other varied surfaces provides different tactile sensations.

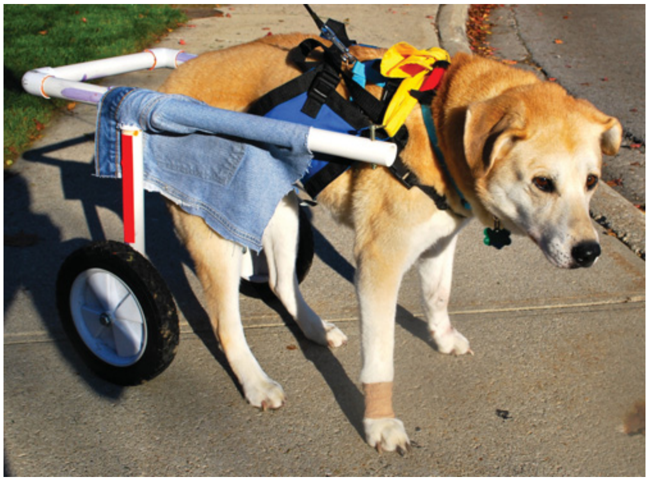


Figure 20.12 Support sling constructed of plastic piping material.

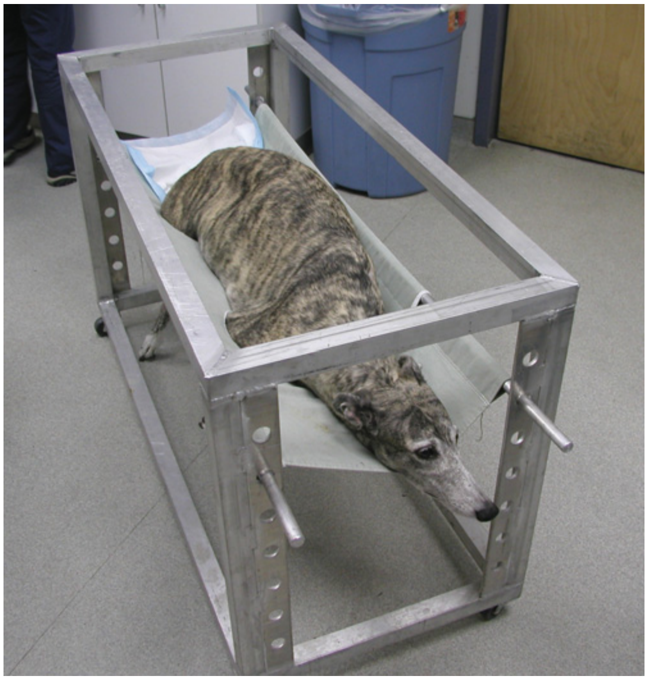


Figure 20.13 Support sling constructed of aluminum-welded pipes.

welded pipes (Fig. 20.13) for long-term use. Sliding pipes can hold canvas or cloth harnesses with holes for each limb. Either design can provide the patient with adequate support to maintain sternal positioning for therapy exercises or chest physiotherapy. Limb edema is decreased with the use of sling therapy, and it provides optimum positioning for massage, range of motion exercises, and nebulization/coupage therapy. Bladder care can be easily addressed while in the sling using manual techniques; the patient can also be encouraged to urinate voluntarily while in an upright position. In addition, placing a patient in a sling provides sternal positioning for feeding, which is important in the recumbent patient to prevent aspiration pneumonia. Patients placed in slings should have the pads of the feet touching the floor mats to encourage voluntary motion. Slings with wheels attached can allow patients to walk about the hospital with little aid or support. Owners can be encouraged to build a sling apparatus device for long-term paresis/paralysis patients. Sling therapy is particularly useful in preventing lung atelectasis and accumulation of respiratory secretions in dependent airways. Lung consolidation can occur with any patient that is recumbent (see "Respiratory care" section above). The sling provides the patient with a means to stay sternally recumbent; this enhances drainage of respiratory secretions, lung expansion, and overall ventilatory efficiency. Caution should be exercised when placing the patient into the sling as the patient may have stiff joints or various orthopedic conditions. Recumbent patients should be placed in a sling every 4–6 hrs, with physical therapy sessions in conjunction with sling therapy, chest physiotherapy, hot or cold packing, bladder care, and feeding. Patients should remain in the sling for 30 min to 1 hr and be monitored closely for discomfort or anxiety. The patient may require additional cervical or thoracic support in the form of pillows or rolled towels while in the sling. Initially, it may be necessary to place a patient in the sling device for shorter periods until the patient has adjusted to being constrained in an upright fashion. During sling therapy, the patient should be monitored closely, particularly if the patient has pneumonia (see "Respiratory care" section above). Respiratory patterns should be monitored to ensure that the animal is not stressed during therapy.

Hydrotherapy is another form of rehabilitation therapy advantageous to the neurologically impaired or recumbent patient. Hydrotherapy, or swimming exercise, provides extensive joint and muscle activity in a non-weight-bearing setting. Hydrotherapy can be achieved using a tub or pool equipped with an electric pump to create waves or ripples against which patients swim (Fig. 20.14). Patients need close supervision during hydrotherapy to prevent drowning or severe injury. Flotation devices and harnesses designed specifically for canine use are recommended during hydrotherapy. Physical support to the cervical and thoracic areas is recommended during hydrotherapy, even when using a flotation device. If the patient becomes distraught or frantic during hydrotherapy, treatment should be

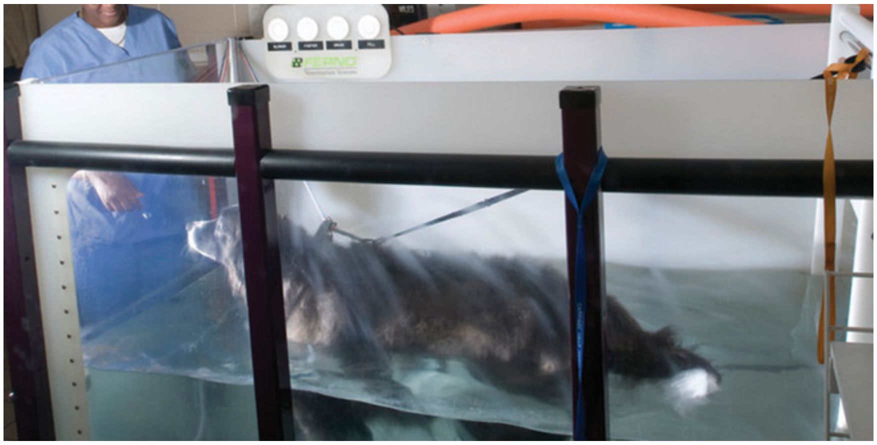


Figure 20.14 Hydrotherapy of a paraparetic patient using an underwater treadmill apparatus.

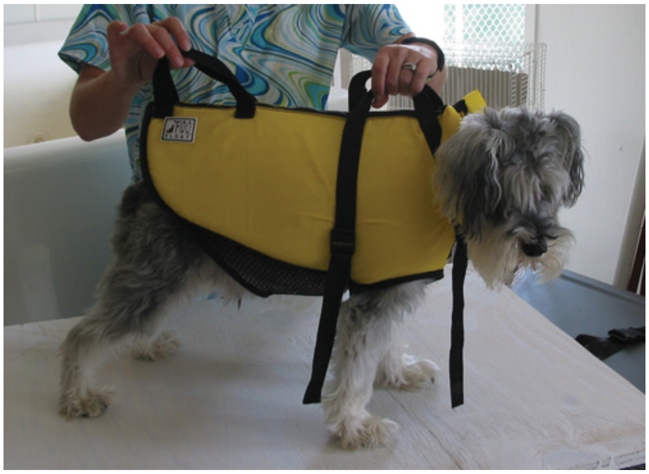


Figure 20.15 Use of a life-vest for a dog to provide thoracic support during hydrotherapy.

discontinued and attempted again the next day. Hydrotherapy should be limited to 5 min per day, as swimming exercises are exhausting. Specialized veterinary life-vests can be utilized as a sling device to help provide thoracic support during hydrotherapy (Fig. 20.15). Many such specialty vests contain handles on the top of the jacket for quick and easy grabbing. Slow, methodical "bobbing" of the patient while wearing a vest in a whirlpool can strengthen periarticular muscles, increase limb perfusion, and improve joint mobility. Underwater treadmill therapy (UWT) offers many advantages to the patient needing exercise for atrophied muscles or to regain range of motion lost due to injury or disease (e.g. IVDD, FCE). UWT can also provide treatment for temporary paralysis and coordination disorders of the musculoskeletal system. UWT allows for variability in exercise speed, temperature, and water depth in order to increase or decrease weight bearing. Buoyancy provided by the water removes pressure from painful limbs; elevated water temperature allows for muscle relaxation, pain reduction, and soft tissue extensibility. As extra balance is required on the treadmill, the viscosity of the water allows for the ability to bear weight on guarded limbs and recruit new muscle groups and complements neuromuscular re-education. The water's viscosity also provides increased proprioceptive and tactile stimulation. Short sessions of UWT followed by longer exercises times are generally recommended; the patient should be monitored closely for signs of fatigue. Slow speeds (0.1–0.6 mph) are used in dogs that have neurologic problems since the viscosity of the water gives patients more reaction time to step correctly instead of dragging their feet. Moderate speeds (1–2 mph) are used for most postsurgical and arthritic patients. Fast speeds (> 2.0 mph) are only used for patients more advanced in their rehabilitation. All patients should be monitored closely during UWT to prevent accidental drowning.

As with any active therapy, overall health must be evaluated before initiating UWT. Flotation jackets and/or harnesses are recommended, particularly if the patient is tetra or paraparetic. Changing the water depth can markedly alter motion and exertion levels. Generally, low water levels (slightly above the carpus) increase carpal and hock flexion and are useful in patients with reduced flexion of these joints. Water levels at or around the elbow provide resistance with minimal buoyancy since the chest is not displacing water. Water levels at or above the scapula have maximum buoyancy for strengthening the limbs with minimal stress on the joint, beneficial in patients with osteoarthritis or recovering from surgery in which full weight-bearing is contraindicated or painful (Box 20.13).

Box 20.13 Hydrotherapy tips.

- Water should be 82–88 degrees Fahrenheit depending on the time of year.
- UWT water should be at the level of the greater trochanter for most patients.
- Speed is dependent on dog size and condition. Generally, neurologic patients are started at 0.1–0.6 mph and adjusted accordingly. The dog should be able to walk at a normal pace.
- Most neurologic patients start with three short sessions of 1–3 min with breaks for massage and PROM.
- Use swim diapers for all neurologic patients. Express the bladder for patients with urinary incontinence and stimulate them to defecate by using a cotton swab in the anal area.
- Animals with diarrhea, poor anal tone, or open sores are not allowed to have hydrotherapy.

Exercise for the recumbent or neurologically compromised patients can be accomplished by using body slings or towels. Towel walking a patient can be a safe way to begin exercises and to encourage muscle movement (Fig. 20.16). It is important to support the paretic area with a towel and to prevent the limbs from dragging on the ground. Tail walking, or using the

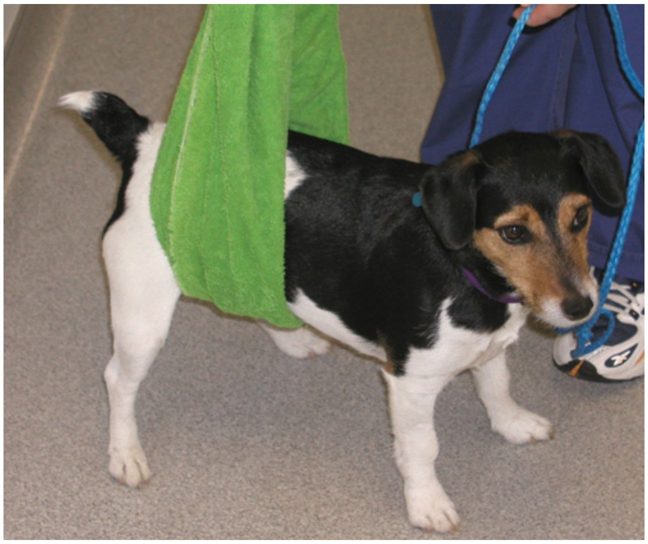


Figure 20.16 Towel walking a paraparetic dog.

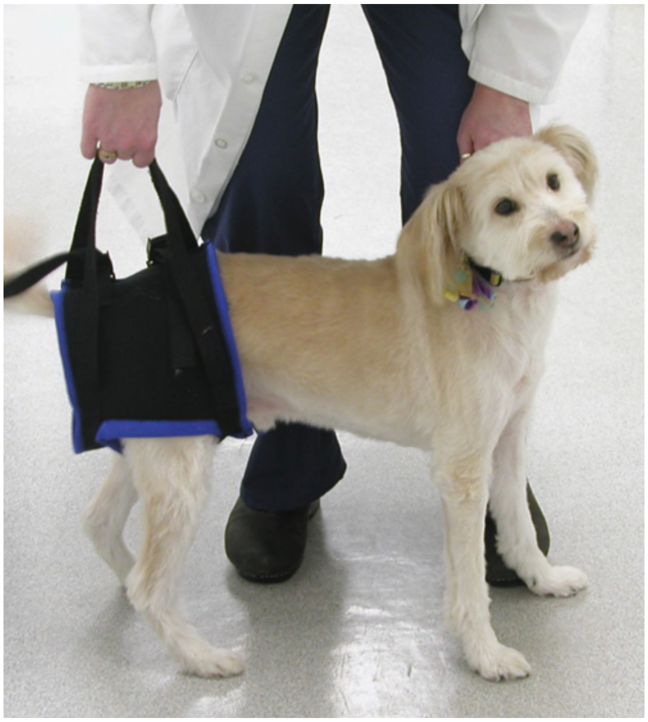
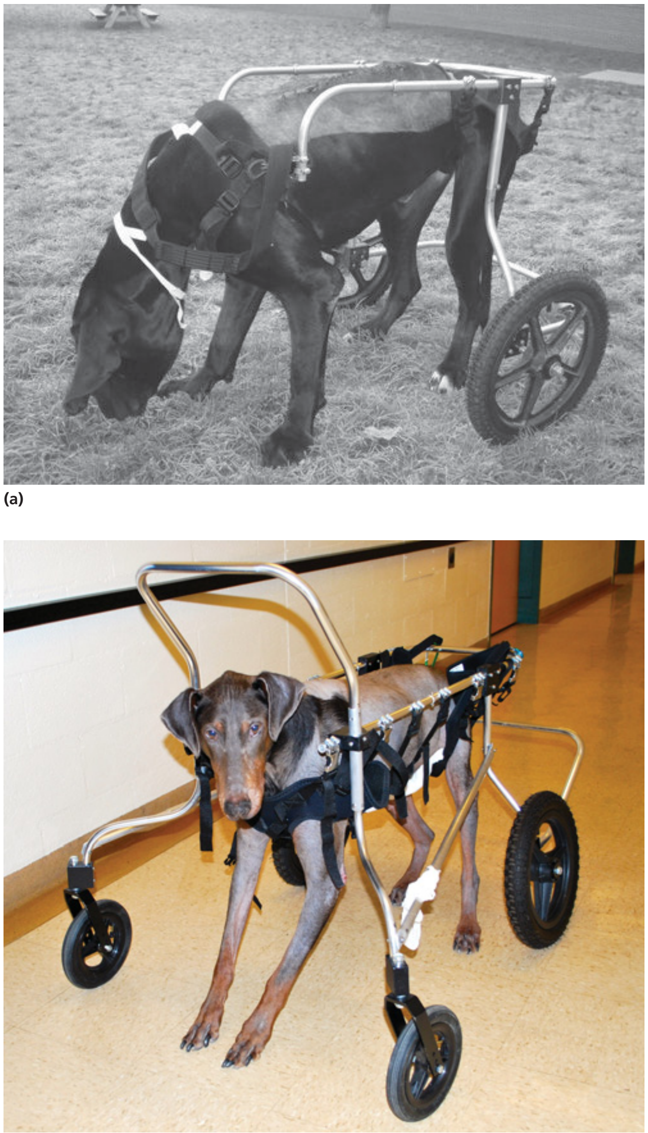


Figure 20.17 Use of a commercially available support device (Walkabout harness) to walk a paraparetic dog.

tail as a means to hold a patient upright, is generally not recommended. Towel walking should not be practiced in patients with unstable vertebral fracture/luxations or patients with orthopedic problems that may be exacerbated by towel walking (e.g. pelvic fractures).

Paraparetic patients can also be exercised by means of body slings. These slings maximize patient comfort, provide superior support, and are convenient for pet owners (Fig. 20.17). The paretic limbs should not be dragged along the ground while the sling is used; rather, the harness should elevate the patient so that the limbs are supported slightly by the ground surface. This will encourage voluntary movement and prevent abrasion of the toes. Pet owners should be encouraged to purchase the body slings and assist their pets in early postsurgical ambulation. Commercially available custom canine carts are also available in four-wheel and two-wheel models for patients with paralysis, paresis, degenerative myelopathy, or generalized weakness. The carts are designed to assist the patient with independent ambulation; the carts must be sized and fitted to ensure comfort and proper function. Most manufacturers will provide the client with specific instructions regarding proper measurements to ensure a custom fit. The mobility carts foster independence that will produce a positive effect on both the animal and the client's attitude. The home environment may need to be altered to allow the animal to ambulate freely without obstruction or accidental injury (Fig. 20.18A and B). Specialized bags are also available for small pets to use at home when not in a cart, designed to prevent urine infections and sores. Hydrotherapy and other rehabilitation therapy exercises are still recommended for the patient using a cart, in order to maintain forelimb strength and range of motion.



(a)

(b)

Figure 20.18 Commercially available custom carts for use in nonambulatory paraparetic (A) and tetraparetic (B) patients.

There are many basic at home therapeutic exercises for the dog to help improve weight bearing, range of motion, and limb strength. Pelvic limb strengthening can be accomplished by stair climbing; choose stairs that are wide and closed. Begin by walking up and down stairs 1–2 times daily, starting with a small number of steps and slowly increase as strength improves. Backward-walking maneuvers can also improve pelvic limb strength and proprioception. Begin by holding the dog's head and gently forcing it to take one or more steps backward, praising the dog for reinforcement. Walking a dog backward for a distance of 6–10 ft, repeating several times, for 2–3 times a day

Box 20.14 Beneficial physiological effects of laser therapy.

- Chromophores in the cell mitochondria absorb the laser light energy and this causes increased oxygen production, adenosine triphosphate (ATP) production, increased cell permeability, DNA production, and decreased cyclooxygenase and prostaglandin E2 production.
- Stimulation of stem cells.
- Promotion of tissue repair through angiogenesis, stimulation of fibroblasts with collagen synthesis, and growth factor release.
- Increased activity of leukocytes.
- Increased healing of nerves, connective tissue, and ligaments.
- Pain reduction through change in nerve conduction and increased levels of endogenous opiates or through stimulation of acupuncture points.

will help gain pelvic limb strength. Other simple therapeutic exercises to strengthen pelvic limbs include sit to stand exercises, improving range of motion and limb strength. Uphill walking can improve spinal extension, pelvic limb strength, and weight bearing. Weight management is also encouraged to promote spinal health and to prevent future injury or disease.

Laser is an acronym for “light amplification by simulated emission of radiation.” Lasers used for therapy are different from surgical lasers and are considered low-level lasers or therapeutic lasers depending on the power they deliver. A laser is by definition collimated and monochromatic. The wavelength determines the penetration of the laser energy. There are a number of proposed physiologic effects of laser therapy (Box 20.14). Laser therapy can also be added to traditional rehabilitation therapy for the temporary relief of postoperative muscle and spinal pain, arthritis pain, or to increase blood circulation to poorly perfused areas in recumbent patients. Laser therapy uses light to stimulate tissues to produce positive physiologic effects such as the reduction of inflammation and subsequent increase in circulation. Components of laser therapy include the wavelength of the laser, power of the probe, frequency, and dosage. The wavelength determines the depth of penetration of the laser light into the tissues; the longer the wavelength, the deeper the penetration (depth of absorption of the light). The power of the probe determines the time to deliver the energy (measured in milliwatts [mW]). The higher the mW, the shorter the time is required for a therapeutic dose to be delivered. The frequency is the rate at which the laser diodes are on and off and it is measured in hertz (Hz). The dosage is the amount of energy needed to produce a therapeutic effect and it is measured in joules. The current recommendations of laser dosing are 2–6 joules/cm^2 for superficial penetration and 8–16 joules/cm^2 for deep penetration (World Association for Laser Therapy, http://www.walt.nu). There are four classes of laser as determined by the number of milliwatts of power. Clinical indications for laser therapy include but are not limited to pain, tendonitis, osteoarthritis, muscle spasms, IVDD, inflammation, scar tissue, wounds, and decubital ulcers (Box 20.15). Laser therapy is applied by slowly scanning an affected area with a small hand device; there is no need for chemical restraint and there is no pain associated with the procedure (Fig. 20.19). Length and number of treatments required are highly variable and based on the underlying disease (Box 20.16). There are also therapeutic devices that combine laser technology with the delivery of a static magnetic field (TENS) to improve tissue health. Such devices will simultaneously operate two emitters in order to improve tissue health.

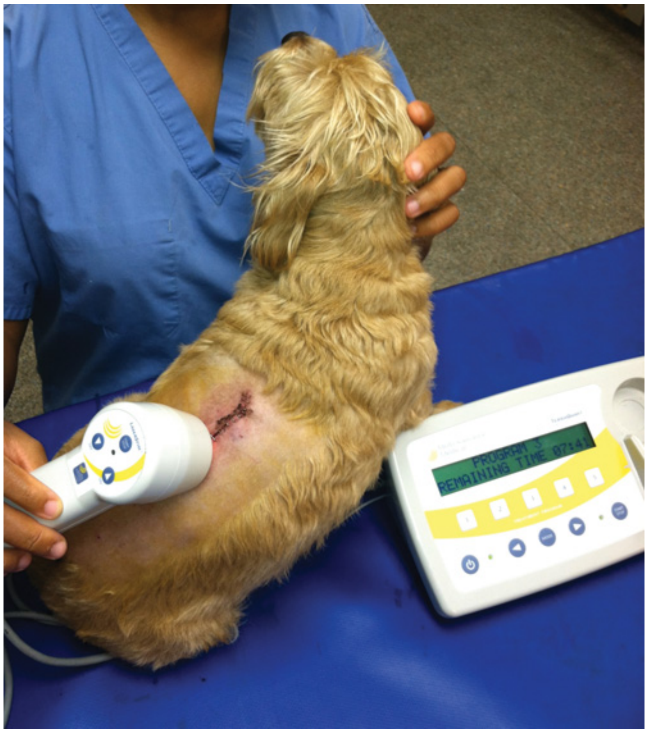


Figure 20.19 Low-level laser therapy for postoperative thoracolumbar intervertebral disc herniation.

Seizure management

Seizures are classified as focal (partial) or generalized. Clinical manifestations of a focal seizure can include rapidly running in circles, hypersalivating, exaggerated chewing motions, or an acute change in consciousness or behavior. Generalized seizures involve the whole body with an alteration or loss of

Box 20.15 Clinical pearls for laser therapy.

- Icing for 5 min improves penetration of laser therapy and can be used in large dogs for areas of deep penetration.
- Laser works well for dogs with IVDD post surgery for a T3–L3 lesion. If laser is applied daily for 5 days post disc surgery, time to ambulation is decreased.
- When using a class 3b and class 4 laser in dogs with dark hair, hold the head off the skin by 1 inch to avoid heating the hair.

Box 20.16 Precautions and contraindications for laser therapy.

- Use protective eyewear and do not treat the eye area.
- Use caution with metal implants.
- Use caution with seizure patients.
- Do not treat over the gravid uterus, neoplasia, growth plates, or open fontanels.
- Dark-colored skin will absorb more light and can undergo excess heating. Adjust your laser settings accordingly.

consciousness. (The subject of seizures is covered in more detail in Chapter 9.) The patient may fall to the ground and rigidly extend its limbs, followed by running or paddling motions, chewing motions, and may also involuntarily urinate or defecate. Seizures may alternate between focal and generalized, with duration ranging from seconds to minutes. Clinical signs of vestibular diseases can often be confused with seizure activity. Signs of vestibular disease include nystagmus, rolling, tilting of the head, circling, asymmetrical ataxia, and salivation from motion sickness (see Chapter 11). Patient support for vestibular patients should include monitoring for vomiting or aspiration, administration of antiemetic or antinausea agents if necessary, supplying padded cages to prevent injury, and ensuring adequate hydration and nutritional intake.

It is important for the technician to take action during either type of seizure. The patient must be immediately placed sternal, with the head angled down to prevent aspiration. The head and neck should be cradled or supported to prevent traumatic injury. Intravenous access should be established for the administration of anticonvulsants, if a catheter is not already in place. Oxygen should be administered immediately after the seizure via flow-by method. The patient may be disoriented, hypersensitive, and possibly aggressive after a seizure. Support the body in sternal position and keep environmental noise to a minimum. Note that the patient may also have dilated pupils, salivate excessively, vocalize, or vomit immediately after the seizure. Rectal temperature should be taken immediately after a seizure. In addition, serum blood glucose should be tested to rule out hypoglycemia as a cause for the seizure. Suction should be performed if the post-ictal patient has excessive salivation or vomitus in the oral cavity in order to prevent aspiration or airway occlusion. Cotton balls may be placed in the ears to minimize sensitivity to sound.

Patients may seizure after myelography. It is important to elevate the head with towels or pillows while the patient is recovering after a myelogram in order to limit seizure activity (Fig. 20.20). The post-myelogram patient should remain on intravenous fluids 24 hrs after the procedure.

Level of consciousness[38]

Recording vital signs should always begin with level of consciousness (LOC). It is important to note that problems associated with the central nervous system (CNS) may be the first clue of forthcoming complications. CNS signs may reflect a systemic disorder or a disorder secondary to either anesthesia or the surgical procedure. Clinical signs may include lethargy, aggression, coma, blindness, or hyperexcitability. History of prolonged anesthesia may also result in hypoxia, embolism, increased ICP or hemorrhage, thrombosis, hypoglycemia or hypocalcemia, and drug reactions. If any abnormalities in the LOC exist, an extensive physical examination, including appropriate hematologic testing, should be emphasized. Pupil size and pupil reactivity should be included in the physical examination. Technicians should also monitor patient mentation using the Modified

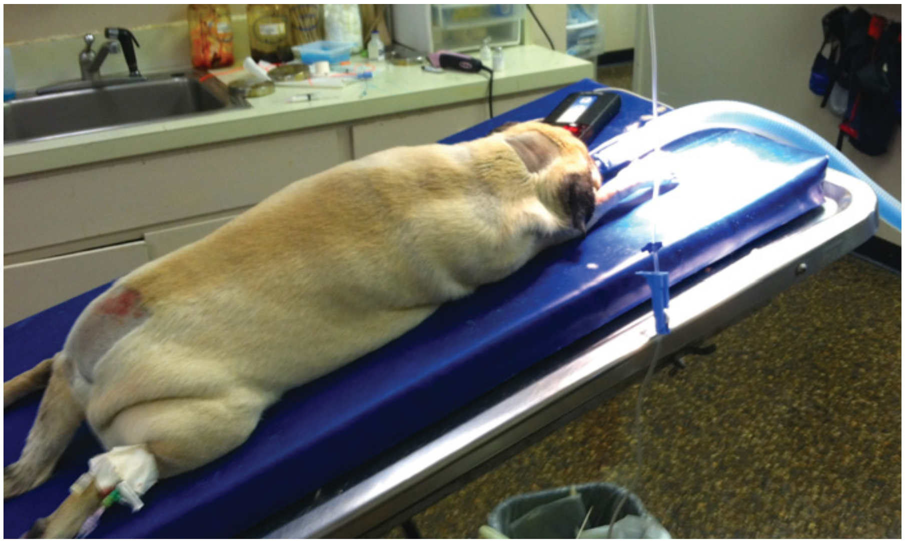


Figure 20.20 Elevation of a dog's head following myelography.

Glasgow Coma Scale (MGCS) system (see Chapter 8). Prognosis is correlated to depth of coma; typically, the lower the score on the MGCS, the worse the prognosis.

Patients with a poor LOC should also be monitored for signs of increased ICP. Poor perfusion of the brain stem can trigger the Cushing's response, which is a massive sympathetic discharge manifested as a high blood pressure and low heart rate (reflex bradycardia). Technicians should monitor heart rate and blood pressure frequently without stress to the patient. Other nursing measures to decrease ICP include:

- Do not occlude the jugular veins.
- Positional techniques—place the head at 30° from the horizontal plane to maximize both venous drainage and arterial supply to the brain.
- Prevent coughing, sneezing or vomiting; consider antiemetic therapy. Avoid nasal cannulas if possible.

Nutrition[30]

Any patient that is anorexic or who has not eaten for 3 days or longer is considered to be at risk for malnutrition. However, particular concern for nutritional insufficiencies includes patients with increased metabolic stress levels, including patients with neurologic diseases or head injuries. The hypermetabolic state these types of patients exhibit results from increased catecholamine releases in order to increase their fuel production. Unfortunately, the increased metabolic rate and subsequent tissue catabolism rapidly exacerbates weakness in patients without nutritional support. Even more serious is the loss of visceral proteins—such as serum proteins, immunoglobulins, and leukocytes—needed to maintain immunocompetence to fight infection. Undernourished patients are three times as likely as well-nourished patients to have major surgical complications. Wound dehiscence, decubital ulcers, sepsis, and pulmonary complications such as pneumonia may occur secondary to poor nutritional status. Pediatric patients are especially susceptible to malnutrition and often present with dangerously low blood glucose levels.

Development of malnutrition can be hospital-related. Frequent diagnostic testing, stress from being apart from owners, lack of sleep, or unregulated pain can cause a patient to stop eating. Good communication between the nursing staff should include a patient's behavior and eating habits during patient rounds. Other practices known to adversely affect the nutritional status of hospitalized patients include the failure to record a daily body weight, lack of nutritional intervention after surgical procedures (particularly if the patient is kept sedated on heavy infusions of analgesia), medications causing inappetence or nausea, and improper diet types.

Nutritional support to patients with neurologic diseases is essential for recovery. Providing nutrition prevents loss of functional body tissue, as there is no true reserve of protein in the body. The enteral route is preferred whenever possible, as this route is safer and much less expensive than parental feeding. There are a variety of enteral tubes used for patients who have at least some digestive and absorptive capability but who are unwilling or unable to consume food by mouth. The location and type of feeding tube depends on both the length of time feedings are anticipated and the patient's injury or illness. Sites of intubation include nasogastric, nasojejunal, esophageal, pharyngeal, and jejunal. Patients with megaesophagus may require long-term gastrostomy tubes to eliminate the risk of aspiration. If patients with megaesophagus are fed by mouth, frequent small amounts of moist "meatballs" are recommended, with the patient eating in an upright position and held upright for a minimum of 30 min after ingestion. Specialized feeding Bailey chairs can be utilized in order to keep the animal upright during and after meals, allowing gravity to take the food into the stomach (www.caninemegaesophagus.com). Patients can also be placed in a large box or padded trash can in order to remain upright after feeding (Fig. 20.21).

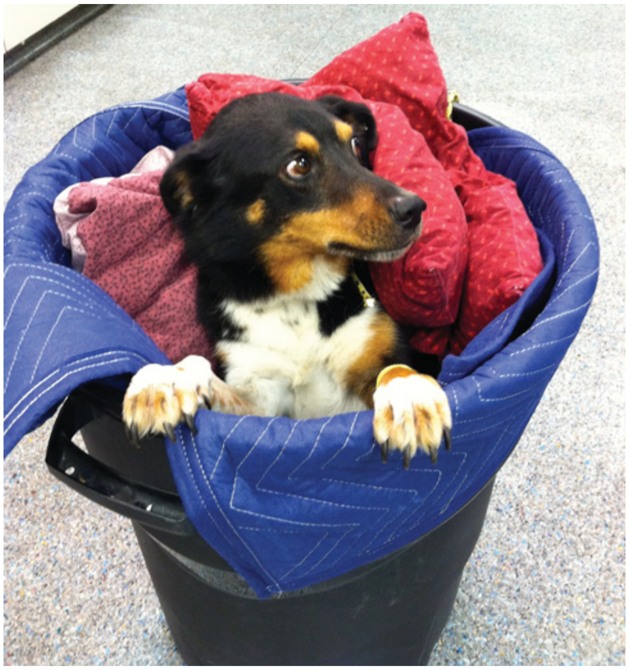


Figure 20.21 Maintenance of a dog with megaesophagus in an upright position following feeding.

Nasogastric, nasojejunal, and jejunostomy tubes are most often used when there is danger of pulmonary aspiration; the pyloric sphincter provides a barrier, which appears to lessen the risk of regurgitation and aspiration. Jejunostomy tubes also have the added advantage of being able to bypass an upper GIT obstruction. Advantages of these particular feeding tubes include ease of insertion, low cost, variability in size and length of the tubes, radio-opaque insertion stylets, and fenestrated ends to facilitate ease of nutritional delivery. Nursing responsibilities often include tube insertion (nasogastric and nasojejunal) in which proper techniques are critical. It is often required to ensure patency after placement by radiographic techniques, although prior to food administration the tube should always be aspirated for negative pressure and proper gastric emptying to avoid gastric distension. Suturing techniques are recommended in lieu of tissue glue, as nasal and skin erosion can occur.

Other types of enteral devices include pharyngeal, esophagostomy, and gastrostomy tubes. Usually intended for the patient needing long-term nutritional support, general disadvantages of these types of feeding tubes include the need for anesthesia. Relatively inexpensive, these specialty tubes generally require the same type of nursing care as other enteral feeding tubes. Regardless of tube type, careful attention to both maintenance and administration of feeding solutions can prevent many complications. Maintenance of the tubes requires regular irrigation to maintain patency, particularly after feedings. Diets should be run through a blender and strained, particularly when using smaller diameter tubes. Very clean techniques in the handling during both tube placement and diet delivery can help prevent many complications. The skin around the tube should be cleaned at least daily, inspected for fluid leaks, and the tape or bandage around the tube changed daily. The tube should be marked with permanent marker where it enters the skin in order to monitor correct placement. A light bandage or dressing is recommended for most feeding tubes to keep the entry site clean. If constant rate infusions are required, the administration bag should contain only a few hours of solution at a time to avoid curdling.

Patient response to feedings is important during administration. Patients that show signs of discomfort during feeding—such as restlessness, salivation, or vomiting—can be exhibiting signs of improper tube position. Other potentially serious complications of tube feedings include pulmonary aspiration, diarrhea, constipation, tube occlusion, peritonitis from improper tube position, and delayed gastric emptying. Such complications can be avoided by checking tube placement prior to feeding, measuring gastric residue before each feeding, monitoring gastric tubes for migration during daily bandage changes, and evaluating both diet type and concurrent medications to determine the cause of the diarrhea or constipation. Auscultation, with a stethoscope over the four quadrants of the abdomen in order to monitor bowel sounds, are recommended in any recumbent patient. Prokinetic agents may be considered if bowel sounds are absent, or if significant gastric residue is present.

To prevent pulmonary aspiration of gastric contents, recumbent dogs should be fed smaller meals more frequently and only when in a sternal position. Certain neurologic conditions can also predispose a patient to aspirate stomach contents. Such conditions include head trauma, coma, seizures, laryngeal/pharyngeal dysfunction, depressed mentation, and abnormalities of esophageal function (e.g. myasthenia gravis). Central depressant medications (sedation) can also impair protective airway reflexes and increase the potential for aspiration. Prevention of aspiration includes ensuring a cuffed endotracheal tube when anesthetized, and fasting for a minimum of 6 hrs prior to sedation. The use of H^2 antagonists and omeprazole to reduce gastric volume and acidity via inhibition of gastric acid secretion in patients considered high-risk for aspiration is advised. Intravenous metoclopramide is recommended for nonfasted patients requiring emergency anesthesia. Before the endotracheal tube is removed, the patient should be awake and have normal laryngeal reflexes.

Bacterial contamination can also occur during enteral tube use. It is important to use clean techniques during tube placement and handling, to keep opened containers of formula refrigerated and discard after 48 hrs, and to routinely change enteral bags and administration lines every 24 hrs.

In some instances, neurologic patients are considered to be overweight. In the metabolically stable patient, obesity may hinder recovery or predispose the patient to slower recovery and further injury. Nutritional management is therefore paramount for successful rehabilitation. Due to the limited activity of many neurologic patients, energy requirements are typically reduced. Normal feeding patterns should be reassessed to ensure appropriate body condition. For example, a tetraparetic or paraparetic patient requires little more than resting energy requirements. Should the patient already be obese, adjustment downward must be accomplished to avoid further weight gain. If weight loss is desired, utilization of higher protein, lower calorie foods may deter lean body wasting during weight loss which is important to optimize lean body mass retention preventing further muscle atrophy.

Calculating energy required

Resting energy requirement (RER) = $(70 \times \text{ideal body weight (IBW) in kg})^{0.75}$

Nonobese energy requirement = $([70\text{–}90] \times \text{IBW in kg})^{0.75}$

Obese energy requirement = $0.7 \times \text{RER}$

Goal energy to achieve 1% weight loss per week until ideal weight is achieved.

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CHAPTER 21

Pharmacologic Management of Pain for Patients with Neurologic Disease

Bruno H. Pypendop & Linda S. Barter

Introduction

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." While many dogs and cats with neurologic disease experience pain, it may be challenging to recognize it in all patients. Pain assessment is somewhat subjective, and the same noxious stimulus may have different effects in different individuals.

In dogs and cats, treatment of acute pain is much better characterized than treatment of chronic pain. This chapter will focus on the physiology of and common pharmacologic options for acute pain management and provide an overview of the current approaches to the treatment of chronic pain in dogs and cats. The pharmacologic treatment of pain should be considered only one part of global pain management, and nonpharmacologic aspects—such as proper nursing, physical therapy, acupuncture—are as important as drug therapy.

Pain physiology[7, 11, 16, 18, 21, 22, 47, 55, 58, 63, 67, 78, 82, 85, 102, 103, 116, 128]

The physiology of pain is complex and, although new information emerges constantly, remains incompletely understood. Broken down into its simplest model, the pain pathway begins with nociceptors detecting a potentially damaging (noxious) stimulus and creating an electrical signal (transduction). This information is then relayed to the central nervous system (CNS; transmission), where the information is integrated and processed. The information is, in turn, relayed to higher brain centers where it is interpreted as pain (perception).

Transduction

Nociceptors are free nerve endings of certain (C and Aδ) primary afferent, or sensory, neurons. They are distributed widely throughout the body, being found in skin, bone, muscle, most internal organs, blood vessels, and meninges. Nociceptors are activated by chemical, thermal, or mechanical stimuli. Examples of noxious stimuli include intense pressure, mechanical stress, heat above 43–45°C, endogenous substances—such as potassium ions, hydrogen ions, and inflammatory mediators (e.g. bradykinin, histamine)—and exogenous substances, such as capsaicin. Nociceptors can respond to one or more type(s) of stimuli and are often classified by the type of stimuli they transduce. Most nociceptors respond to multiple types of stimuli and are thus known as polymodal nociceptors. There also exists a population of "silent" nociceptors that normally have very high activation thresholds. Only after their activation threshold has been lowered by some mechanism can they convert a noxious stimulus into a nerve action potential.

Activation of nociceptors results in the production of a depolarizing electrical current, or a generator potential, within the neuron terminal. Ion channels expressed in nociceptors, such as those belonging to the transient receptor potential (TRP) family, function to transduce the noxious stimuli. The transient receptor potential vanilloid subtype 1 (TRPV1) is a nonselective cation channel that has been identified in dorsal root ganglia, spinal, and peripheral nociceptive nerve terminals. This receptor can be activated by heat greater than 43°C, low pH, capsaicin, and a variety of other proalgesic substances. Inflammatory mediators such as ATP, bradykinin, trypsin, and some prostaglandins potentiate TRPV1 receptor function by activation of protein kinase signaling pathways within the neuron and subsequent phosphorylation of TRPV1. Recently, the bioactive phospholipid lysophosphatidic acid (LPA), a molecule for which a role in neuropathic pain has been described and whose amounts increase subsequent to tissue injury, has been shown to directly activate TRPV1 receptors. Previously LPA was thought to modulate intracellular pain signaling pathways through action on LPA specific membrane G-protein coupled receptors.

Additional ion channels have been implicated in directly transducing noxious stimuli, including those activated by

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changes in mechanical stretch or osmolality, ATP-gated ion channels, and acid-sensing ion channels; however, their exact roles have yet to be fully elucidated.

Nociceptors have the ability to increase their level of sensitivity following tissue injury or repetitive stimulation. Many channels and receptors expressed by nociceptive neurons are not directly activated by noxious stimuli but instead play important roles in modulating the responses of the primary transducing elements. As already mentioned, transduction of a noxious stimulus creates a generator potential in the nerve terminal. If this generator potential is of sufficient magnitude, it will initiate an action potential in the neuron, which is then transmitted in an all-or-none fashion along the neuron to the spinal cord. Depolarization of the nociceptive nerve terminal has additional effects, such as local release of neurotransmitters, like the neuropeptides substance P and calcitonin gene-related peptide (CGRP). These neuropeptides produce vascular leakage and local edema, contributing to the phenomenon of neurogenic inflammation. Bradykinin can now move into tissues from the plasma out of the now "leaky" vasculature, causing further vasodilation in addition to activating and sensitizing nociceptors. The products of arachidonic acid metabolism, especially prostaglandins, also contribute to this sensitization by having facilitatory actions on nociceptive transduction channels, like TRPV1, and on sodium channels responsible for transmitting action potentials. Inflammatory cell migration, cytokine production, and degranulation of mast cells with local release of histamine and serotonin, all exacerbate this response and cause further release of inflammatory mediators. This sensitized state resulting from a reduction in threshold and increase in responsiveness of nociceptors is known as *peripheral sensitization* and creates the clinically observed phenomenon of primary hyperalgesia. Not only can intracellular signaling be modified with chronic pain states but also the expression of TRPV1 channels has been shown to be upregulated in neuropathic pain models.

After nerve injury myelin degenerates, macrophages and neutrophils infiltrate. These changes are accompanied by the release of proinflammatory cytokines, inflammatory mediators, and nerve growth factor—all of which promote the development of hyperalgesia and allodynia.

The peripheral expression of opioid receptors has been demonstrated to occur during inflammation. These receptors are typically coupled to inhibitory Gi/Go proteins, activation of which leads to the inhibition of voltage-gated calcium channels. The effect of this is to reduce the peripheral nerve terminal calcium ion concentrations subsequent to the creation of a generator potential. This, in turn, reduces the release of neurotransmitters such as substance P. Overall, the effect is to reduce sensitization of nociceptors, thus providing analgesia, in addition to having anti-inflammatory actions.

Transmission

Primary afferent neurons have cell bodies located within the dorsal root ganglion and some brain stem nuclei, in addition to peripheral and central processes. The electrical signal generated during transduction of a noxious stimulus is transmitted from the peripheral axon as a single action potential or a series of action potentials through the neuron to the spinal cord dorsal horn. Under physiologic conditions, those primary afferent neurons responsible for transmission of noxious stimuli are A-delta and C fibers. Both fiber types are small in diameter; however, A-delta fibers are thinly myelinated, thus faster conducting, and mediate what is typically described as sharp pain, first pain, or superficial pain. C fibers are smaller in diameter and unmyelinated; therefore, they conduct more slowly than A-delta fibers. C fibers are responsible for transmitting the dull or burning second pain sensation, as well as the type of pain sensation referred to as *deep pain* sensation (nociception).

Central processes from nociceptive primary afferents terminate in laminae I, II, and IV of the dorsal horn, where they synapse with second-order sensory neurons. These second-order neurons are of two main types: spinal projection neurons and interneurons. Spinal projection neurons innervate higher centers and the interneurons serve a variety of functions, such as providing polysynaptic connections between primary afferent and projection neurons, and spinal modulation of synaptic transmission.

At their synapses within the spinal cord the primary afferent neurons release two main classes of neurotransmitters: the excitatory amino acids, primarily glutamate, and the neuropeptides, primarily substance P. On the postsynaptic membrane are the target receptors for glutamate, such as NMDA (*N*-methyl-d-aspartate) and AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) receptors, and target receptors for the neurokinins, neurokinin receptor subtypes 1 and 2 (NK1, NK2). These receptors are all ligand-gated cation channels, and as such their activation results in the depolarization of the postsynaptic cell. There are a number of extrasynaptic receptors which function to modulate activity at this synapse. Enhancement of neurotransmitter release by the presynaptic cell is effected by presynaptic NMDA receptors. Alpha-2 adrenergic receptors, opioid receptors, gamma-aminobutyric acidB ($GABA_B$) receptors, and serotonergic (5HT) receptors are located extrasynaptically on both the presynaptic and postsynaptic cell membranes. Activation of these receptors produces analgesia, presynaptically by inhibiting neurotransmitter release and postsynaptically by hyperpolarizing the cell, making transmission of the noxious stimulus more difficult.

The responsiveness of second-order sensory neurons to stimuli can be altered by many direct and indirect factors, such that they play a dynamic role in information processing at the spinal cord level. Ongoing nociceptive input sensitizes NMDA receptors in addition to altering intracellular signaling cascades. Local networks of inhibitory and excitatory neurons within the spinal cord (formed by interneurons) modulate the function of both the primary and secondary sensory neurons. Spinal cord inhibitory neurons use GABA and glycine as their major neurotransmitters. Both neurotransmitters act as ligands for ionotropic receptors that function as chloride channels ($GABA_A$ and $GABA_C$ and glycine receptors). In most neurons, activation of these receptors hyperpolarizes the cell membrane and inhibits neuronal signal transmission. Additionally, GABA also acts as a ligand for a G-protein couple receptor ($GABA_B$) that activates a subset of potassium ion channels, thus hyperpolarizing the cell membrane. Removal of GABA-ergic and glycinergic inhibition can lead to exaggerated nociceptive responses. For example, the inhibition of glycine release from interneurons (adenosine and nocistatin), a reduction (alteration) in transmembrane chloride gradient (reduced KCC2 cotransporter expression in damaged neurons), and the selective death of GABA-ergic/glycinergic interneurons are all possible mechanisms for development of neuropathic pain.

Prostaglandins, in addition to their peripheral actions, can act centrally to enhance nociceptive transmission. Activation of intracellular phosphorylation pathways, for example the action of PGE2 on an EP2 receptor, initiates an intracellular pathway that activates protein kinase A (PKA). This effectively reduces inhibitory glycinergic transmission and results in centrally mediated sensitization.

Many short- and longer-term changes in neuronal cell function underlie some pain mechanisms. Increases in the excitability of central nociceptive neurons can lead to their being activated by low levels of input from C or Aδ fibers (hyperalgesia). Changes in these central neurons can result in their being activated by Aβ fibers and can produce a situation where the stimulus they normally transduce (touch) now elicits a painful response. This is known as allodynia. Additionally, prostaglandins can induce transcriptional and posttranslational changes in normally non-nociceptive A-β fibers creating in them a nociceptive phenotype.

Perception

Once the sensory input from many primary afferents has been integrated by the second-order sensory neurons, information is transmitted locally to motor systems to initiate protective reflex responses and supraspinally in ascending tracts to the brain stem, thalamus, and cerebral cortex. A number of ascending pathways (or tracts) of neurons convey noxious information to higher centers, including the spinothalamic, spinomesencephalic, spinocervicothalamic, and spinoreticular tracts. The classic spinothalamic tract description in humans is that of a primarily contralateral pathway. Though this pathway is also thought to be clinically important in dogs and cats, it is a multisynaptic, bilateral pathway in these species (Fig. 21.1). Supraspinal transmission of nociceptive information initiates autonomic nervous system responses, alerts the cerebral cortex, and creates the perception of pain. In addition, it also evokes descending modulatory pathways systems that can either increase or decrease the activity of dorsal horn neurons via interactions with either or both the primary and secondary sensory afferent neurons.

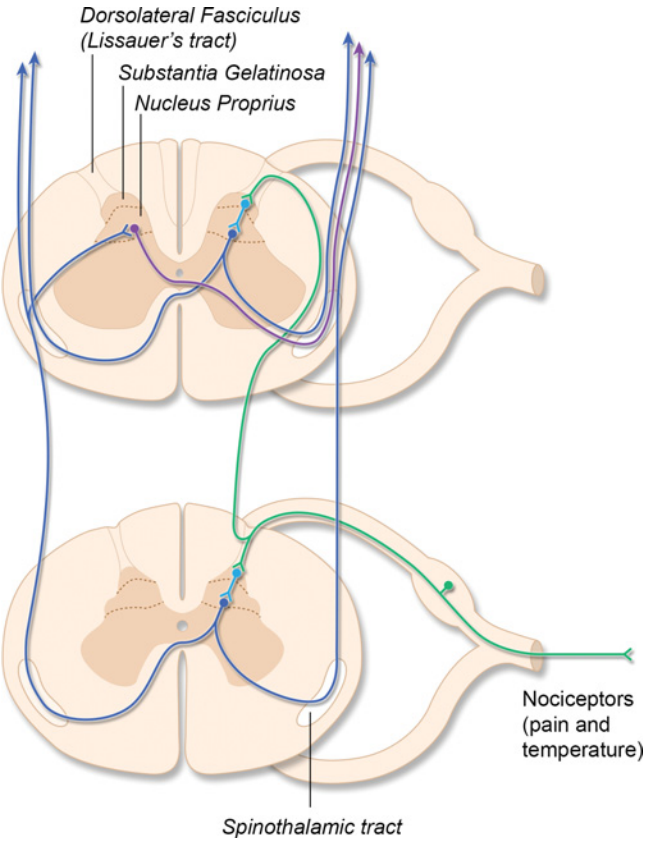

Figure 21.1 Schematic illustration of the classic spinothalamic tract for nociception in the dog and cat. (Adapted from Burke and Colter, 1990.)[14]

Reorganization of the CNS also occurs following peripheral noxious stimulation. Functional brain imaging has allowed investigation of central neuronal plasticity. As an example, following partial sciatic nerve ligation in rats, a reorganization of lateral thalamic networks could be demonstrated. This included changes in somatosensory representation as areas associated with the noxiously stimulated body part expanding into adjacent ones. In people with phantom limb pain and complex regional pain syndrome, changes in somatosensory representation are associated with pain and hyperalgesia.

Assessment of pain in animals

Before pain can be treated, it needs to be recognized. Assessment of pain in animals is not easy; signs can be subtle and are not usually specific for pain. Pain cannot be objectively proven, so in people it is commonly considered what the patient says it is. In animals, it is what the observer says it is; if the observer is wrong, the patient may suffer. There is no standard for the assessment of pain in animals. Many scoring systems have been published, but very few have been validated. Validation itself is problematic due to absence of a "gold standard" and difficulty with quantification, as pain has no units. Nevertheless, these difficulties should not be used as an excuse to ignore pain.

A pain-scoring system needs to be valid, reliable, sensitive, and simple enough to be used in a busy clinical setting. There are many to choose from, including simple descriptive scales, numeric rating scales, and visual analog scales. It is, however, generally accepted that scoring systems that include assessment of behaviors and interaction with the animal are best. The American Animal Hospital Association standards for pain management stipulate that pain assessment should be considered part of every patient evaluation, regardless of the presenting complaint. As such, assessment of pain should be considered part of every physical examination.

If a patient is thought to experience pain, appropriate treatment should be established. In addition to the ethical obligation to alleviate suffering, there is abundant evidence that untreated pain has significant deleterious effects. However, clinicians are often reluctant to treat pain, owing to concerns about undesirable effects, limited availability of data, and/or misconceptions regarding pain perception and treatment in animals. Many authors consider pain in animals undertreated.

Different types of pain, responding differently to treatment, have been described. Acute pain immediately follows tissue injury and is the typical type of pain observed postoperatively. Chronic pain persists after the initial pain-causing insult has resolved. Acute pain is generally considered a protective mechanism to prevent further injury, and chronic pain is pathologic in the sense that it serves no apparent purpose. Neuropathic pain is a type of chronic pain caused by a primary lesion or dysfunction of the nervous system as opposed to nociceptive pain, which is pain resulting from the normal result of the stimulation of nociceptors. In addition, exposure to noxious stimulation may result in modifications of perceptions—such as hyperalgesia (increased response to a normally painful stimulus) and allodynia (pain due to a normally nonpainful stimulus)—complicating pain assessment and treatment.

Pharmacologic management of pain

Opioids[16, 21, 27, 29, 30, 36, 37, 45, 48, 49, 66, 70, 72, 78, 80, 86, 88, 91 99, 114, 115]

Opioids are widely used in the management of pain. They are often considered the first line of treatment for acute pain, particularly surgical pain. Opioids act on opioid receptors, which are found within the CNS and may be expressed or upregulated in peripheral tissues following trauma or inflammation. Different types of opioid receptors (μ or OP3, δ or OP1, κ or OP2) have been described, and commonly used drugs act on one or more of these receptor types.

Individuals appear to be unique in terms of number, morphology, and distribution of opioid receptors, and these differences are genetically determined. It is not surprising, therefore, that some individuals experience much better pain relief from opioid agonists than others. Moreover, some human patients may not tolerate the side effects or may experience very different levels of pain relief with one drug versus an equianalgesic dose of another from the same class (e.g. full μ-agonists). Although these phenomena have not been reported in animals, consideration should be given to trying a different drug in the cases where unacceptable adverse effect or inadequate pain relief are obtained.

Opioid analgesia is most effective for the treatment of acute pain; efficacy for chronic pain is variable. Most opioids produce dose-dependent sedation and have potential adverse effects, such as bradycardia, respiratory depression, vomiting, constipation, dysphoria, histamine release, hypothermia (dogs), hyperthermia (cats, drug-dependence), tachycardia (cats, high doses), and hypertension (cats, high doses). Adverse effects are usually mild if appropriate dose regimens are selected and bradycardia can be prevented or treated with anticholinergics. Clinically significant respiratory depression is rare in dogs and cats, except when using high doses of opioids, for example as part of a balanced anesthetic technique (during which mechanical ventilation should be provided). Vomiting is more common with morphine than other drugs. Histamine release is seen only with morphine and meperidine, and the speed and route of administration plays a role: a greater degree of histamine release occurs with fast versus slow administration and with the intravenous (IV) versus intramuscular (IM) or subcutaneous (SQ) routes. Opioid-induced dysphoria appears more common in cats and some dog breeds (e.g. Siberian Husky); however, true excitement ("morphine-mania") in cats is rare and associated with the administration of excessively large doses.

Dose recommendations for opioids commonly used in dogs and cats are presented in Table 21.1. Morphine, a full μ-agonist, is the prototypical opioid to which other drugs are compared. Comparison of opioids is often based on potency or efficacy of the drugs. It is important to distinguish between potency and efficacy (Fig. 21.2). *Potency* defines how much of a drug is needed to reach a given effect (and therefore the dose), whereas *efficacy* determines the maximum possible effect (the amount of analgesia that can be obtained). For example, butorphanol is more potent but less efficacious than morphine. Practically, this means that the dose of butorphanol needed to treat mild pain is less than that of morphine, but that morphine will be able to relieve severe pain whereas butorphanol will not. In general, all full μ-agonists have similar, high efficacy, whereas partial agonists and agonist-antagonists have lower efficacy. The effects of an opioid agonist can indeed be partly or fully reversed concurrent with the administration of a partial agonist, an agonist–antagonist, or a pure antagonist (such as naloxone).

Morphine is obtained from the poppy *Papaver somniferum* and available as an injectable solution for IV, IM, or SQ administration, as a preservative-free injectable solution for epidural or subarachnoid administration, and as oral preparations. Morphine has a relatively slow onset and duration of effect of 3–4 hrs.

Table 21.1 Opioids commonly used in dogs and cats.

Drug	Canine Dosage	Feline Dosage
Morphine	0.1–1.0 mg/kg IV (slow), IM, SQ, q 4 hr CRI: 0.1–0.3 mg/kg/hr IV	0.05–0.2 mg/kg IV (slow), IM, SQ, q 4 hr CRI: 0.02–0.1 mg/kg/hr IV
Oxymorphone	0.05–0.1 mg/kg IV, IM, SQ, q 4 hr	0.03–0.05 mg/kg IV, IM, SQ, q 4 hr
Hydromorphone	0.05–0.2 mg/kg IV, IM, SQ, q 4 hr	0.03–0.05 mg/kg IV, IM, SQ, q 4 hr
Methadone	0.1–1.0 mg/kg IV, IM, SQ, q 4 hr	0.1–0.5 mg/kg IV, IM, SQ, q 4 hr
Meperidine	1–10 mg/kg IM, SQ, q 1 hr	1–5 mg/kg IM, SQ, q 1–2 hr
Fentanyl	0.002–0.01 mg/kg IV, IM, SQ, q 30 min–2 hr CRI: 0.003–0.06 mg/kg/hr IV TDDS: <10 kg: 25 μg/hr 10–20 kg: 50 μg/hr 20–30 kg: 75 μg/hr >30 kg: 100 μg/hr	0.001–0.005 mg/kg IV, IM, SQ, q 30 min–2 hr CRI: 0.003–0.03 mg/kg/hr IV TDDS: 25 μg/hr
Butorphanol	0.1–0.4 mg/kg IV, IM, SQ, q 1–2 hr 0.5–2.0 mg/kg PO, q 6 hr	0.1–0.4 mg/kg IV, IM, SQ, q 3–5 hr 0.4–1.0 mg/kg PO, q 8 hr
Buprenorphine	0.01–0.02 mg/kg IV, IM, SQ, q 4–8 hr	0.01–0.02 mg/kg IV, IM, SQ, q 4–8 hr 0.02 mg/kg buccally q 6–8 hr

CRI, continuous rate infusion; TDDS, transdermal delivery system.

Injection of morphine often causes nausea and vomiting, and IV administration causes histamine release and, as such, should be performed with caution. Morphine produces the greatest degree of sedation among the opioid agonists; however, it appears to cause dysphoria in cats more commonly than some other opioids, such as oxymorphone, hydromorphone, or methadone. Morphine is inexpensive and until recently the most widely used opioid in humans worldwide. It is a Drug Enforcement Administration (DEA) schedule II drug.

Oxymorphone, synthesized from morphine, is a full μ-agonist with 10 times the potency of morphine. It can be administered IV, IM, or SQ. Oxymorphone has a faster onset, a similar duration, and lower incidence of vomiting and dysphoria than morphine. Oxymorphone is significantly more expensive than morphine and is a DEA schedule II drug.

Hydromorphone, also synthesized from morphine, is a full μ-agonist with properties similar to those of oxymorphone. In cats, dysphoria appears to be more frequent after hydromorphone administration compared with oxymorphone, particularly if the higher end of the dose range is used. The use of this drug in cats appears to be associated with hyperthermia. Hydromorphone is often considered an inexpensive alternative to oxymorphone. It is a DEA schedule II drug.

Methadone is a synthetic opioid of the phenylheptylamine class. Its potency and pharmacologic properties are similar to those of morphine. Methadone, however, does not cause histamine release after IV administration, and vomiting associated with its administration is extremely uncommon. In addition, methadone appears to antagonize the NMDA receptor, which may contribute to its analgesic effect. Onset of effect is about 20 min after IM or SQ injection, and duration is 3–4 hrs. Methadone is expensive in the United States, but inexpensive in Europe. It is a DEA schedule II drug.

Meperidine (pethidine) is a synthetic opioid of the phenylpiperidine class. Its potency is less than that of morphine and its duration of action is short in dogs and cats (1 hr or less at clinically recommended dosages). Meperidine has significant κ-agonistic effects, local anesthetic effects, and may cause CNS excitation. It has anticholinergic-like activities and may increase heart rate. Meperidine blocks the neuronal reuptake of serotonin and should not be used in patients receiving monoamine oxidase inhibitors (MAOI) or serotonin reuptake inhibitors (e.g. selegiline). Use of meperidine in these patients may cause delirium, hyperthermia, hyper- or hypotension, rigidity, convulsions, coma, and death. Meperidine is inexpensive and is a DEA schedule II drug.

Fentanyl is a derivative of meperidine, with different pharmacologic properties. Fentanyl is a potent μ-agonist (approximately 100 times that of morphine), which, when used at high doses, can cause significant bradycardia and respiratory depression. As such, high doses should be reserved for anesthetized, intubated patients that can be mechanically ventilated, and pretreatment with anticholinergics is recommended. The duration of action of fentanyl is short, and it is typically given as a constant rate infusion. Fentanyl is available as a transdermal delivery system (TDDS, or “patch”) that potentially provides analgesia for up to 3 days after application. Plasma concentrations (and hence effect) after TDDS application are slow to rise (12–24 hrs) and very variable between individuals. Fentanyl is a DEA schedule II drug.

Butorphanol is a synthetic agonist-antagonist opioid that exerts an agonist effect on κ-receptors and an antagonist effect on κ-receptors. The efficacy of butorphanol is limited and it should therefore be reserved for the treatment of mild to moderate pain. Duration of the analgesic effect is short in dogs, approximately 1 hr; it may be longer in cats (3–5 hrs). Butorphanol

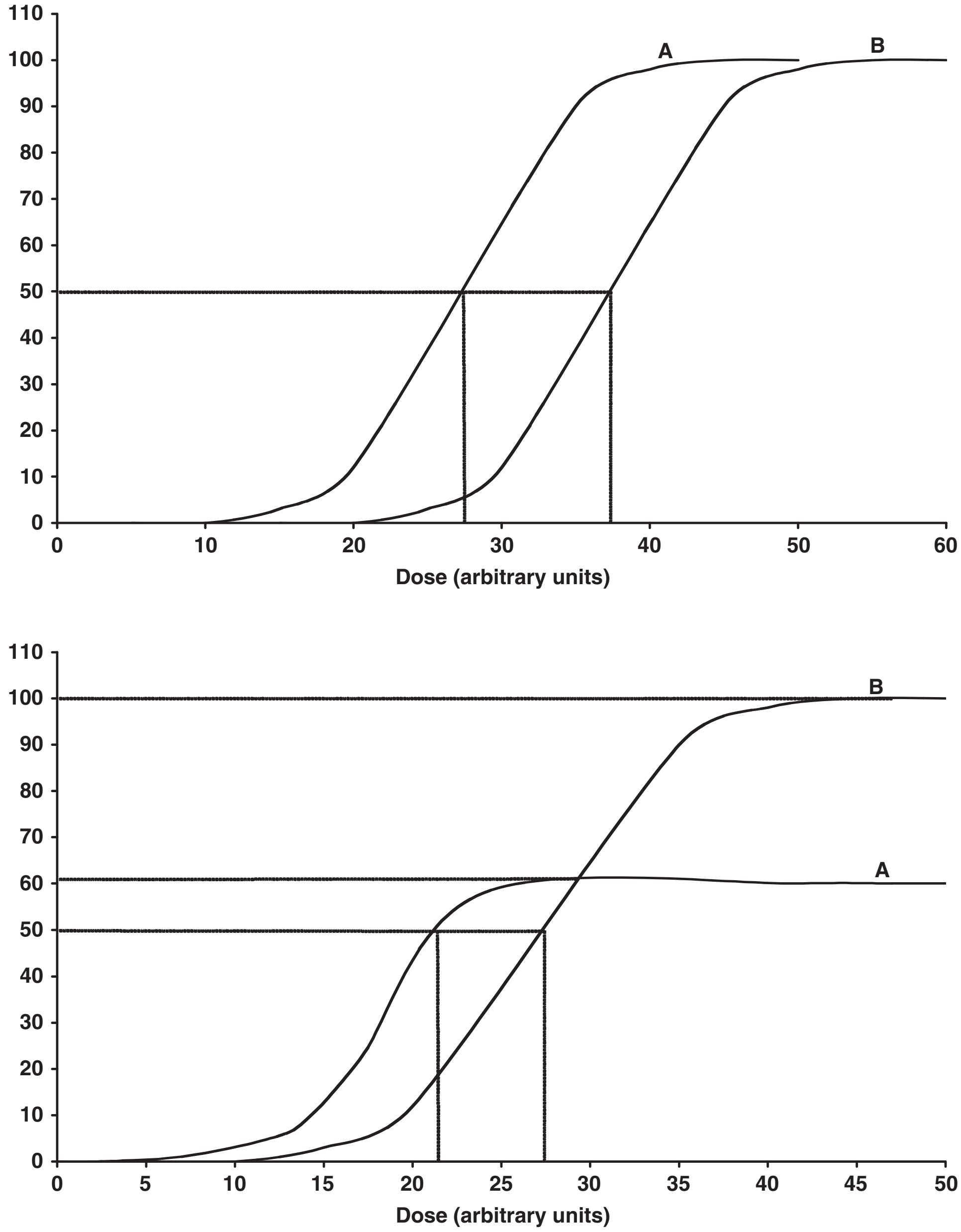

Figure 21.2 Potency and efficacy. Top graph: drugs A and B have identical efficacy, as illustrated by their maximal effect, but drug A is more potent than drug B, as illustrated by its lower ED_{50} (dose producing 50% of the maximum effect). Bottom graph: drug A is more potent than drug B, as illustrated by its lower ED_{50}, but drug B is more efficacious than drug A, as illustrated by its higher maximum effect.

should not be administered concurrently with μ-agonists unless reversal of the μ-agonists effects are desired. An oral formulation of butorphanol is licensed for use in dogs and cats in the United States. Butorphanol is a DEA schedule IV drug.

Buprenorphine, a semi-synthetic derivative of thebaine, is a partial μ-agonist; it exerts only part of the effects of a full μ-agonist. Buprenorphine is 25–50 times more potent than morphine; however, its efficacy is limited, at least in dogs, where its use should be reserved for treatment of mild to moderate pain. In contrast, clinical research suggests buprenorphine may be a better analgesic than some full agonists in cats, although some of these studies are limited by the fact that only one dose was tested, and that the drugs compared may therefore not have been administered at equipotent doses. Buprenorphine has a high affinity for μ-receptors and may be difficult to antagonize. Even though clinically significant respiratory depression is uncommon after buprenorphine, when observed, mechanical ventilation may be required due to the difficulty of antagonizing the effects. Buprenorphine has a slow onset (up to 30 min after IV administration) but a long duration of action (6–8 hrs) and has been shown to be effective after buccal administration in dogs and cats. Buprenorphine is a DEA schedule III drug.

Nonsteroidal anti-inflammatory drugs[2, 5, 9, 10, 12, 13, 17, 24, 25, 33–35, 38, 40, 45, 50, 52, 53, 64, 65, 68, 69, 71, 73, 74, 77, 83, 90, 95, 96, 104, 105, 107, 109, 111, 114, 117, 124, 127]

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX), the enzyme responsible for the formation of prostaglandins and thromboxane in response to tissue damage and inflammation. Some drugs (ketoprofen, tepoxalin) also inhibit lipoxygenase (LOX), which is responsible for the synthesis of leukotrienes. Leukotrienes and prostaglandins are involved in the transduction of inflammatory pain; decreased production results in analgesia. Moreover, central mechanisms of pain processing may also rely on prostaglandin synthesis.

Two isoforms of COX (COX-1 and COX-2) are known to exist. Classically, COX-1 has been described to be constitutive and responsible for the synthesis of prostaglandins involved in homeostasis (gastric protection, renal vasodilation, etc.), while COX-2 is induced by inflammation and synthesizes high concentrations of the prostaglandins responsible for inflammation and pain. Therefore, much research has been directed toward drugs that specifically inhibit COX-2, which in theory would be almost devoid of adverse effects. It is not that clear-cut, and COX-1 is now known to contribute to the production of inflammatory eicosanoids, and COX-2 contributes to the production of eicosanoids involved in homeostasis. NSAIDs for animal use that preferentially or selectively inhibit COX-2 include meloxicam, etodolac, deracoxib, and robenacoxib. The reported selectivity for one COX isoform over another may vary between species and tissue.

NSAIDs are effective analgesics, particularly in cases of acute inflammatory pain. In some studies of postoperative pain, some NSAIDs were more effective than opioids. The analgesic potency of NSAIDs may be dissociated from their anti-inflammatory potency. NSAIDs are also widely used to treat chronic osteoarthritic pain; however, they are thought to be devoid of efficacy in the management of other types of chronic pain.

Most NSAIDs are available as an oral formulation and some also as an injectable solution. NSAIDs usually have a long duration of action (12–24 hrs) and can be used in conjunction with opioids.

Adverse effects induced by NSAIDs are related to inhibition of the homeostatic functions of prostaglandins and thromboxanes. They include gastrointestinal irritation and bleeding, renal injury, and inhibition of coagulation. Therefore, NSAIDs should not be used in animals with a history of gastrointestinal disease, renal disease, or in those at risk of hypotension or bleeding. Liver toxicity has been reported with carprofen in dogs. The preoperative administration of NSAIDs is controversial: although it could be argued the efficacy of these drugs would be greatest if administered before tissue injury and upregulation of prostaglandin synthesis, the effects of these drugs on coagulation and renal perfusion should be considered. Cats appear more sensitive than dogs to the toxic effects of NSAIDs, in part related to their relative deficiency in glucuronide conjugation.

Dose recommendations for NSAIDs commonly used in dogs and cats are presented in Table 21.2. Only two drugs (meloxicam and robenacoxib) are licensed for use in cats in the United States. The label for meloxicam restricts that use to a single SQ injection and contains a strong warning not to repeat the administration due to the risk of renal failure. Robenacoxib is approved for use for 3 days in cats. Other drugs reported in Table 21.2 at this time would be considered off-label and are for information only.

- Ketoprofen is a nonselective COX inhibitor that also inhibits LOX. It is a potent anti-inflammatory and analgesic drug. In the United States, ketoprofen is available as an injectable solution and is licensed for use in horses only. In Europe, oral tablets are also available, and the drug is licensed for dogs and cats.
- Carprofen is a nonselective weak COX inhibitor. Most of its effects are likely mediated centrally. It is a potent analgesic and has been widely used in dogs and cats in many countries. In

Table 21.2 Nonsteroidal anti-inflammatory drugs commonly used in dogs and cats.

Drug	Trade name	Canine dosage	Feline dosage
Ketoprofen	Ketofen	1–2 mg/kg PO, SQ, IV, q 24 hrs	1–2 mg/kg PO, SQ, IV, q 24 hrs
Carprofen	Rimadyl	2–4 mg/kg PO, SQ, IV, q 12–24 hrs	2–4 mg/kg PO, SQ, IV, q 12–24 hrs
Meloxicam	Metacam	0.1–0.2 mg/kg PO, q 24 hrs 0.2–0.3 mg/kg SQ, IV, q 24 hrs	0.1–0.2 mg/kg PO, q 24 hrs 0.2–0.3 mg/kg SQ, IV, q 24 hrs
Etodolac	Etogesic	10–15 mg/kg PO q 24 hrs	—
Deracoxib[a]	Deramaxx	1–4 mg/kg PO q 24 hrs	—
Tepoxalin[b]	Zubrin	10–20 mg/kg PO q 24 hrs	—
Robenacoxib	Onsior	—	1 mg/kg PO, q 24 hrs

[a] Deracoxib is a COX-2 selective antagonist. In vitro, concentrations corresponding to doses up to 4 mg/kg did not significantly inhibit COX-1 in canine plasma. Deracoxib is available as chewable tablets for oral use in dogs.

[b] Tepoxalin is a COX and LOX inhibitor. Its selectivity for COX-2 is unknown in dogs; however, in sheep, it has a COX-2 : COX-1 inhibitory ratio of about 30 (i.e. it preferentially inhibits COX-2). Tepoxalin is available as tablets for oral use in dogs.

the United States, carprofen is licensed in dogs only. It is available as an injectable solution and as oral tablets. The injectable solution is licensed for IV and SQ use in European countries and Australia, but only for SQ use in the United States.
- Meloxicam preferably inhibits COX-2 and is licensed for use in dogs and cats in the United States. Meloxicam is available as an oral suspension and injectable solution. The US label authorizes IV and SQ administrations in dogs, but only SQ in cats.
- Etodolac preferably inhibits COX-2. It is available as tablets for use in dogs.
- Tepoxalin is a COX and LOX inhibitor. Its selectivity for COX-2 is unknown in dogs; however, in sheep, it has a COX-2/COX-1 inhibitory ratio of about 30 (i.e. it preferentially inhibits COX-2). Tepoxalin is available as tablets for oral use in dogs.
- Deracoxib is reported to be a selective COX-2 inhibitor at clinical doses. It is approved for the treatment of osteoarthritis and postoperative orthopedic pain in dogs. Cases of duodenal perforation associated with the administration of deracoxib have been reported.
- Robenacoxib was recently introduced in the US. It preferably inhibits COX-2 and is available as tablets for use in cats. Its indication according to the label is the control of postoperative pain following orthopedic surgery, ovariohysterectomy, and castration. One study has shown noninferiority compared to carprofen for the treatment of osteoarthritis in dogs.

N-methyl-d-aspartate receptor antagonists[6, 19, 41, 42, 46, 51, 59, 62, 63, 76, 79, 97, 101, 105, 108, 122, 125]

N-methyl-d-aspartate receptor antagonists are ionotropic glutamate receptors. When activated, NMDA receptors become permeable to cations, primarily calcium. NMDA receptors are involved in excitatory synaptic transmission, including the transmission of nociceptive information. Additionally, NMDA receptors appear to be involved in the central sensitization mechanisms and the development of wind-up.

Dissociative anesthetics (ketamine, tiletamine) are noncompetitive NMDA antagonists acting at a site within the ion channel of the receptor producing an open-channel blockade. Ketamine has been shown to produce analgesia at subanesthetic doses and may be effective for acute, and some types of chronic, pain. Ketamine may potentiate the analgesic effects of opioids. Adverse effects of ketamine include rigidity, convulsions, tachycardia, hypertension, increased secretions, and increased intracranial pressure. For analgesia, the dose recommended in dogs is 0.5 mg/kg IV as a loading dose, followed by a constant rate infusion of 2–10 μg/kg/min. Higher doses may be more effective.

Amantadine, a drug originally developed as an antiviral agent, antagonizes NMDA receptors, and has anecdotally been combined with other analgesics in dogs and cats. In a recent study in cats, amantadine was shown to decrease the effective antinociceptive dose of oxymorphone, an opioid, in some (but not all) subjects. The dose used anecdotally is 3–5 mg/kg PO, once a day. Other drugs that antagonize NMDA receptors include some opioids (methadone, meperidine) and nitrous oxide.

Alpha-2 adrenoceptor agonists[4, 23, 43, 60, 61, 94, 106, 120, 121]

Alpha-2 adrenoceptor agonists (alpha-2 agonists) produce analgesia by stimulating receptors in the spinal cord dorsal horn and brain stem, where modulation of nociceptive signals occurs. Moreover, alpha-2 agonists exert antihyperalgesic effects through the inhibition of nitric oxide release. Peripheral mechanisms may also be involved in the analgesic effects of alpha-2 agonists, particularly after nerve injury. Alpha-2 agonists potentiate opioid-induced analgesia.

The primary indication for the use of alpha-2 agonists in dogs and cats is sedation. It has been reported that these drugs produce analgesia at doses lower than needed to produce sedation. Two drugs of this category commonly used in small animals are xylazine and medetomidine. The analgesic effects of xylazine are reportedly short lived, whereas those of medetomidine are long-lasting analgesia. Alpha-2 agonists may be efficacious for some types of chronic pain.

Adverse effects of alpha-2 agonists include vomiting, bradycardia, low cardiac output, vasoconstriction, hyper- or hypotension, hyperglycemia, and diuresis. Most of these effects are dose-dependent and reach a ceiling; however, they are likely to be observed even at low doses, such as those used for analgesia.

Medetomidine can be used to provide analgesia and sedation, particularly in combination with other drugs. Doses for that indication are anecdotal. In both dogs and cats, 1–5 μg/kg IM or IV, followed if needed by a constant rate infusion of 1–5 μg/kg/hr, appears to provide good analgesia, particularly when combined with opioids. The analgesic effects of dexmedetomidine have been studied in dogs and cats. In both species, the analgesic effects appear short-lived, and the analgesic use of this drug therefore requires the administration by IV infusion. In dogs, 3–5 μg/kg/hr are predicted to produce significant analgesia.

Local anesthetics[1, 15, 26, 31, 84, 87, 92, 93, 113, 123]

Local anesthetics exert antagonist effects on voltage-gated sodium channels and as such can produce analgesia by blocking nerve transmission. These drugs are effective when administered locally, topically, or systemically. A review of local anesthetic techniques is beyond the purpose of this chapter; however, local anesthesia should be considered for painful conditions whenever possible. Transdermal delivery systems are available for lidocaine, allowing the noninvasive administration of the drug if a patch can be placed over the painful area.

The systemic administration of lidocaine has been shown to produce analgesia in various pain models. Anecdotal evidence in dogs suggests that a single IV administration of lidocaine may relieve some types of neuropathic pain for several days or weeks. Lidocaine can also be administered as a constant rate infusion to treat acute pain, such as surgical pain. Typical doses are 0.5–2 mg/kg IV bolus or loading dose, followed by 30–120 μg/kg/min as a constant rate infusion.

Adverse effects of lidocaine are plasma concentration dependent and involve the CNS (at lower concentrations) and the cardiovascular system (at higher concentrations). Effects on the CNS include weakness, fasciculations, seizures, coma, and respiratory arrest; effects on the cardiovascular system include hypotension, arrhythmias, and cardiac arrest. Cats may be more sensitive than dogs to the toxic effects of IV lidocaine. In anesthetized cats, dose-dependent cardiovascular depression of clinical significance was seen with IV lidocaine. Moreover, no analgesic effect of lidocaine could be demonstrated in cats using a model of thermal nociception.

Other[3, 8, 20, 28, 39, 40, 44, 89, 98, 100, 112, 126]

Other drugs such as tricyclic antidepressants and anticonvulsants have been successfully used to treat chronic pain in humans. Information on the usefulness of these drugs in dogs and cats is anecdotal. Gabapentin, an anticonvulsant, appears to have been successfully used in dogs to treat some types of chronic pain unresponsive to opioids, including cancer pain. Recommended doses range between 10 and 50 mg/kg/day (usually divided in two to three administrations), with 30 mg/kg reportedly being effective. A newer derivative of gabapentin, pregabalin, may also have some promise as a pain reliever in dogs. Tramadol, a weak opioid agonist and norepinephrine and serotonin reuptake antagonist, has been used in dogs and cats, both for acute and chronic pain. No scientific information on dose or efficacy is available in cats. In dogs, the recommended dose is 2–5 mg/kg.

Drug combinations[54–57, 81]

Evidence in people strongly suggests that pain can be better controlled when using more than one class of drugs and by combining pharmacologic with nonpharmacologic approaches. This has led to the concept of multimodal or balanced analgesia. For example, clinical experience suggests that better surgical pain control is achieved when opioids and NSAIDs are combined than when either drug is used alone. Similarly, the combinations of opioids and alpha-2 agonists and opioids and NMDA antagonists appear to have synergistic effects. A popular drug combination in veterinary practice is morphine–lidocaine–ketamine (MLK). Although such combinations have theoretical benefits by treating pain by multiple mechanisms, some caution may be necessary: pharmacodynamic and pharmacokinetic interactions are often poorly studied or not studied at all, and indications are sometimes poorly defined. For example, even though MLK is widely used for analgesia in both dogs and cats, to date, only one study in dogs is available; this investigation examined the effects on anesthetic requirements and not on pain. In addition, the results of that study did not demonstrate that the combination had any benefit when compared to morphine alone.

Sedatives[75, 110, 118, 119]

Sedation is sometimes necessary in addition to analgesia to treat anxiety or to keep a patient quiet. Sedation should never be used instead of adequate pain relief. Since it is sometimes difficult to differentiate between signs of pain or dysphoria (the latter being an indication for sedation), it is desirable to assume that such signs are related to pain and to treat accordingly with analgesic drugs. If the condition does not improve or worsens after administration of high doses of analgesics, it is reasonable to add a sedative.

Drugs commonly used for sedation in dogs and cats include acepromazine and alpha-2 agonists. Alpha-2 agonists are discussed above; they provide analgesia in addition to sedation. Doses reported for analgesia are mildly to moderately sedative. Acepromazine, a phenothiazine, is devoid of analgesic effects. It is a long-acting drug that also causes hypothermia and hypotension for which no reversal agents are available. Doses used for sedation are 0.005–0.03 mg/kg IV, IM, or SQ in both dogs and cats. The onset is slow (30–45 min) after IM or SQ administration. Although acepromazine has historically been considered contraindicated in patients prone to seizure activity, recent evidence casts doubt on this long-held dogma, especially when considering the use of low doses.

Management of pain associated with spinal cord injury[32, 116]

The treatment modalities described above are mainly effective for the treatment of acute, nociceptive pain. Spinal cord injury is often, in addition, associated with neuropathic pain, either central (i.e. spinal cord) or peripheral (i.e. nerve roots) in origin. The treatment of neuropathic pain is more challenging, and little evidence is available in dogs and cats.

In humans, tricyclic antidepressants, anticonvulsants (gabapentin), and mixed serotonin-norepinephrine reuptake inhibitors are considered the first line of treatment, and opioids (including tramadol) are the second line. Cannabinoids may be effective. In severe cases, the subarachnoid administration of alpha-2 agonists (clonidine) and/or opioids (morphine) may provide additional pain relief.

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CHAPTER 22

Complementary and Alternative Therapy for Patients with Neurologic Disease

Karen L. Kline

Introduction

Neurologic disease in the canine and feline patient can affect multiple locations, specifically the brain, the spinal cord, and neuromuscular systems. A multitude of clinical signs can be observed, from behavioral changes to seizures to weakness to paralysis to, simply, pain. The incorporation of complementary and alternative medicine into conventional medical practice in the human arena is piquing interest in the subject in veterinary medicine as well. Complementary and alternative veterinary medicine (CAVM) encompasses a broad spectrum of treatment modalities to include acupuncture, chiropractic, herbology, light therapy, and massage therapy. Other therapies—such as therapeutic ultrasound, electrical stimulation, and physiotherapy to include aquatherapy (pool swimming, underwater treadmill) as well as land therapies—exist and are used alone or in combination with the above treatments. The goals of incorporating complementary medicine practice into conventional practice are to (1) improve the quality of life of the patient and owner, (2) diminish pain, and (3) incorporate a more holistic view of the veterinary patient. The use of CAVM in the treatment of neurologic disease has the same goals as previously mentioned. The use of CAVM for neurologic disease includes selective and adjunctive treatment of seizures, cerebrovascular disease, vestibular disease, intervertebral disc disease, caudal cervical spondylomyelopathy, high-velocity disc injury, fibrocartilaginous embolism, myopathies, and neuropathies. CAVM may be helpful to those patients who (1) have nonsurgical lesions, (2) are geriatric, (3) are anesthetic risks, (4) are recovering from or coping with a surgical or medical neurologic malady, or (5) are in pain. The key point to remember is that CAVM can be used in combination with conventional medicine once a definitive diagnosis has been established and all options are offered to the owner. This chapter aims to familiarize the reader with CAVM and its use in the treatment of various neurologic diseases that affect companion animals and provide scientific evidence for its validity and efficacy.

Acupuncture[1–34]

Acupuncture has been used for thousands of years and has its roots in Chinese and ancient Indian cultures. It was first introduced into Western civilization in the early 1900s and has since gained popularity as a mode of therapy for multiple diseases. Acupuncture is based on two of the fundamental concepts of Chinese medicine and philosophy: yin and yang, and qi. The theory behind acupuncture involves the stimulation of specific anatomic points in the body to achieve a therapeutic effect. This scientific theory of acupuncture revolves around the acupoint, of which there are an estimated 365 on the body surface. An acupoint can vary in size from 2 mm to 50 mm and is composed of the triad of connective tissue, a nerve bundle, and a vascular bundle; this triad has been recognized through electron microscopy. Acupoints are joined by theorized meridians or pathways; there are 14 major meridians that run on the body surface and connect the acupoints, which have a very low electrical resistance. The stimulation of acupoints has been shown to stimulate the release of inflammatory mediators such as corticosteroids, endorphins, and enkephalins. The scientific basis of acupuncture is being studied through multiple NIH grants and there are a number of theories surrounding its efficacy. Several processes have been proposed to explain acupuncture's effects, focusing mainly on pain. When acupuncture points are stimulated, the central nervous system (CNS) is stimulated to release chemicals such as hormones into the muscle, spinal cord, and brain that may help to change the experience of pain and to

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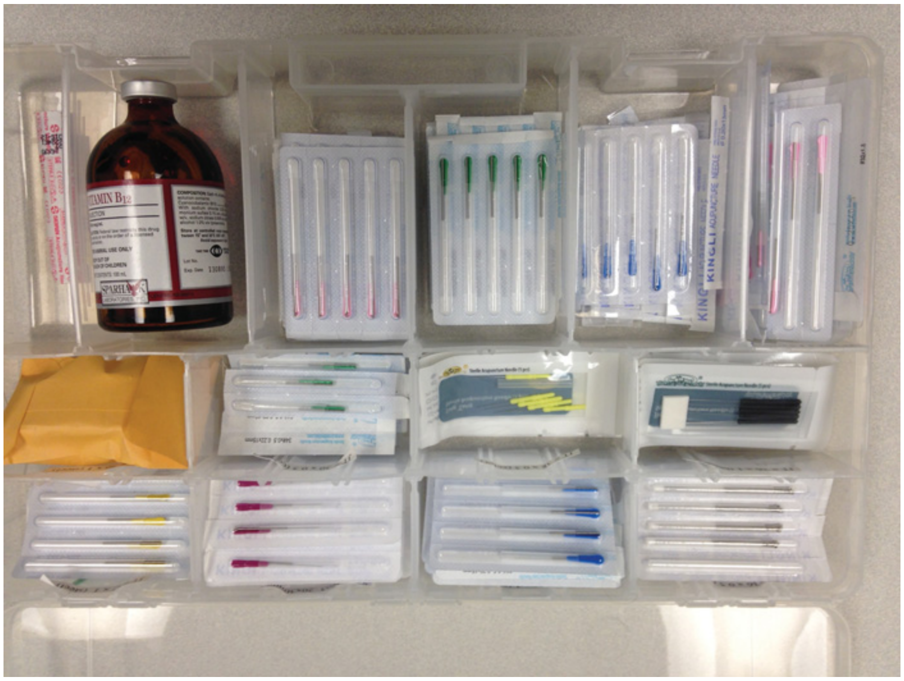

Figure 22.1 Examples of various acupuncture needles used in practice. (Courtesy of Dr. Joseph J. Wakshlag, Cornell University. With permission.)

promote the body's natural healing abilities. Three main mechanisms are proposed:

- Conduction of electromagnetic signals in which stimulated acupoints are thought to be conductors of such signals at an increased rate and thus promote the flow of biochemicals such as endorphins and enkephalins, as well as stimulating immune system cells.
- Activation of opioid systems, in which several types of opioids may be released centrally during treatment, thus decreasing pain.
- Changes in brain chemistry, sensation and involuntary body functions by the altering release of neurotransmitters and neurohormones in a positive manner.

(Another theory, the "gate theory," is explained in more detail in the "Physical therapy" section below.) Acupuncture therapy can be administered using needles alone, needles and electrical stimulation (Fig. 22.1–22.4), acupressure, aquapuncture (injection of Vitamin B12 or saline into acupuncture points), and low-intensity light therapy (cold Laser therapy). Each modality of therapy is tailored to the individual patient's signs, symptoms, and temperament, and treatments can be done on a daily, weekly, or monthly basis, again depending upon the underlying problem and goals of therapy. Neurologic conditions amenable to acupuncture therapy include brain disorders, such as probable symptomatic epilepsy; seizures secondary to past structural insult (symptomatic epilepsy), such as trauma, stroke, or past inflammation (Fig. 22.5) or infection; head trauma; cerebrovascular events; vestibular disorders, such as geriatric peripheral vestibular disease,

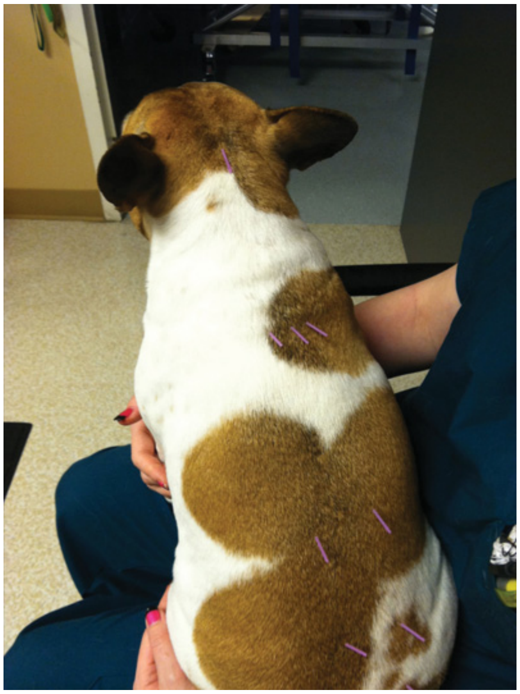

Figure 22.2 This patient had previous thoracolumbar disc surgery via a hemilaminectomy and has had periodic bouts of pain postoperatively. The acupuncture needles are placed locally and remotely from the area of pain. The needles are kept in place for 20 min.

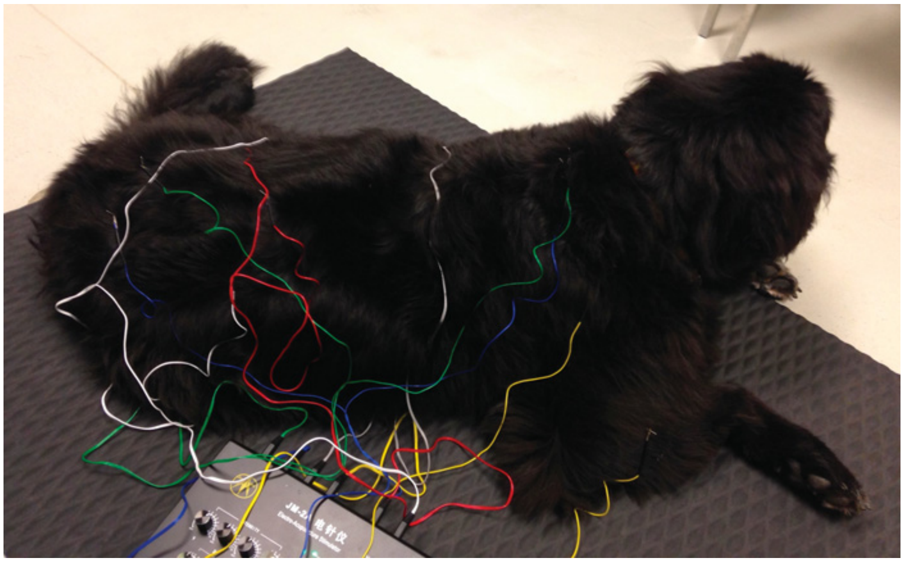

Figure 22.3 Dog receiving treatment with electroacupuncture. The electroacupuncture unit is seen in the lower part of the image. (Courtesy of Dr. Joseph J. Wakshlag, Cornell University. With permission.)

otitis media/interna; spinal cord disorders, such as nonsurgical intervertebral disc disease (high velocity disc, fibrocartilaginous embolism [FCE]) of the cervical, thoracolumbar, or lumbosacral regions (Fig. 22.6, Fig. 22.7); and neuromuscular disorders, such as masticatory myositis, cranial nerve (CN) VII paralysis, and trigeminal neuritis.

Chiropractic[14, 15, 20, 30, 35]

Chiropractic manipulation has been a mode of therapy in human medicine for a number of years and, like acupuncture, has become very popular in the treatment of companion animals. Chiropractic theory is based upon manual spinal

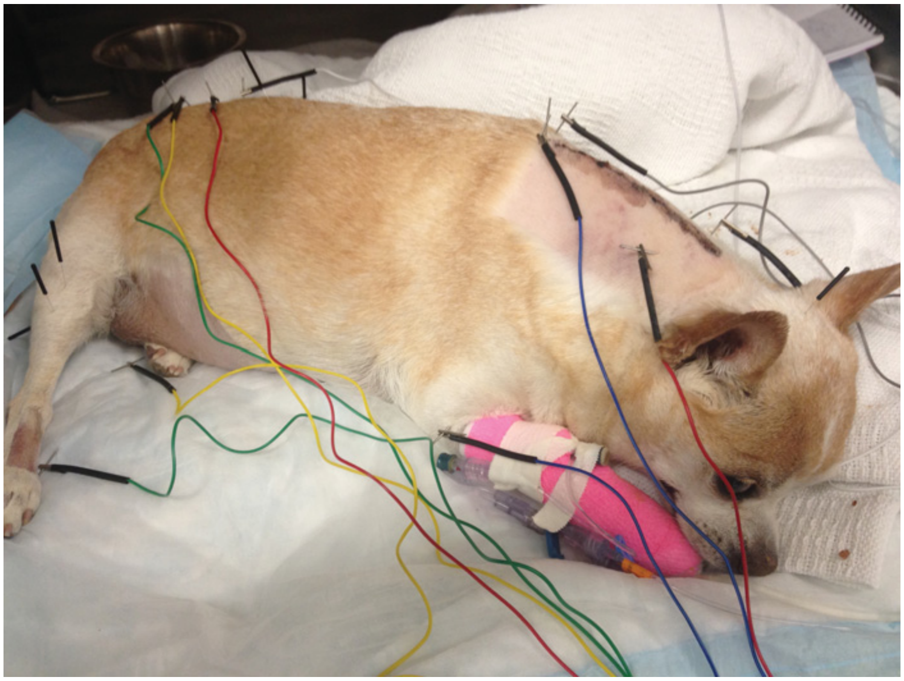

Figure 22.4 Dog recovering from a dorsal laminectomy receiving treatment with electroacupuncture. (Courtesy of Dr. Joseph J. Wakshlag, Cornell University. With permission.)

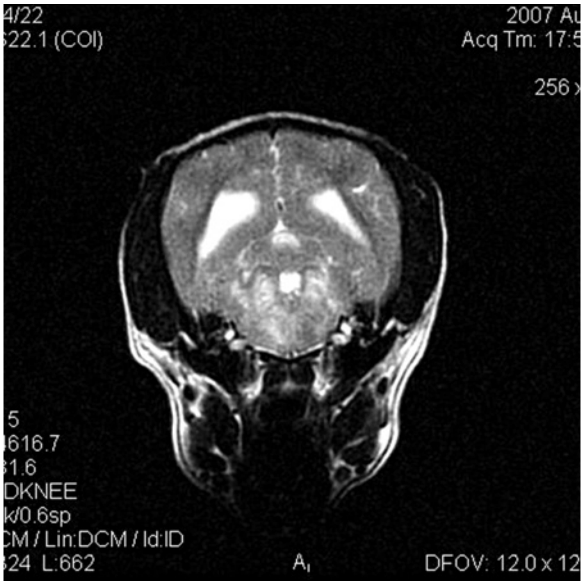

Figure 22.5 MRI of a dog with a central vestibular localization. MRI and cerebrospinal fluid analysis were consistent with a presumptive diagnosis of granulomatous meningoencephalomyelitis. Acupuncture and electroacupuncture therapy were instituted in addition to standard immunosuppressive treatment to help alleviate the vestibular signs.

Figure 22.6 Image of a dog presented for recurrent neck pain. MRI of his cervical vertebral region revealed multiple intervertebral disc protrusions at C3–C4, C4–C5, and C5–C6. This patient was managed nonsurgically with acupuncture and gabapentin.

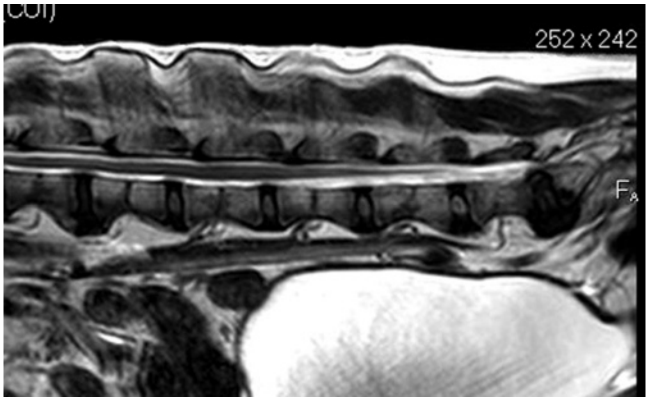

Figure 22.7 MRI of a dog with degenerative lumbosacral stenosis. The patient was treated with a dorsal laminectomy and followed up with acupuncture and hydrotherapy and did well.

manipulations and revolves around the relationship and interactions between spine biomechanics, and neurologic mechanisms. Therapy is aimed at the vertebral column to alter disease progression. Multiple terminologies are used in chiropractic care. The term “subluxation” is commonly used and implies an abnormal positional relationship of the vertebral bodies that can have an effect upon normal biomechanical and neurologic function, although multiple definitions arise in the medical and veterinary discussion of chiropractic medicine. The pathophysiology of subluxation has numerous theories and includes the *facilitation hypothesis*, which states that subluxations produce a lowered threshold for firing in spinal cord segments. Other theories include somatoantonomic dysfunction, nerve compression, compressive myelopathy, fixation, axoplasmic aberration, and the neurodystrophic hypothesis, to name a few. Therapeutic methods include spinal manipulation, and spinal adjustment. Spinal manipulation is categorized as mechanical and neurologic. Again, the mechanical effects are defined as subluxation, characterized as a spinal joint strain or sprain associated with local and referred pain and muscle spasms. The neurologic effects are both direct and indirect, and affect both the central and peripheral nervous systems. Spinal manipulation involves low-velocity, low-amplitude manual thrusts to multiple spinal joints to extend them slightly beyond their normal passive range of motion (PROM). An adjustment is a specific physical action designed to restore the biomechanics of the vertebral column, and thus indirectly influences neurologic function. It is a high-velocity force applied in a specific direction to a specific vertebra. In human medicine, chiropractic research has demonstrated short-term benefits in the treatment of acute lower back pain, headache, and neck pain. The effects on other musculoskeletal systems are more neutral. Spinal mobilization has been shown to have a number of physiological effects, including reduction of muscle spasms and inhibition of nociceptive transmissions, with the goal of improving joint function and pain alleviation. In veterinary medicine, similar concepts apply, with multiple applications that range from active movement of the joints between vertebral segments to those using low-force techniques. Multiple techniques and treatment theories (ranging from the role of CSF in spinal column function to potential neuropathology at the intervertebral foramen) make this treatment modality, in veterinary medicine, controversial. The goal of the veterinary chiropractor is to divide the spinal column into function or "motor units" for a more concise concept of the biomechanics of spinal movements, misalignments, and adjustments of subluxated segments. A motor unit comprises two adjacent vertebrae, the intervertebral disc, articular facets, ligaments, muscles, tendons, nerves, and blood vessels that unite the two vertebrae as one unit. The chiropractic philosophy is based upon the concepts of homeostasis; this therapy, like acupuncture and other alternative therapies, must be tailored to the individual patient and performed when an adequate diagnosis has been made and all options have been discussed with the client.

Indications for chiropractic therapy in the neurologic small animal patient can include:

- spinal hyperpathia (cervical, thoracolumbar, lumbar) in the absence of progressive neurologic deficits in cases of intervertebral disc disease or high-velocity disc injury
- neuromuscular disease such as myopathy (inflammatory, immune mediated, or infectious myositis) or neuropathic disease associated with endocrine disease, such as hypothyroidism or idiopathic causes
- muscle ligament, bone or tendon pain most commonly associated with underlying orthopedic disease that is either chronic or acute (i.e. traumatic)
- degenerative disease (spondylosis associated with the vertebral column).

However, the role of veterinary chiropractic has not been fully researched in veterinary medicine and questions still exist regarding its indications for use and its true efficacy. It is not, a replacement for conventional therapy if the patient is exhibiting a deteriorating spinal cord condition, such as intervertebral disc rupture causing acute paralysis, or neoplasia.

Massage therapy[14, 15, 20, 30, 36]

Massage therapy in veterinary medicine has increased in popularity in recent years. It is especially popular in the equine sector, but is also used quite extensively as a subcategory of physical therapy in small animal medicine and surgery. It is defined as the intentional and systematic manipulation of the soft tissues of the body to enhance health and healing. The primary characteristics of massage are the applications of touch and movement. The scientific rationale behind this therapy implies that the function of the hands and the mechanical pressure exerted on cutaneous and subcutaneous structures affect the body. Enhancement of blood and lymph circulation is achieved resulting in increased oxygen supply and, in theory, the removal of endogenous waste products. It is theorized that direct mechanical pressure and its effects mediated by the nervous system can benefit areas of increased muscle tension. It is also theorized that massage stimulates the parasympathetic nervous system. That can result in relaxation and pain reduction through two different neural-gating mechanism theories. One, as mentioned previously in the effects of acupuncture, is the gate theory of pain control, which states that a gate or gates exist throughout the spinal cord. Peripheral pain messages travel to these spinal cord gates and, depending on whether the gates are open or closed, the pain message travels on to the brain, where it is recognized. Involved, as well, are two types of nerves: the A-delta, small diameter fibers that originate from nociceptive (pain) receptors and the A-beta, large diameter fibers that are sensitive to touch, pressure, and warmth. Both are theorized to stimulate T-cells in the spinal cord and then send messages to the brain. T-cell activity is also mediated through the substantia gelatinosa (SG), which is also associated with the spinal cord and receives input from the A-beta fibers. When the SG is stimulated, the T-cell activity closes "the gate." Opposite to this, the delta fibers sensitive to pain interfere with this SG activity, thus the T-cell activity is increased and "the gate" opens, allowing pain impulses to be recognized by the brain. This theory implies that massage therapy closes "the gate" (stimulates the A-beta fibers) and thus decreases the patient's pain perception. The second theory states that massage increases restorative sleep, resulting in the decreased release of substance P, a pain transmitter. Relaxation through massage is thought to decrease O_2 consumption, and metabolic rate, reduce blood lactate, decrease blood pressure, decrease muscle tension, and increase blood flow, although reports in human literature have been mixed.

Massage therapy in veterinary medicine is best used as an adjunctive therapy. Techniques of massage include trigger-point massage (myotherapy or myofascial-trigger point massage), acupressure, ice massage, effleurage, petrissage, and friction or deep cross-fiber friction. In addition, passive movements as part of passive range-of-motion exercises can be classified as a form of massage because of its requiring hands-on contact; such movements are performed within the limits of the soft tissue without stretching, and the goal is to improve synovial joint fluid production and increase joint mobility. The use and benefits of massage have been described more thoroughly in the equine, but its use with small animal patients is increasing in popularity.

Neurologic conditions that would benefit from massage therapy as an adjunctive treatment include patients with trauma to the forebrain and vestibular systems, cerebrovascular accidents, spinal cord injuries such as postoperative intervertebral disc rupture patients, nonsurgical spinal cord injury such as FCE, and high-velocity disc injury, concussive spinal cord injuries, brachial plexus avulsions, and selected peripheral myopathies and neuropathies. The key to therapy is to identify the underlying disease process and to institute adjunctive massage during the recovery period. Care must be taken to choose the correct patient and the correct initiation and application of the therapy.

Therapeutic ultrasound[14, 15, 20, 37, 38]

Therapeutic ultrasound is a heat-producing modality effective in postacute or chronic injury. Ultra-high frequency, 1 MHz sound waves can transfer energy to the affected tissues molecular causing an oscillatory motion. This oscillation leads to increase temperature in this tissue. Temporarily increased extensibility of the soft tissues (ligaments, tendons, fibrous scar tissue) can occur with such heating and, combined with range of motion exercise, can induce improvement. Ultrasound is absorbed by collagen-dense tissue, and tissues with high fluid content (blood and muscle) absorb sound waves better. Nerve has a high coefficient of ultrasound absorption. Ultrasound may prove useful in the treatment of peripheral nerve and muscle injuries when used appropriately.

Ultrasound also is used for its heating effects; this comes from mechanical activity in the tissue as sound waves increase molecular motion. Increases in tissue temperatures cause an increase in circulation and nerve conduction velocity. Pain threshold is increased and metabolic activity is stimulated. Ultrasound can also be used to deactivate muscle trigger points and acupuncture points. The nonthermal effects of ultrasound are also theorized. Movement of the ultrasound wave through the tissues produces cellular responses that aid in the stimulation of tissue repair. Fibroblasts are stimulated to produce more collagen during the granulation stage of repair, which begins about 3 days after injury. In addition, the entry of calcium ions that effect cellular activity are theorized to promote granulation. The use of therapeutic ultrasound for neurologic disease in the small animal veterinary patient is in its early stages, but it may prove useful primarily in diseases of the neuromuscular system (muscle and nerve) and may be of tremendous value in the future.

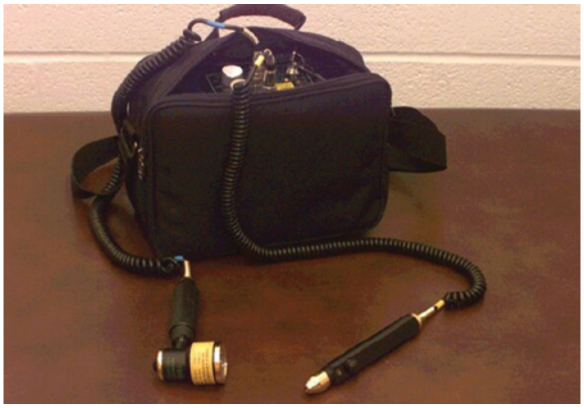

Figure 22.8 Portable low-energy photon therapy (LEPT) unit. These units can be used for stimulation of local acupoints as well as wound healing.

Therapeutic laser[20, 39]

Therapeutic laser (light amplification by stimulated emission of radiation) used in veterinary medicine has gained popularity in the veterinary world and is especially useful:

- in the treatment of a multitude of neurologic disorders of the brain, spinal cord, and neuromuscular systems
- when promoting wound-healing
- in cases where there is an aversion to acupuncture needles.

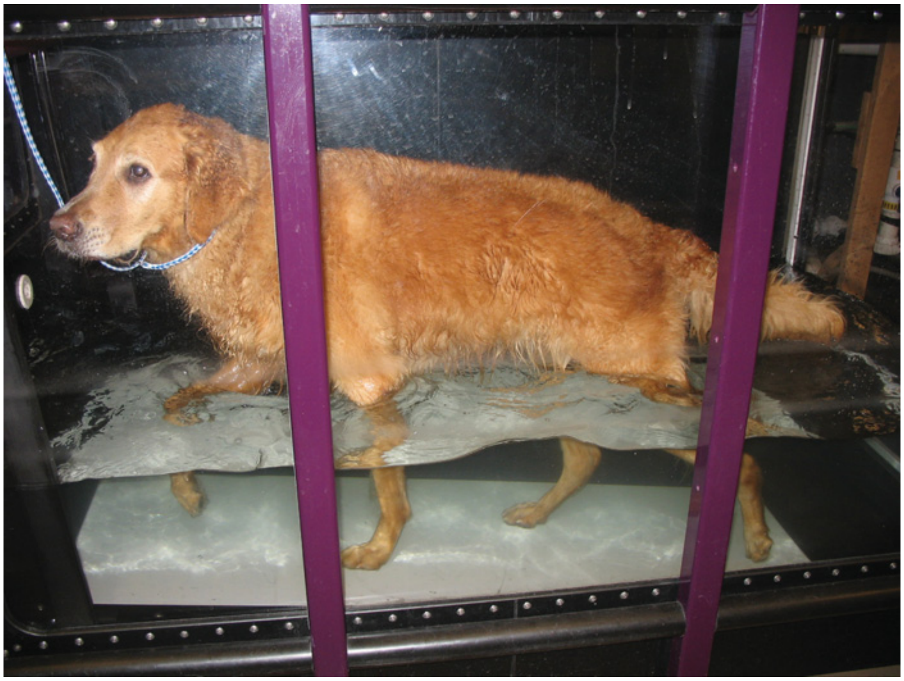

Figure 22.9 Underwater treadmill therapy plays an integral role in the rehabilitation of the neurologic patient. Spinal injuries as well as neuromuscular injuries respond well to this particular form of rehabilitation.

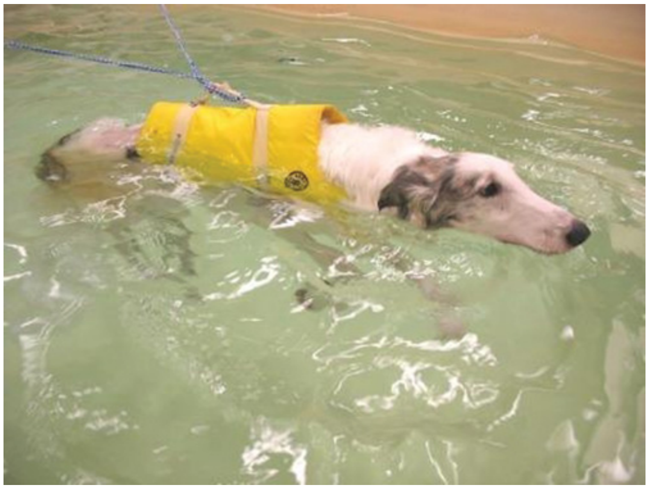

Figure 22.10 Aquatherapy has been shown to hasten the recovery of neurologic patients in patients, such as this dog that presented with a T11–T12 intervertebral disc rupture. The treatments consist of daily swimming and manual physical therapy sessions.

Traditional use includes pre- and postoperative pain management, biomodulation, soft tissue trauma and edema, wounds, ulcers tendonitis, and fasciitis. The most common laser types are the visible helium–neon (HeNe) lasers, invisible infrared (IR), gallium arsenide (GaAS) lasers and gallium aluminum arsenide (GaA1As) lasers. Diode lasers are used for the treatment of myofascial pain. Therapeutic lasers first became available in the 1970s and since 1990 2500 articles have been listed on MEDLINE on low-level laser therapy (LLLT). LLLT is a type of therapy that does not cause a thermal response but does cause a cellular chemical response. A more correct terminology is the term low-energy photon therapy (LEPT). The laser emits electromagnetic waves of 600 to 1000 nm that penetrate tissue; depth of penetration depends on tissue type and its absorption spectra. The above-mentioned lasers are designed to be used in contact with tissue. The beam is applied perpendicular to the target. LLLT is absorbed strongly by blood proteins; if gentle pressure is applied, the depth of penetration is increased. It is theorized that LEPT has both anti-inflammatory and analgesic properties, but that a correct diagnosis prior to use is mandatory. LEPT is also used to treat trigger points (TPs) acupuncture points (APs), and tender local points (*ahshi* points), as well as painful joints, muscles, tendons, wounds, and ulcers (Fig. 22.8). The neurologic applications of LEPT are aimed at pain management, the treatment of neuralgia caused or maintained by active trigger points in scars, and trigeminal neuralgia with an emphasis on trigger points, local *ahshi* points, and paravertebral *ahshi* points. In past studies, LEPT was theorized to be an effective adjunctive tool for the noninvasive treatment of peripheral nerve and spinal cord injuries in rats and dogs. In the author's experience, it is quite helpful in the postoperative treatment of dogs with hemilaminectomies and ventral slots operated on for ruptured intervertebral discs with associated soft tissue pain and

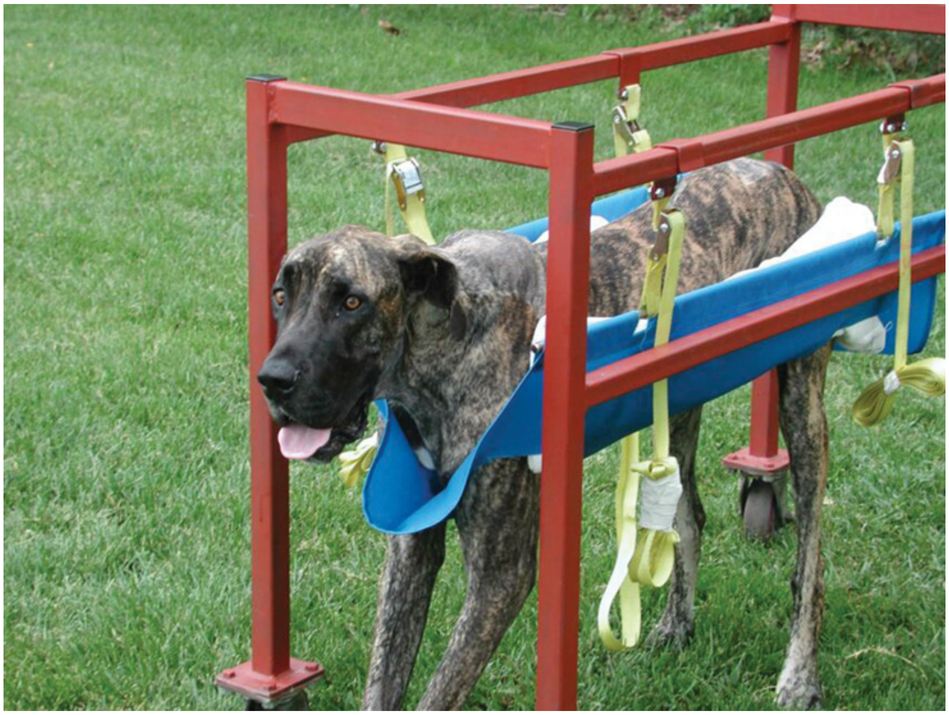

Figure 22.11 Great Dane dog with cervical spondylomyelopathy treated with a dorsal laminectomy at C4–C5. The recovery of this patient was hastened with assisted mobility devices, such as this cart, and extensive physical therapy.

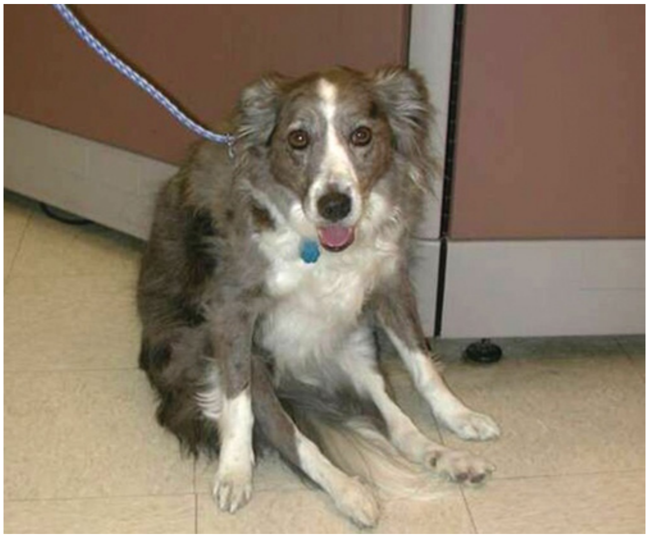

Figure 22.12 Classic stance of a T3–L3 myelopathy dog. This dog was in the backyard and running to catch a Frisbee, yelped, and 20 min later was paretic in the pelvic limbs. MRI of the thoracolumbar spine revealed findings consistent with a low-volume, high-velocity disc extrusion (type III). The dog had extensive treatment with aquatherapy and went on to recover without surgical intervention.

swelling, as well as those animals with neck or spinal pain that are, through appropriate diagnostics, found to have nonsurgical lesions (high-velocity disc, FCE) and normal cerebrospinal fluid analysis. It is not indicated when an underlying compressive lesion is detected that can be corrected surgically. Presently, the class IV laser is the most popular laser available. It is being widely used in the veterinary world. Recently, Multiwave Locked System (MLS) therapy and High Intensity Laser therapy have become popular modalities in the treatment of a variety of not only neurologic but also musculoskeletal diseases. The MLS system is theorized as having strong anti-inflammatory, anti-edema, and analgesic effects using continuous and pulsed laser emissions with different IR wavelengths within a short treatment period. Studies are ongoing that describe the use of laser therapy in veterinary neurologic disorders. Units are now commonly being used in veterinary practices as complementary modalities of treatment. The results are showing great promise.

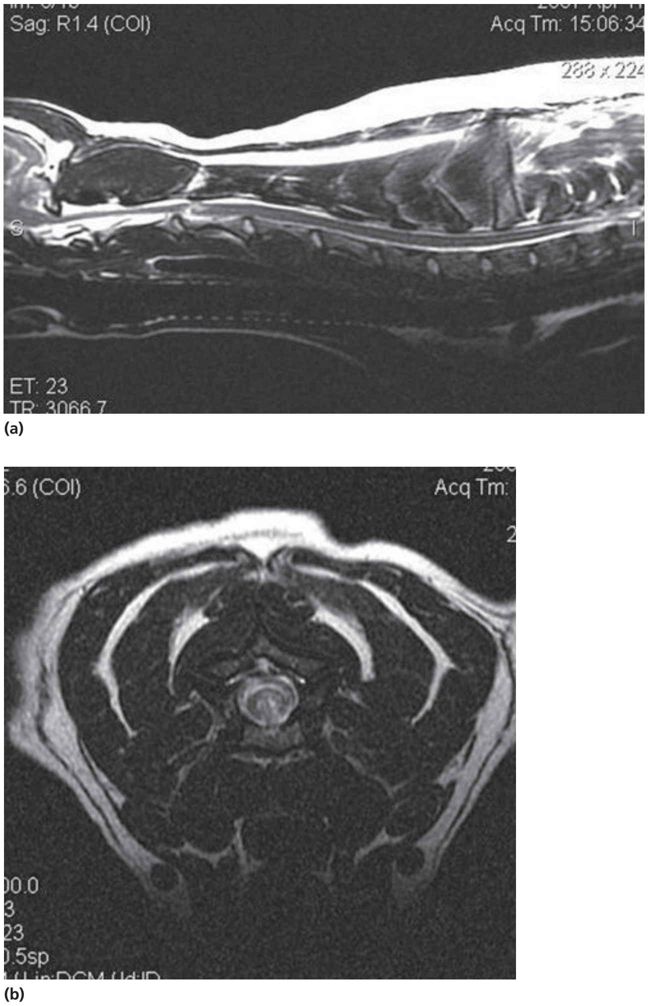

Figure 22.13 (A) Sagittal T2-weighted MRI of the cervical spine of a dog with a sudden onset of tetraparesis after exercise. (B) Transverse T2-weighted MRI. The diagnosis was a low-volume/high-velocity disc extrusion (type III) at C2–C3. Note intramedullary hyperintensity at C2–C3 in both images. Since these disc extrusions are concussive but not compressive, surgery was not performed. After weeks of rehabilitation and extensive physiotherapy, the dog was ambulatory and went on to make a full recovery.

Physical therapy[14, 15, 20, 40–46]

As mentioned above with massage therapy, physical therapy can be used as a beneficial adjunctive therapy in the rehabilitation process of the neurologic patient. Physical therapy involves the use of certain physical measures in the treatment and evaluation of diseases. The techniques used are dependent upon the location, type, and extent of the injury. Techniques include the physical modalities of electricity, light, sound, magnetics, heat, cold, manual techniques, and movement. These techniques are thought to benefit or affect the blood and lymphatic circulatory systems, the neuromuscular system, and intercell and intracell messenger systems, especially when injury, and thus imbalance, occurs. The goals of physical therapy are multiple, but optimally include the relief of pain and a return to a full range of movement and strength. Both of these goals can be accomplished when exercise is incorporated in the treatment regime.

Examples of physical therapy modalities can include electrical stimulation, aqua therapy (pool swimming or underwater treadmill; Fig. 22.9, Fig. 22.10), PROM exercises, and other physical agent modalities that have been mentioned above and in other chapters in this text. Electrical stimulation involves the application of electrical currents to an affected area either directly

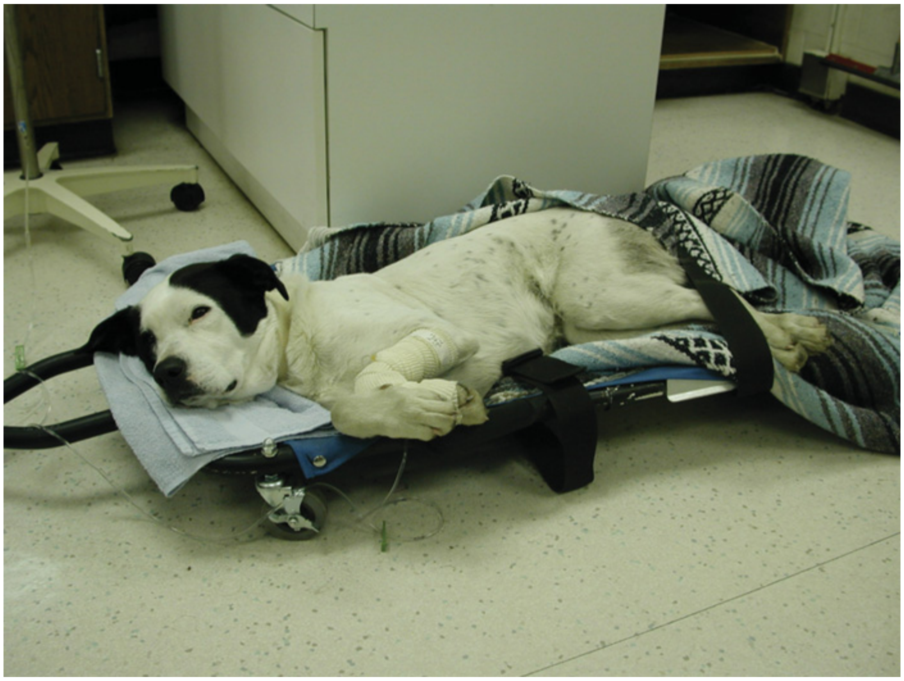

Figure 22.14 This patient presented after being hit by a car. She sustained an L3–L4 spinal luxation and had no conscious pain perception (nociception). Vertebral stapling was performed and she recovered motor function with extensive rehabilitation and physical therapy.

or through acupuncture needles. The therapeutic electric simulator emits a type of energy with wavelengths and frequencies classified as "electromagnetic radiation." Electrical stimulating currents that affect muscle and nerve tissues have the longest wavelength and lowest frequencies of any modality of the electromagnetic spectrum. Therapeutic electrical stimulation is capable of providing pain relief, stimulating edema absorption, promoting wound healing, and producing muscle contraction to decrease atrophy and to reduce spasm. Applications for its use in the veterinary neurologic patient include dogs with postoperative intervertebral disc disease involving hemilaminectomy, ventral slot surgery, or dorsal laminectomy of the cervical and lumbar spine (Fig. 22.11), postoperative brachial plexus lesions with or without result sensory neuropathies, nonhealing lick granulomas, and selected neuromuscular disorders such as idiopathic CN VII neuropathy, masticatory myositis, and ischemic myoneuropathy. When used adjunctively, electrical stimulation can provide pain relief, as well as potentially increased return to at least partial function. In humans, electrical stimulation has been used on patients with head trauma and cerebrovascular accidents. Aquatherapy incorporates a wide range of activities to include underwater treadmill and pool exercises such as swimming. The indications for aquatherapy are wide reaching and are especially useful for the recovering neurosurgical patient who needs intensive physical and mental stimulation for a prolonged period. Exercising in water is effective for improving muscular endurance, muscle strength, cardiopulmonary endurance, range of motion, agility, and psychological wellbeing, while minimizing pain. Indications for aquatherapy are the same as those listed above and it is especially useful in those animals that are rehabilitating from spinal surgery and those that are recuperating from nonsurgical spinal injuries such as high-velocity discs and fibrocartilaginous embolism (Fig. 22.12–22.14). Neuromuscular diseases such as myopathy secondary to trauma or recumbency also are great candidates for physiotherapy, especially aquatherapy (Fig. 22.15). The results of such therapies are, in some cases, remarkable.

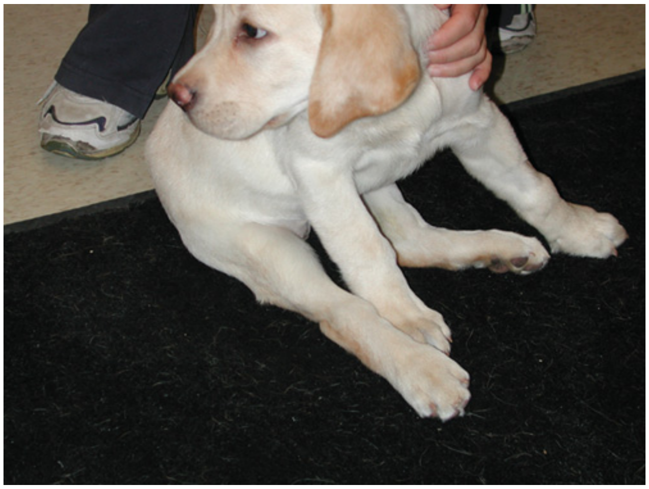

Figure 22.15 This puppy was diagnosed with *Neospora caninum* and had extensor rigidity of the right pelvic limb. He was treated with antibiotics and had extensive physical therapy, including aquatherapy and acupuncture, which helped lead to functional recovery.

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CHAPTER 23

Neurotoxicological Syndromes

David C. Dorman

Introduction[45]

There are thousands of species of plants, household products, prescription drugs, and nonprescription drugs in the United States that could result in companion animal exposure. On occasion, serious poisonings, with or without neurologic signs, can occur following exposure to these agents. This chapter focuses on common poisons that are known to induce neurotoxicity in companion animals. Earlier editions of this textbook have included agents that remain of interest to veterinarians. These include 4-aminopyridine (Avitrol), cocaine, 5-fluorouracil (5-FU), lindane, and other organochlorine insecticides, penitrems, strychnine, sodium fluoroacetate (compound 1080), hexachlorophene, methionine, morphine, and the organophosphate insecticide chlorpyrifos, especially as it relates to organophosphate-induced delayed neuropathy (OPIDN).

Unfortunately, no single document can adequately address even a small fraction of the potentially toxic agents that exist. An invaluable resource for veterinarians and clients remains the ASPCA's National Animal Poison Control Center (www.napcc.aspca.org), which provides a fee-for-service, round-the-clock toxicology telephone "hotline" (900-680-0000 or 888-426-4435). The center can provide veterinarians with specific treatment protocols and toxicity data for many of these agents.

Clinical signs (e.g. seizures) have been used to organize the chapter. This scheme is, however, simplistic because many neurotoxicants induce multiple effects, and veterinarians may miss observing critical phases of the toxic syndrome. For example, clinical signs in animals exposed to an organophosphate insecticide often include salivation, lacrimation, urination, and defecation (SLUD), miosis, bradycardia, muscle tremors, amongst others. However, some these signs (e.g. SLUD) often develop early in the course of the toxic syndrome and only a subset of these signs may be present when an animal is seen by the veterinarian. Neurologic signs can also develop due to effects on other organ systems. For example, severe hepatobiliary injury is often associated with hepatic encephalopathy. Differentiating primary from secondary neurotoxicity relies in part on the identification of additional body systems that are involved.

Diagnostic considerations[8, 16, 19, 74, 88, 89, 108, 146, 147, 158]

The first diagnostic challenge often is to determine whether an animal has been poisoned (or is at risk of developing toxicosis if an exposure occurred). Three interrelated factors help establish a toxicological diagnosis: (1) history of exposure, (2) determination of whether the exposure dose is sufficient to induce toxicity, and (3) development of compatible clinical signs. Additional findings that may further support a diagnosis of primary neurotoxicosis include (1) an acute onset and/or rapid progression of neurologic signs in a previously normal animal, (2) neurologic signs in the absence of multiple organ system involvement, (3) more than one animal involved, and (4) multifocal involvement of the nervous system (i.e. mixed cranial nerve, peripheral nervous system [PNS], and neuromuscular involvement). In all cases, a presumptive diagnosis should not be based upon a single factor.

Chemical analysis of tissues remains an important criterion and often serves as the "gold standard" for confirming a toxicological diagnosis. Freshly frozen postmortem tissue samples (1–10 g), including brain, liver, kidney, fat, GI contents, and skin (when dermal exposure occurred), should be collected for toxicological (chemical) analysis. Positive forensic findings are not always definitive proof of poisoning; conversely, negative findings don't always rule out poisoning. Neurophysiological evaluations (e.g. electroencephalography [EEG], electromyography [EMG], evoked potentials) may occasionally provide ancillary clinical evidence consistent with poisoning. Alterations in peripheral blood samples are often nondiagnostic, but cerebrospinal fluid (CSF) analysis may be of use in certain instances.

Macroscopic changes related to neurotoxicant exposure may include gross lesions or alterations in the size of a major brain region. Samples of brain, spinal cord (e.g. cervical and

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lumbar intumescences), and peripheral nerves (e.g. sciatic nerve) should be collected for histopathologic examinations from animals in which neurotoxicosis is suspected. Peripheral nerve tissue samples should be fixed while mildly stretched to prevent contraction artifacts. Morphologic lesions are often lacking in many neurotoxic syndromes, hence an absence of lesions can be as important diagnostically as their presence. In the veterinary clinical setting, samples are usually fixed by immersion in neutral buffered 10% formalin. Immersion-fixed neural tissues often exhibit artifacts (e.g. dark neurons, myelin bubbling, and neuropil vacuolation) associated with handling at necropsy and/or sub-optimal processing. In all cases, the careful correlation of data collected from the history, clinical and neurologic examinations, and supportive diagnostic tests is used to make a presumptive diagnosis of neurotoxicosis.

Treatment considerations[36, 40, 61, 66, 68, 70, 73, 120, 144, 195]

Several reviews of the management of the poisoned dog and cat are available. The basic strategies used in the treatment of a poisoned animal are relatively straightforward and include (1) initiation of life support, (2) reducing the absorption of a chemical and/or enhancing its elimination, and (3) antagonism of pharmacologic effects.

A. Gastrointestinal decontamination
Gastrointestinal (GI) decontamination remains the most common therapeutic interventions used in clinical veterinary toxicology. GI decontamination is usually used following dermal exposure since oral exposure occurs in companion animals following grooming. The simplest method involves the administration of an emetic by an owner or veterinarian. Emesis is most productive if performed within 2–3 hrs post ingestion (earlier is better!). This timeframe is influenced by the exposure dose, presence of food in the GI tract, and the rate at which GI absorption occurs. Feeding the animal a small moist meal before inducing vomiting can increase the chances of an adequate emesis. Even with repeated emesis, use of an emetic generally removes only 40–60% of the stomach's contents. Common contraindications for the use of emetics include (a) ingestion of a corrosive agent; (b) rodents, rabbits, horses, or other species incapable of safely vomiting; and (c) severe hypoxia, dyspnea, central nervous system (CNS) depression including coma, seizures, or pre-seizure activity, or other conditions that impair pharyngeal reflexes. Common emetics for home use include syrup of ipecac (dog: 1–2 mL/kg, cat: 3.3 mL/kg, PO) and 3% hydrogen peroxide (5–25 mL/5 kg, PO). Apomorphine (dog, 0.03 mg/kg, IV), and xylazine (cat, 0.44 mg/kg, IM, or SQ; dog, 1.1 mg/kg IM or SQ) can be used in a clinic setting. Apomorphine is a centrally acting emetic. Side effects such as CNS and respiratory depression, ataxia, excitement, and protracted vomiting can be seen with apomorphine. Many of these side effects can be reversed with naloxone (0.04 mg/kg IV, SQ, and IM.). Xylazine is an alpha 2-adrenergic agonist, which can cause bradycardia, hypotension, reduced respiratory rate, and CNS depression. The side effects of xylazine often outweigh the benefits for its use as an emetic. Yohimbine (0.1 mg/kg, IV) can be used to reverse xylazine.

In some cases (e.g. potentially lethal oral exposures have occurred), gastric or enterogastric lavage under general anesthesia is indicated. Examples of neurotoxic agents when enterogastric lavage may be indicated would include strychnine, metaldehyde, tricyclic antidepressants, 5-fluorouracil, and isoniazid. Gastric lavage should not be performed in cases of caustic or petroleum distillate ingestion.

Activated charcoal powder (1–4 g/kg, PO) combined with a saline (magnesium or sodium sulfate at 250 mg/kg, PO) or osmotic cathartic as a suspension in water (10 X volume) is also administered orally or by gastric tube. Unless otherwise indicated, the reader should assume that charcoal and a saline cathartic should be used for recent oral exposures (i.e. ingestion occurred within 1–2 hrs) to the agents discussed in the text.

B. Control of seizures and CNS excitation
Seizures and severe CNS excitation induced by a wide range of neurotoxicants are often controlled with diazepam (0.5 mg/kg, IV, repeated as needed every 10 min for up to three doses). Seizures may also initially be controlled with propofol (0.1 to 0.6 mg/kg/min, IV). The use of propofol requires establishing an airway and constant patient monitoring. Other seizure control medications (e.g. phenobarbital at 2.0 to 5.0 mg/kg, IV, q 20 min up to two times) may also be needed when diazepam or propofol fail to abolish seizure activity. As a rule, phenothiazine tranquilizers are best avoided in poisoned animals because they may aggravate CNS depression and, in some cases, may induce extrapyramidal effects, seizures, and hypotension. More detailed information on the management of seizures is provided in Chapter 9.

C. Control of CNS or respiratory depression
Naloxone is specifically recommended for the treatment of exogenous opiate (e.g. morphine, codeine) toxicosis because it lacks opiate agonist activity. The plasma half-life and duration of action of naloxone is relatively short (45 to 90 min), thus repeated doses (0.04 mg/kg, either IV, IM, or subcutaneous) are often required for the treatment of opiate-induced coma. Naloxone has also been used to manage nonopiate-induced CNS depression (i.e. from barbiturates and benzodiazepines). The value of analeptics (e.g. doxapram, nikethamide) in the treatment of poisoned animals is debatable at best, given that it is difficult to stabilize patients given these drugs. Potential adverse effects associated with doxapram include hypertension, arrhythmias, dyspnea, convulsions, and rebound CNS depression.

D. Enhanced clearance following ingestion

Increasing renal clearance through diuresis with or without ion trapping has limited application in neurotoxicology. One reason is that many neurotoxicants are highly fat-soluble and lipophilic agents are poorly excreted by the kidney without prior (hepatic) metabolism to more hydrophilic metabolites. In rare cases (e.g. amphetamine, phencyclidine), urine acidification with ammonium chloride (100 to 200 mg/kg/day, PO divided four times daily) or ascorbic acid (20 to 30 mg/kg, PO) is used to ion-trap weak organic bases. Urine acidification is, however, contraindicated if the animal has reduced renal function or if myoglobinuria is present (e.g. secondary to muscle damage). One emerging approach to enhancing whole body elimination is so-called lipid therapy. The administration of an intravenous lipid emulsion (ILE) was initially used in human medicine to manage local anesthetic systemic toxicity. The use of ILEs has subsequently shown promise as an effective antidote for other drug poisonings (e.g. ivermectin, moxidectin, verapamil). ILE is composed of neutral, medium to long-chain plant-based triglycerides. Formulations contain 10–30% lipid. The pharmacological mode of action of ILE remains unknown but may relate to beneficial metabolic effects and/or changing the lipophilicity of the blood resulting in the sequestration of fat-soluble materials in the blood ("lipid sink"). A recent in vitro study has shown that the binding of drugs to a lipid emulsion is favored when the drug is highly lipophilic (i.e. positive lipid partition constant) and has a large volume of distribution (i.e. the drug distributes into the fat and muscle).

Potential adverse effects associated with ILE therapy include untoward drug–drug interaction (i.e. ILE may affect the efficacy of anticonvulsants and other therapies), pancreatitis, lipid emboli, product contamination (e.g. microbial growth if inappropriate handling or storage occurs), hypersensitivity reactions, and so-called fat overload syndrome, which is characterized by hyperlipidemia, hepatomegaly, icterus, and hemolysis. Lipemia secondary to ILE administration can also interfere with certain clinical chemistry tests (e.g. blood glucose).

Several different ILE infusion protocols have been published. ILE therapy should use a 20% lipid solution that is given slowly as an intravenous infusion over 2–15 min. Typical loading (bolus) doses range from 1.5 to 2.0 mL/kg. A continuous rate infusion (CRI) at 0.06 to 0.5 mL/kg/min for 30–60 min is then used. Up to three bolus and CRI (total) infusions can be given. Repeated ILE administration should be considered if an animal remains symptomatic and the serum is clear of lipemia. ILE should not be repeated if the serum appears orange or yellow. The use of ILE therapy remains in its infancy in veterinary medicine and the ASPCA's National Animal Poison Control Center has been at the forefront of this treatment approach. Consultation with this group prior to initiating ILE therapy is advised.

Poisons associated with CNS stimulation and seizures[6, 9, 11, 15, 21, 22, 33, 37, 41, 44, 47, 56, 60, 63, 67, 69, 71, 76, 79, 84, 90, 97, 99–101, 109–111, 113, 119, 123, 126–128, 130, 135, 139, 152, 168, 170, 171, 181, 185, 187, 189, 191, 192, 200]

Within this chapter, "seizures" refers to involuntary, paroxysmal brain disturbances usually manifested by uncontrollable muscular activity (e.g. paddling), abnormal psychomotor behavior (e.g. fly biting, tail chasing), autonomic dysfunction (e.g. urination, defecation, salivation), and altered behavior during the immediate postictal phase (e.g. CNS excitation, depression). Box 23.1 lists several poisons associated with CNS stimulation or seizures.

Exposure to "seizurogenic" agents may result in hyperactivity, hyperesthesia, muscle tremors and fasciculations, and behavioral manifestations (e.g. aggression). Head trauma may result secondary to toxicant-induced ataxia and seizures. A recent review of cases presented to a German veterinary hospital revealed that toxicant exposure could account for approximately 4% of all cases of seizure disorders in dogs. Another recent

Box 23.1 Neurotoxic agents associated with CNS stimulation and seizures in companion animals and/or other veterinary species.

Aluminum phosphide
4-Aminopyridine (Avitrol)
Amphetamines
Benzyl alcohol
Bromethalin
Brunfelsia australis (yesterday, today and tomorrow tree)
Caffeine
Carbamate insecticides
Carbon monoxide
Cicuta sp. (water hemlock)
Cocaine
N,N-Diethyl-m-toluamide (DEET)
Fluoroacetate (1080)
5-Fluorouracil
Ivermectin
Lead
Marijuana (rare)
Mercury
Metaldehyde
Methylphenidate
Methylxanthines (caffeine, chocolate)
Narcissus sp. (daffodil, jonquil)
Opiates (cats)
Organochlorine insecticides (e.g. lindane)
Organophosphorus insecticides
Pemoline
Piperazine
Pseudoephedrine
Pyrethrin and pyrethroid insecticides
Strychnine
Synthetic cannabinoids
Tetanus toxin
Thiaminase
Tremorgenic mycotoxins (e.g. penitrem)
Tricyclic antidepressants (e.g. imipramine)
Zinc phosphide

Agents presented in either the current edition or previous editions of this textbook are identified using either bold or italic text, respectively. See also Khan (2012).[95]

United Kingdom study examining dogs with toxicant-induced status epilepticus showed that recurrent seizure episodes did not occur following prolonged (> 30 min) seizures. These results suggest that long-term treatment with antiepileptic drugs after the initial toxicant-induced seizure has been controlled isn't warranted.

A. Amphetamine and amphetamine derivatives

Amphetamine poisoning in dogs and cats most commonly results from the accidental ingestion of amphetamine-based stimulants. These medications are used for the treatment of attention deficit hyperactivity disorder (ADHD) and/or narcolepsy. Examples of prescription amphetamine derivatives include Adderall (amphetamine and dextroamphetamine salts), Dexidrine (dextroamphetamine salts), and Desoxyn (methamphetamine hydrochloride). Amphetamine-based drugs are also increasingly used for recreational (i.e. illegal) purposes.

The primary therapeutic action of amphetamines is monoamine (e.g. dopamine, norepinephrine) release. Amphetamine is chemically and structurally related to dopamine and noradrenaline and is a competitive substrate for the norepinephrine reuptake transporter (NET) and dopamine reuptake transporter (DAT). Amphetamine is actively transported into monoaminergic nerve terminals and induces impulse-independent release of cytosolic catecholamines. Since amphetamine's isomers compete with endogenous catecholamines for transport into presynaptic terminals via NET and DAT, they delay synaptic neurotransmitter clearance. Amphetamine stimulates the release of catecholamines (e.g. norepinephrine) from the adrenal glands as well as the cerebral cortex, medullary respiratory center, and reticular activating system.

Amphetamine poisoning may result in cardiac and CNS effects. Clinical signs develop within 1–2 hrs after ingestion and may include hyperactivity, mydriasis, hyperthermia, tachycardia, lactic acidosis, hypertension, and (infrequently) seizures. Hematological effects in dogs have also been reported and include a marked decrease in the number of nucleated red blood cells and leukogram abnormalities consistent with glucocorticoid-mediated stress. Amphetamine-induced hyperpyrexia with secondary bone marrow damage may account for the observed metarubricytosis.

The amphetamine-like drug pemoline has largely been discontinued in the United States due to concerns related to hepatic toxicity. Pemoline has been shown to cause clinical signs in dogs at doses of > 2.8 mg/kg. The types of clinical signs detected in dogs with pemoline toxicosis are similar to those reported in dogs that ingested amphetamine and include agitation, tachycardia, hyperresponsiveness, hyperthermia, and mydriasis. Clinical signs and symptoms seen in children with pemoline toxicosis include sinus tachycardia, hypertension, hyperactivity, choreoathetoid movements, and hallucinations.

The treatment of amphetamine toxicosis rests upon early GI decontamination and supportive care (including control of cardiac arrhythmias and hyperthermia). Modestly enhanced amphetamine elimination may occur following ion trapping with urine acidification. Chlorpromazine (10–18 mg/kg, IV) or haloperidol (1 mg/kg, IV) given after administration of a lethal intravenous dose of amphetamine sulfate (10 mg/kg) experimentally reduced the hyperthermia severity and also increased survival rates in amphetamine-poisoned dogs. Diazepam may also be used to control seizures and may assist in calming the affected animal. Although amphetamine poisoning is rarely recognized in animals, its true incidence may be higher because of the reluctance of owners to admit to illegal drug use. The reported estimated acute oral LD_{50} in rodents ranges from 10–30 mg/kg. Amphetamine may be detected in blood, CSF, and other tissue samples.

B. Methylphenidate

Methylphenidate is also used to control ADHD and narcolepsy in humans. Unlike the amphetamines, the pharmacologic mode of action of methylphenidate (as the d-isomer) is to inhibit noradrenaline and dopamine reuptake at the nerve terminus. Despite this difference, the pharmacodynamics of methylphenidate are similar to those of the amphetamines, with peak effects occurring 30–45 min after dosing. Immediate and extended release formulations of these drugs are available.

The LD_{50} for methylphenidate in companion animals has not been established. An LD_{50} value of 190 mg/kg has been reported in mice. The reported mean dose of methylphenidate seen in clinically affected dogs referred to the ASPCA's National Animal Poison Control Center was 14.1 mg/kg (lowest dose was 0.39 mg/kg). The most frequently reported clinical signs seen in companion animals following methylphenidate ingestion included agitation, hyperactivity, pacing, clinging, inappropriate urination, circling, excitation, lethargy, anxiety, muscle fasciculations and tremors, CNS depression, and ataxia. The cardiopulmonary and digestive systems are also frequently affected in exposed dogs. Additional clinical signs and symptoms reported with methylphenidate overdose in humans include hallucinations, seizures, tachycardia, cardiac arrhythmias, hypertension, and hyperthermia.

Oral administration of methylphenidate results in rapid and nearly complete GI absorption; therefore, rapid GI decontamination is required (especially with the immediate release formulation). Control of cardiac arrhythmias, and hyperthermia, and the judicious correction of acid-base and electrolyte disturbances may also be required. Chlorpromazine (3 mg/kg, IV) or acepromazine (0.025 to 0.2 mg/kg, IV, IM, or SC) may be used to control hyperactivity, tremors, and other pacing, excitement, and CNS abnormalities. Propranolol (0.02 to 1.0 mg/kg, IV or 0.1 to 0.2 mg/kg, PO, q

8 hrs) may be used to control tachycardia and certain other cardiac arrhythmias.

C. Caffeine

The methylxanthine caffeine can be found in chocolate, coffee, and tea. Energy drinks and other similar products also contain appreciable quantities of caffeine. Drinks made from the fruit of the guarana (*Paullinia cupana*) plant can also contain high levels of caffeine. Clinical signs of caffeine toxicosis in dogs and cats generally develop within several hours of ingestion and may include vomiting (often the first sign), restlessness, hyperactivity, ataxia, muscle tremors, tachycardia, cardiac arrhythmias, seizures, polyuria/polydipsia, hyperthermia, cyanosis, and coma. Histologic lesions in the brain or spinal cord are usually lacking. The exact toxicological mechanism of action of caffeine is not known but may include inhibition of phosphodiesterase, enhanced catecholamine release, adenosine antagonism, or increased calcium entry into the cell. Caffeine toxicosis in animals most commonly occurs following the ingestion of chocolate; however, accidental poisonings may also occur from the ingestion of caffeine-containing products. Poisoning in a parrot resulting from chocolate ingestion has also been reported. Caffeine is well absorbed from the GI tract, and is highly metabolized by the liver to its inactive metabolites methyluric acid and methylxanthine. The plasma half-life of caffeine in dogs is approximately 4.5 hrs. The treatment of caffeine toxicosis in animals is usually symptomatic and supportive. Fluid therapy to enhance diuresis, anticonvulsants, antiarrhythmics, and repeated oral activated charcoal administrations are generally recommended. The oral LD_{50} of caffeine in the dog is approximately 140 mg/kg.

D. *Brunfelsia australis* (yesterday, today, and tomorrow tree)

This tropical tree is increasingly grown in the United States because of its colorful flowers and drought resistance. The flowers turn from purple (yesterday), to lavender (today), and white (tomorrow) as they mature. The smooth muscle relaxant scopoletin and the presumed convulsants hopeanine and brunfelsamidine have been isolated from this plant. Clinical signs reported in dogs with suspected *Brunfelsia* poisoning included vomiting, diarrhea, salivation, lethargy, moderate ptyalism, mydriasis, abdominal pain on palpation, bradycardia, “manic-type” behavior, ataxia, muscle fasciculations, rigidity (“sawhorse stance”), and seizures. Clinical management includes GI decontamination and symptomatic and supportive care including anticonvulsants.

E. Lead

The incidence of lead toxicosis in companion animals appears to be decreasing; nevertheless, it remains an important clinical problem. Historical sources of lead include lead-based paints, battery plates, certain caulking compounds and putties, linoleum, plumbing solder, roofing material, and asphalt. Water from lead plumbing, glazed crockery pots, and streams polluted by lead-contaminated effluent also may contain toxic concentrations of lead. Ingestion of older (pre-1978) lead-based household paints remains an important source of companion animal poisoning. Inhalation of lead may also pose a concern in confined areas where lead-based dusts or fumes are present (e.g. gun firing ranges).

Generally, only 5–10% of ingested lead is absorbed in adults, but 40–50% is absorbed from the GI tract in juveniles, thus young animals are more susceptible to lead poisoning than are adults. Lead may dissolve to an appreciable degree in the acid environment of the stomach, greatly increasing its absorption. In contrast, metallic lead shots or bullets lodged in tissue do not readily dissolve except in joints or abscesses. Once absorbed, lead readily passes membrane barriers such as the blood–brain barrier and the placenta. Distribution is primarily to the kidney cortex, liver, and bone; the bone contains up to 98% of the total body lead burden. When the bone becomes saturated, signs of toxicosis may develop suddenly.

Signs of lead toxicosis are generally referable to the nervous and GI systems. Neurologic signs with acute onset tend to predominate with higher exposure levels, while GI signs and chronic illness may be more common with lower exposures. However, both systems may be affected concurrently. In decreasing order of frequency, signs in dogs and cats are vomiting, seizures, anorexia, hysteria, and weight loss. In both dogs and cats, seizures are a common neurologic sign; therefore, lead toxicosis should be considered in any animal exhibiting seizures. EEG changes in dogs with lead-induced neurologic signs are not pathognomonic and may include intermittent or continuous high-amplitude slow wave activity. Hysteria is also commonly reported and is characterized by barking and crying continuously, running in many directions without purpose, indiscriminate biting of animate and inanimate objects, and other behavioral changes. Other neurologic signs include ataxia, tremors, and blindness. Animals may also develop aggression, dementia, pica, megaesophagus, and coma. Additional neurologic signs reported in cats include CNS depression, cerebellar or vestibular ataxia, and vertical nystagmus. Megaesophagus attributable to lead toxicosis has also been reported in cats. Differential diagnoses based upon history and clinical signs include rabies, canine distemper, epilepsy, encephalitis, spinal cord trauma, and other poisons. Lead poisoning likely remains more common in dogs than in cats.

Blood-lead determination remains the single best indicator of relatively recent exposure to lead. Whole blood (heparinized or EDTA-containing tubes) rather than serum should be used since $> 90\%$ of circulating lead is bound to erythrocytes. Although a valuable indicator of exposure, blood-lead concentrations do not reflect the length of exposure, total body burden amount of lead, or severity of clinical signs. Other diagnostic laboratory tests include urine lead or urine δ-aminolevulinic acid (ALA) concentrations and blood zinc protoporphyrin (ZPP) levels. Signs of lead toxicosis may resolve fairly quickly following the initiation of therapy, despite concurrent high blood-lead concentrations. Cats may exhibit signs of lead toxicosis at lower blood-lead concentrations than dogs. The finding of numerous erythrocytes with basophilic stippling and/or immature (especially nucleated) erythrocytes without evidence of anemia is suggestive of lead poisoning; however, this hematologic effect is often lacking in dogs and cats. Other causes of nucleated red blood cells (e.g. endotoxemia, leukemia, splenic diseases) should also be considered. Paint chips or other lead objects within the GI tract may occasionally be detected on abdominal radiographs. Radiopaque material in the GI tract helps to rule in lead, but negative findings do not rule it out.

For postmortem diagnosis, fresh frozen liver and kidney tissue should be submitted for lead chemical assay. Histologic changes potentially induced by lead include renal tubular necrosis and amorphous acid-fast intranuclear inclusions in hepatocytes and renal tubular epithelial cells. Lesions occur in the CNS (lead encephalopathy) as well as in the PNS (lead neuropathy). The likely primary lesion in acute human lead encephalopathy is breakdown of the blood–brain barrier, and similar effects are also observed in animals. Brain capillaries may be dilated, narrowed, necrotic, or thrombosed, and endothelial cells often swell. The consequent extravasation of fluid results in cerebral and cerebellar edema. Accompanying these vascular changes is neuronal necrosis (cerebrocortical and Purkinje cells) with secondary reactive gliosis and astrocytic scar formation. Neuronal lesions may be caused directly by lead rather than by defective vascular function since neuronal necrosis without vascular injury has been observed in acute experimental lead toxicity. In the PNS, lead neuropathy in humans, experimental animals, and cats is manifested by Wallerian axonal degeneration and segmental demyelination affecting primarily motor nerves.

The treatment of lead poisoning is directed at controlling seizures and other life-threatening signs, removing lead from the GI tract, elimination of absorbed lead from soft tissue and bone, and identifying the source in order to prevent further exposure. Small pieces of metallic lead and lead paint chips can be removed from the GI tract with emetics and saline cathartics. Larger lead objects in the stomach or intestine may require endoscopic or surgical removal.

Historically, the most commonly used chelator for lead has been $CaNa_2EDTA$. This agent has been used in a variety of animal species. In both cats and dogs, $CaNa_2EDTA$ is given subcutaneously at 18.75 to 27.5 mg/kg, every 6 hrs, for 2–5 days. Prior to injection, $CaNa_2EDTA$ should be diluted to a final concentration of 10 mg/mL in 5% dextrose solution. Higher concentrations of $CaNa_2EDTA$ may cause pain at the injection site. Intravenous injection may be more effective, but requires additional labor resources. Continuous $CaNa_2EDTA$ therapy should not last more than 5 days because of $CaNa_2EDTA$'s effects on the normal growth of the intestinal epithelium, enhanced zinc elimination, and nephrotoxicity. However, multiple treatments are occasionally necessary and each 5 days of treatment should be followed by a 5-day rest period. The clinical condition of the animal and blood-lead measurements is used to determine when to stop therapy. Due to $CaNa_2EDTA$-induced increases in zinc elimination, oral zinc supplementation at 2 mg/kg may be necessary in dogs on low-zinc diets or those given multiple chelation treatments.

D-penicillamine has also been recommended for asymptomatic dogs as a home-based follow-up therapy to inpatient chelation therapy, especially in animals with persistently elevated blood-lead concentrations. D-penicillamine is given orally at 110 mg/kg daily for 2 wks followed by a 1-wk rest. To prevent chelation of essential metals in the diet, D-penicillamine should be administered on an empty stomach (30 min before feeding). It may be necessary to divide the daily dose and give it every 6–8 hrs or decrease the total dose to 33–55 mg/kg daily if adverse effects—such as vomiting, listlessness, or anorexia—persist. Antiemetic drugs may also be administered 30 min to 1 hr before the D-penicillamine to reduce vomiting. D-penicillamine is well-absorbed from the GI tract. D-penicillamine is metabolized by the liver with very little excreted unchanged, and elimination is primarily via the kidney and liver. Side effects associated with D-penicillamine use include reversible proteinuria and hematuria. It may also enhance the absorption of lead from the GI tract; therefore, GI tract decontamination prior to chelation therapy and prevention of further exposure to lead are important.

The use of 2,3-dimercaptosuccinic acid (DMSA) has dramatically improved lead chelation therapy. In contrast to other chelators, DMSA is a relatively selective, orally active, water-soluble chelating agent. Orally administered DMSA apparently does not increase lead absorption from the GI tract, and potentially may reduce it. It is still imperative to prevent ongoing oral exposure to lead; however, if re-exposure should occur (as in an outpatient setting), concurrent treatment with DMSA is unlikely to pose a particular risk. Side effects of DMSA reported in humans are limited. Elevations in serum alanine transaminase have been reported in humans, but these also may be induced by lead toxicosis. DMSA appears not to have a clinically significant effect on the excretion of essential minerals including calcium, magnesium, iron, copper, and zinc. Dogs and cats treated with DMSA (10 mg/kg of body weight, PO, q 8 hrs) for 10 days had reduced blood-lead concentrations and eliminated clinical signs of lead poisoning. Thiamine hydrochloride (2 mg/kg every 6 hrs) may be beneficial in lead-poisoned dogs, although its efficacy has not been proven experimentally.

Another factor that should be considered is the possibility that children or adults may also have been exposed to lead from the same source as their pets. This is especially true if the exposure history includes possible risk factors for exposure like a recent remodeling of an older home that contains lead-based paints.

F. Permethrin and other pyrethrin and pyrethroid insecticides

Pyrethrins are natural insecticides, while pyrethroids (e.g. permethrin, fenvalerate) are more stable synthetic insecticides. Toxicological mechanisms of action of these insecticides include interference with sodium channels, enhanced sodium ion conductance, and postsynaptic γ–aminobutyric acid (GABA) receptor-chloride ionophore complex blockade. Pyrethrins and pyrethroids possess low acute oral toxicity to mammals (acute oral LD_{50}s range from 25 to 10,000 mg/kg) due to their rapid hydrolysis in the GI tract and liver metabolism. Synergists (e.g. piperonyl butoxide, N-octyl-bicycloheptene dicarboximide [MGK 264]) are often added to insecticide formulations to decrease pyrethrin and pyrethroid metabolism and increase their insecticidal activity. It is likely that esterases involved in pyrethrin and pyrethroid insecticide metabolism may also be inhibited by prior organophosphorus or carbamate insecticide exposure, increasing the likelihood of pyrethrin toxicosis.

The use of permethrin-based "spot-on" formulations (contain 45–65% permethrin) has been associated with toxicity in cats and occasionally dogs. Toxicosis generally develops within hours of exposure, but may be delayed as a result of prolonged exposure from dermal absorption or grooming. Initial clinical signs associated with the application of permethrin spot-on products include paresthesia manifested by ear twitching, paw and tail flicking, hyperexcitability, and hyperesthesia. Paresthesia to spot-on products may be treated by applying a vitamin E-based oil, olive oil, or corn oil on the site of insecticide application. More severe clinical signs associated with the development of pyrethrin or pyrethroid insecticide poisoning in cats and dogs include muscle tremors, increased salivation, ataxia, vomiting, CNS depression, hyperexcitability or hyperactivity, seizures, dyspnea and death. The toxic syndrome is considered reversible in most sublethally exposed animals with complete recovery often occurring within 72 hrs. Gross or microscopic lesions are typically absent. Chemical analysis for insecticide residues on the skin or in the GI tract of exposed animals may be used to confirm topical or oral exposure to these agents. Elevated tissue concentrations of these insecticides, especially brain and fat, may also help to support a tentative diagnosis of lethal poisoning. Direct correlation between tissue concentrations and severity of clinical signs (including death) for most insecticides has not been determined for cats or dogs.

Treatment of toxicosis is largely supportive (washing skin, GI tract decontamination, seizure control, fluids, oxygen, and respiration support). Atropine (0.04 mg/kg, SQ) may diminish the degree of salivation and diarrhea in pyrethrin- or pyrethroid-poisoned cats. Unlike its use in organophosphorus or carbamate insecticide toxicosis, however, atropine is not considered a direct antidotal therapy for pyrethrin or pyrethroid insecticide poisoning. Methocarbamol (50 mg/kg, IV, repeat as needed to a maximum dose of 330 mg/kg/day) has been advocated for the control of permethrin-induced muscle tremors. ILE therapy has also been advocated for resolving cases in which animals have severe CNS signs (e.g. severe tremors, seizures).

Toxicants causing paralysis[1, 34, 38, 40, 46, 78, 132, 154, 161, 169, 197, 198]

Ataxia, paresis, and paralysis are gait alterations associated with dysfunction of the central or peripheral nervous systems. Ataxia is defined as a failure of muscle coordination, paresis as a partial loss or impairment of motor function, and paralysis as complete loss or impairment of motor function in a body part. The reader is referred to Box 23.2's potential toxic agents Some of these agents may also result in respiratory paralysis (e.g. aminoglycoside antibiotics).

A. Cycad palms

Cycads are a relatively primitive subtropical and tropical seed plant with a stout woody trunk and large stiff evergreen leaves. The starch obtained from the stems and processed seeds from certain cycad species is used as food by some indigenous tribes. An interesting association between the incidence of an amyotrophic lateral sclerosis/Parkinson's disease complex (ALS/PDC) and the consumption of cycad-based food products among certain inhabitants of the island of Guam has been of broad interest to the neurotoxicology community. The cycad neurotoxin β-methylamino-L-alanine (BMAA) has been postulated to play a role in these diseases. Experimental studies performed in rhesus monkeys has shown that BMAA ingestion can result in limb muscle atrophy, nonreactive degeneration of anterior horn neurons, degeneration and partial loss of pyramidal neurons of the motor cortex, and conduction deficits in the central motor pathway. It appears that BMAA may induce its neurotoxic effects via an excitatory toxic mode of action. Excitotoxic cell death involves prolonged depolarization of neurons, changes in intracellular calcium concentrations, and the activation of enzymatic and nuclear mechanisms of cell death. The main excitatory amino acid receptors are quisqualate/α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), *N*-methyl-d-aspartate (NMDA), and metabolic glutamate receptors (mGluR), all of which are activated by glutamate and similar substances. This mode of action is shared by many other neurotoxicants.

Cycad poisoning in species of veterinary relevance also occurs. Cattle can be affected with neurologic and hepatic-gastrointestinal diseases appearing as somewhat distinct toxic syndromes. Neurologic manifestations include ataxia,

Box 23.2 Neurotoxic agents that cause muscle weakness, ataxia, or paralysis (denoted with *) in companion animals and/or other veterinary species.

Aminoglycoside antibiotics*
Amitraz
Baclofen
Benzyl alcohol
Black widow spider
Botulinum*
Bromethalin*****
DEET
Carbon disulfide*
Cholinesterase inhibitors
Ciguatera*
Curare*
Cycad palms*
2,4-dichlorophenoxyacetic acid (2,4-D)
Ethylene glycol
5-Fluorouracil
*Hexachlorophene**
Ivermectin
Latrodectus spp. (black widow spider)*
d-Limonene
Macadamia nuts
Marijuana
Melaleuca oil
Mercury
Methionine
Metronidazole
Moxidectin*
Nicotine*
*Organophosphorus compounds (OPIDN)**
Saxitoxin and neosaxitoxin*
Succinylcholine*
Tetrodotoxin*
Thiaminase
Ticks (*Dermacentor sp.; Amblyomma sp.*)*

*Imidacloprid.
Agents presented in either the current edition or previous editions of this textbook are identified using either bold or italic text, respectively. See also Khan (2012).[95]

lameness, conscious proprioceptive deficits, and axonal degeneration in the spinal cord and degeneration of the spinal ganglia. The most common signs in dogs ingesting cycad plants are associated with the GI and hepatic systems and include vomiting (± blood), diarrhea (± blood), and anorexia. Severe GI signs and hepatic damage with icterus and markedly elevated bilirubin concentrations and serum alanine aminotransferase and alkaline phosphatase activities often develop rapidly (within 24 hrs of consumption). These clinical signs are most likely due to the presence of the toxin methylazoxymethanol in the cycad plant. Neurologic signs occur in approximately 50% of all cases and include CNS depression, proprioceptive defects, coma, and seizures. A paralytic syndrome similar to that seen in people and cattle has not to date been reported and may reflect the need for repeated exposure to the cycad neurotoxin. A similar chronic paralytic effect (neurolathyrism) is seen in people and livestock that consume grass pea (*Lathyrus sativus*). Neurolathyrism is likely associated with the consumption of the glutamate structural analogue oxalyldiaminopropionic acid (ODAP). Treatment of cycad toxicosis primarily depends upon supportive care (e.g. GI tract decontamination, seizure control, fluids, oxygen, respiration support).

B. Moxidectin

Moxidectin is a second-generation macrocyclic lactone used for parasite control in animals. The principal mode of action of moxidectin is binding to γ-aminobutyric (GABA) and glutamate-gated chloride channels. Numerous preparations of moxidectin are available, including tablet and sustained release injectable for the prevention of heartworm disease in dogs, injectable and oral drenches for sheep, a pour-on formulation for cattle and deer, and sustained release injectable formulations for cattle and sheep. Unlike certain other macrocyclic lactones (e.g. ivermectin), moxidectin is poorly transported by p-glycoproteins. In general, moxidectin is slowly absorbed from the GI tract, and fecal excretion of the parent compound is the main elimination pathway.

Clinical signs reported in dogs poisoned with moxidectin include an acute onset of seizures followed by paralysis and coma. Other clinical signs have included ataxia, generalized muscle tremors, paresis, hypersalivation, temporary blindness, and disorientation. Toxic doses associated with these neurologic effects ranged from 1.89 to 2.85 mg/kg. Moxidectin toxicosis can be managed initially using GI decontamination with supportive care (e.g. diazepam, glycopyrrolate, IV fluids, and mechanical ventilation) as needed. Moxidectin toxicosis has also been treated using ILE therapy. In one canine case, an emulsion of 20% soybean oil in water was administered intravenously as a bolus of 2 mL/kg followed by 4 mL/kg/hr for 4 hrs beginning 10 hrs after exposure and was administered again at a rate of 0.5 mL/kg/min for 30 min beginning 25.5 hrs post exposure. Mild improvement was seen after the first dose, and dramatic improvement was noted within 30 min of the second dose. The puppy's neurologic status returned to normal within 6 hrs of the second administration, with no relapses.

Poisons associated with CNS depression, stupor, or coma[10, 12, 23, 31, 59, 81, 85, 87, 91, 93, 104, 105, 117, 118, 121, 140, 148, 150, 151, 157, 178, 179, 188, 193]

Box 23.3 lists poisons associated with CNS depression. CNS depression, stupor, and coma all represent states of altered consciousness. "Depression" connotes a lethargic animal that is incapable of responding to the environment in a normal manner.

Box 23.3 Common neurotoxic agents associated with CNS depression and semicoma in companion animals and/or other veterinary species.

Barbiturates
Benzodiazepines
Benzyl alcohol
Bromethalin
Cannabis sativa (marijuana)
Carbamate insecticides
Carbon monoxide
Citrus oil extracts
N,N-diethyl-m-toluamide (DEET)
Ethanol
Ethylene glycol
Ivermectin
Lead
Levamisole
d-Limonene
Mercury
Metaldehyde
Methionine
Opiates (e.g. morphine)
Organophosphorus insecticides
Phenothiazine tranquilizers
Piperazine
Pyrethrin and pyrethroid insecticides
Synthetic cannabinoids
Thiaminase
Zinc phosphide

Agents presented in either the current edition or previous editions of this textbook are identified using either bold or italic text, respectively. See also Khan (2012).[95]

Semicoma is a stuporous state in which the animal only responds to painful stimuli. In coma, animals are unconscious and unresponsive to any stimulation. The presence of CNS depression alone is not useful diagnostically since it often occurs in any ill or intoxicated animal. Agents that induce CNS depression may also inhibit cardiopulmonary function, resulting in hypotension, respiratory depression, and secondary cerebral hypoxia.

A. Barbiturates

Barbiturate use in human medicine has decreased significantly in recent years, while barbiturates are still widely used in veterinary medicine. Animal poisoning may be the result of the ingestion of barbiturate-based drugs, ingestion of barbiturate euthanized animals, ingestion of illicit street preparations, or from iatrogenic overdose. Potentially toxic barbiturate residues can remain in carcasses for several years. Barbiturates have multiple mechanisms of action, including inhibiting calcium accumulation in neural tissue, inhibition of neurotransmitter release, and GABA-mimetic action within the CNS. Profound respiratory and CNS depression, general anesthesia, hypothermia, hypotension, shock, cyanosis, and coma are the predominant clinical signs observed following barbiturate exposure. Dyskinesia has also been reported in a dog given phenobarbital to control seizures. Other adverse effects of phenobarbital therapy reported in dogs include blood dyscrasias, liver failure, sedation, agitation, ataxia, paraparesis, polyuria, polydipsia, and polyphagia. Death in acute poisoning cases is usually caused by respiratory arrest. The reported oral median lethal dose of pentobarbital in the dog is 85 mg/kg. Although a minimum oral lethal dose is unknown, it is presumably somewhat greater than the 28–30 mg/kg recommended orally to produce anesthesia.

Barbiturates are commonly classified according to their duration of effect into long, intermediate, short, or ultra-short acting. In general, barbiturates are rapidly distributed throughout the body, although their distribution is influenced by the lipid solubility of the individual agent. Dependent on animal species and chemical form, barbiturates are metabolized extensively by the hepatic microsomal enzyme system and are also eliminated by renal excretion. Nonhepatic metabolism (kidney, brain, other tissues) may also contribute to the metabolism of some barbiturates. Termination of biologic activity is by redistribution in the body and side-chain oxidation. Significant amounts of phenobarbital are excreted unchanged by the kidney in a pH-dependent process.

Treatment of barbiturate poisoning involves GI tract decontamination (e.g. emetics, repeated administration of activated charcoal, gastric lavage) and the initiation of life-supportive measures (e.g. ventilation support, fluid therapy). Forced *alkaline* diuresis may also be of benefit in phenobarbital toxicoses. Hemodialysis and hemoperfusion are also employed in severely affected human patients. Redistribution of these drugs from adipose tissue back to the plasma may cause continued CNS depression; therefore, repeated patient monitoring is required. Pentobarbital concentrations can be identified in animal tissues, urine, and blood using gas chromatography–mass spectrometry (GCMS) and other analytical chemistry approaches. Studies in rabbits given thiopental suggest that ILE therapy significantly increased the depth, but not the duration, of thiopental anesthesia. This observation suggests that lipid emulsion serves to increase peak brain thiopental concentration when administered immediately after induction. These findings also appear to contradict the lipid sink theory as the main mechanism of action for ILE therapy.

B. Avermectins

The macrocyclic lactones (avermectins and milbemycins) are products, or chemical derivatives thereof, of soil microorganisms belonging to the genus *Streptomyces*. Avermectins include ivermectin, abamectin, doramectin, eprinomectin, and selamectin. This discussion will center on ivermectin as a prototype for this class of drugs. Ivermectin is a naturally occurring combination of the polycyclic lactones 22,23-dihydroavermectin β1a and β1b. Ivermectin is used as an anthelmintic in cattle, horses, and swine, and has been approved for the prevention of canine heartworm infection (6 μg/kg, PO, monthly). Ivermectin toxicosis in dogs and cats often follows the inappropriate administration of ivermectin-based equine anthelmintic by the animal's owner.

Ivermectin neurotoxicity is related to its agonist effects at the GABA-chloride channel. The normally inhibitory neurotransmitter GABA is found in the CNS of mammals (cerebellum, cerebral and limbic cortices, extrapyramidal system, horizontal layer of the retina), whereas GABA acts peripherally in invertebrates. Ivermectin potentiates synaptic GABA effects by enhancing its presynaptic release and by enhancing the binding of GABA to its postsynaptic receptors.

Drug transporters can significantly influence the pharmacokinetics and pharmacodynamics of the avermectins. P-glycoprotein 1 (permeability glycoprotein, abbreviated in the literature as P-gp or Pgp) is also known as multidrug resistance protein 1 (*MDR1*) or ATP-binding cassette subfamily B member 1 (*ABCB1*) or cluster of differentiation 243 (*CD243*). P-glycoprotein is encoded by the *ABCB1* gene. P-glycoprotein is found within the blood–brain barrier of mammals and it excludes ivermectin and certain other drugs from entering the brain. Human *MDR1* polymorphisms have been described and have been known to alter drug pharmacokinetics and a patient's susceptibility to Parkinson's disease, inflammatory bowel disease, refractory seizures, and other diseases. Collie and Collie-cross or herding dogs with the *ABCB1* gene mutation are particularly sensitive to ivermectin and other macrocyclic lactones. In Collies and other dogs that are homozygous for the mutant allele, ivermectin is toxic at single doses > 0.12 mg/kg, whereas heterozygous dogs have an intermediate susceptibility to ivermectin.

Although some individuals are extremely sensitive, any member of a breed or species could become poisoned with avermectins if an extremely high exposure was to occur. Avermectin toxicity has been reported to occur in breeds without the *ABCB1* mutation. The oral LD_{50} of ivermectin in Beagle dogs is reportedly 80 mg/kg. Ivermectin poisoning typically results in an acute (within 4–6 hrs after ingestion) onset of ataxia, muscle tremors, seizures (rarely observed), disorientation, mild to severe CNS depression, and sometimes coma, which may be prolonged or proceed to cause death. Some dogs develop reversible mydriasis, decreased menace response, and apparent blindness. Vomiting, diarrhea, hyperthermia, bradycardia, and sinus arrhythmia have also been reported. There are no characteristic histological lesions in ivermectin-poisoned animals. Ivermectin is poorly absorbed from the GI tract and it undergoes limited liver metabolism. Peak plasma concentrations are reached within 3 hrs after oral administration, and the plasma half-life in non-Collie breed dogs has been reported to be 2–3 days.

Activated charcoal and a saline cathartic are suggested if an animal has been recently exposed to ivermectin by the oral route. Picrotoxin and physostigmine have been advocated as possible antidotes for ivermectin toxicosis; however, these agents should only be used if life-threatening signs (e.g. coma) are present. Dogs with severe signs require intensive supportive therapy and full recovery may take several weeks. The use of ILE therapy has been shown to be of benefit in ivermectin-poisoned dogs and cats. The $GABA_A$ antagonist, flumazenil, has also been used to reverse the neurotoxic effects of ivermectin in an experimental rodent model.

Toxicants affecting the autonomic nervous system[2, 3, 62, 92, 115, 136, 145, 184]

One of the important neurotransmitters in the nervous system is acetylcholine. Acetylcholine is synthesized from acetyl-CoA and choline by choline acetyltransferase. Following synthesis, acetylcholine functions at the following sites: (1) all preganglionic nerve terminals of the autonomic nervous system, (2) all postganglionic parasympathetic nerve terminals, (3) the neuromuscular junction, (4) the adrenal medulla, (5) the CNS, and (6) the postganglionic sympathetic nerve terminal at sweat glands. Cholinergic muscarinic receptors are linked to second messenger systems via G proteins (so-called metabotropic receptors), and acetylcholine binding causes stimulation of the parasympathetic nervous system. Nicotinic receptors form ion channels (i.e. ionotropic receptors) and are located at the neuromuscular junction of skeletal muscles, at all ganglia of the autonomic nervous system, in the adrenal medulla, and in the CNS. The brief action of acetylcholine in the synaptic cleft is assured by the rapid acetylcholinesterase-catalyzed hydrolysis of acetylcholine into choline and acetate.

Toxicants listed in Table 23.1 generally induce clinical signs as the result of interference with the cholinergic nervous system. Stimulation of the autonomic nervous system results in bronchoconstriction, muscle tremors, stimulation of exocrine glands (e.g. salivation, lacrimation), bradycardia, and CNS effects. Blockade of the autonomic nervous system depends upon the type of cholinergic receptor involved. Inhibition of muscarinic receptor function (e.g. receptor blockade by atropine) may result in decreased GI motility, urinary retention, tachycardia, CNS depression or stimulation, hyperthermia, and (at high doses) coma and skeletal paralysis. Nicotinic receptor blockade (e.g. curare) results in the blockade of ganglia and skeletal muscles, resulting in muscle paralysis.

A. Nicotine and imidacloprid Several over-the-counter nicotine-based 2- or 4-mg polacrilex chewing gums and replacement transdermal patches are available in the United States for the treatment of nicotine dependence. Nicotine polacrilex is a resin complex of nicotine and polacrilin which is a cation-exchange resin prepared from methacrylic acid and divinylbenzene. The gum also contains sorbitol as a sweetener and buffering agents to enhance buccal absorption of nicotine. The rate of release of nicotine from the resin complex in chewing gum is variable and depends upon the vigor and duration of chewing. Nicotine

Table 23.1 Common toxicants that primarily affect the autonomic nervous system in companion animals and/or other veterinary species.

Anticholinergics	Tertiary amines: aminopentamide, atropine, benztropine, scopolamine. Quaternary amines: atropine methyl nitrate, homatropine methyl bromide, propantheline, glycopyrrolate, scopolamine methyl bromide
Selected anticholinergic plants	*Amanita sp.* (amanita mushrooms); *Solanum nigrum* (black nightshade); *Atropa belladonna* (belladonna); *Solanum pseudocapsicum* (Jerusalem cherry); *Datura* sp. (Jimson weed, Angel's trumpet)
Muscarinic toxicants	Muscarine, methacholine, bethanechol, carbachol, pilocarpine, muscarinic mushrooms (e.g. *Amanita muscaria*, *Inocybe* spp.)
Nicotinic toxicants	*Conium maculatum* (poison hemlock); *Nicotiana* sp. (tobacco); **nicotine sulfate**; **imidacloprid**, levamisole
Cholinesterase inhibitors	**Carbamate and organophosphorus insecticides**; *Anabaena flos-aquae* (blue-green algae)

Agents presented in either the current edition or previous editions of this textbook are identified using either bold or underlined text, respectively.

transdermal patches typically contain 8.3 to 114 mg of the free alkaloid. All patches have significant residues of nicotine (2 to 83 mg) even after 24 hrs of application. Other sources of nicotine include smokeless tobacco, cigarettes (contain approximately 15–25 mg nicotine), cigars, and related products.

Nicotine is a cholinergic (nicotinic) receptor agonist that exhibits both stimulant (low-dose) and depressant (high-dose) effects in the peripheral and central nervous systems. Nicotine's cardiovascular effects are usually dose dependent. Nicotine may increase circulating levels of cortisol and catecholamines. Nicotine is extremely toxic (minimal oral lethal dose in dogs and cats is approximately 10 mg/kg), and toxic effects develop rapidly after ingestion. Nicotine-induced clinical effects may include tremors, hypertension, tachycardia, tachypnea, vomiting, hypersalivation, CNS depression or excitation, mydriasis, ataxia, weakness, seizures, and death from respiratory paralysis. Interestingly, dogs that ingested one or two nicotine transdermal patches had only vomiting in spite of nearly complete nicotine absorption from the patch.

The nicotine analogue imidacloprid has similar toxicological effects. Imidacloprid is a widely used neonicotinoid insecticide. Other members in this class of insecticide include acetamiprid, clothianidin, dinotefuran, nitenpyram, thiacloprid, and thiamethoxam. Imidacloprid binds to the postsynaptic nicotinic acetylcholine receptor resulting in sustained activation. Imidacloprid is rapidly absorbed from the GI tract and is metabolized by the liver to the active metabolite 6-chloronicotinic acid. Imidacloprid is poorly distributed to the CNS. Based on human case reports, clinical manifestations of neonicotinoid insecticide toxicity resemble those seen with acute nicotine poisoning.

The management of nicotine or imidacloprid overdose generally involves gastric decontamination followed by symptomatic and supportive therapy. If vomiting has not occurred following an acute ingestion of nicotine, the stomach should be emptied immediately by inducing emesis or by gastric lavage. Activated charcoal and a saline cathartic should be given immediately following gastric emptying. Activated charcoal should be given every 6–8 hrs following ingestion of transdermal patches since delayed nicotine release may occur. Vigorous fluid support and additional appropriate therapy should be instituted if hypotension or cardiovascular collapse occurs. Seizures should be treated with standard anticonvulsants such as diazepam. Atropine may be given for bradycardia, excessive bronchoconstriction, or diarrhea. Assisted pulmonary ventilation may be necessary for the management of respiratory paralysis.

B. Organophosphorus (OP) and carbamate insecticides

Organophosphorus and carbamate insecticides remain an important toxicant of concern to veterinarians. These insecticides are potent inhibitors of acetylcholinesterase and produce muscarinic (salivation, lacrimation, bronchial secretion, vomiting, diarrhea), nicotinic (tremors, respiratory paralysis), and CNS (seizures, miosis, hyperactivity) effects. Exposure of cats to the OP insecticide chlorpyrifos has been infrequently associated with the development of organophosphate-induced delayed neuropathy (OPIDN). Carbamate insecticides are reversible acetylcholinesterase inhibitors, while OP insecticides bind covalently to the enzyme, resulting in an irreversible inhibition of the enzyme. Recovery following exposure to an OP insecticide is therefore dependent upon the resynthesis of acetylcholinesterase. Tolerance to some cholinergic effects of cholinesterase-inhibiting compounds may be due to a compensatory down-regulation of muscarinic receptors. Poisonings from OP (e.g. chlorpyrifos, dichlorvos) and carbamate (e.g. aldicarb, methomyl, carbofuran) insecticides are commonly the result of deliberate topical application, accidental ingestion, or malicious poisoning.

Measurement of whole blood, brain, or retinal acetylcholinesterase activity is diagnostically useful in cases in which an exposure to an OP or carbamate insecticide may have occurred. Depending on the diagnostic laboratory's preference, whole blood samples (collected in the appropriate anticoagulant), serum, plasma, retinal, or brain tissue (one hemisphere) should be frozen and shipped on ice. The presence of reduced acetylcholinesterase activity (< 50% normal activity) in blood, brain, or retinal tissues is supportive of a diagnosis of OP or carbamate insecticide toxicosis. In contrast to OP insecticides, transient inhibition by carbamate insecticides makes an assessment of acetylcholinesterase activity more difficult, since acetylcholinesterase activity may be reactivated spontaneously in vivo or following incubation, during tissue shipment, following incubation (as occurs with some methods of measuring acetylcholinesterase activity), or during storage. In contrast, cholinesterase activity in tissues from OP insecticide-poisoned animals is not altered by incubation.

Important differences exist between dog and cat cholinesterase activity. Feline whole blood cholinesterase activity is composed primarily of a pseudocholinesterase (butyrylcholinesterase) that is extremely sensitive to inhibition by OP insecticides. A significant decrease in whole blood acetylcholinesterase activity is, therefore, anticipated in a clinically affected cat suspected of being poisoned with an OP insecticide. However, reduced blood cholinesterase activity may also occur in exposed cats that are not clinically affected. Therefore, the prognostic value of this test is difficult to assess. Furthermore, significant inhibition of brain cholinesterase activity may occur in cats and dogs with normal blood cholinesterase activity (i.e. false negative).

Treatment of OP or carbamate insecticide-poisoned animals should begin with the institution of life-saving symptomatic therapy. High doses of atropine sulfate (0.1–0.2 mg/kg, repeat as needed) can be used to alleviate respiratory distress caused by severe bradycardia and excessive bronchiolar constriction and hypersecretion. Atropine will not, however, abolish muscle tremors and other signs due to excessive nicotinic stimulation. The initial dose of atropine is often divided, with one-quarter given intravenously and the remainder given either subcutaneously or intramuscularly. Since long-term atropine therapy may be required, one should use the lowest dose that alleviates the dyspnea and bradycardia. The reversal of excessive salivation may serve as a useful clinical marker of effective atropinization; however, pupil size is an unreliable indicator of atropinization in cats and dogs. The dose of atropine should be decreased or discontinued if tachycardia, GI stasis, severe behavioral changes (e.g. delirium), or hyperthermia develops.

Enzyme reactivators are also used for the treatment of OP insecticide toxicosis. Reactivators act on the OP insecticide-acetylcholinesterase complex to free the enzyme and restore normal function. These agents are only effective if covalent binding of the OP insecticide to acetylcholinesterase has not yet occurred. This covalent binding is referred to as "aging" and typically occurs within 24 hrs of the initial binding of the insecticide to the enzyme. Many texts suggest that enzyme reactivators are no longer effective 18–24 hrs after exposure; however, enzyme reactivators may still be useful even after 24 hrs. The reason for this is that freshly synthesized acetylcholinesterase is sensitive to inhibition of activity from insecticide that has not undergone detoxification. One scenario where this may occur involves dermal exposures where the skin and subcutaneous fat may serve as a depository for some insecticides. Redistribution from this depot results in continued enzyme exposure to the insecticide with subsequent aging. This newly formed and inhibited, but not yet aged, enzyme-insecticide complex is the site of action for the enzyme reactivators.

Of the enzyme reactivators, pralidoxime chloride has received the widest clinical use in veterinary medicine. Pralidoxime chloride is given (20 mg/kg, IM, repeated every 12 hrs), to relieve muscle tremors and other nicotinic signs and should be continued until these signs are abolished or until additional prolonged benefit (lasting more than a day) is no longer observed. Pralidoxime chloride is generally of low toxicity; however, overdoses can result in tachycardia and other cardiac arrhythmias.

It is critical that further exposures to OP and carbamate insecticides be avoided until the animal is fully recovered. Exposure to another acetylcholinesterase inhibitor should therefore not be allowed for up to 4–6 wks after the initial exposure. Animals recovering from chlorpyrifos toxicosis may exhibit prolonged anorexia and may require supplemental feeding to maintain caloric intake. Recumbent animals with OPIDN should be placed in padded cages to prevent the development of decubital ulcers.

Neurotoxic chemicals with mixed effects on the CNS[4, 17, 18, 20, 24, 25, 29, 30, 32, 35, 39, 42, 43, 48–53, 55, 57, 58, 64, 65, 75, 77, 80, 82, 83, 86, 94, 96, 102, 103, 107, 112, 114, 122, 124, 125, 129, 131, 133, 134, 141, 142, 149, 153, 162, 163, 165, 172–175, 182, 186, 190, 194, 196, 199]

Box 23.4 includes toxicants that produce a combination of nervous system clinical signs. Many of these agents may produce either CNS stimulation or depression depending upon the exposure dose, the species of animal involved, and the stage of the

Box 23.4 Common neurotoxic agents with mixed effects on the CNS in companion animals and/or other veterinary species.

Boric acid
Bromethalin
Carbon disulfide
Carbon monoxide
Chlorhexidine
N,N-diethyl-m-toluamide (DEET)
Ethylene glycol
Hexachlorophene
Lead
LSD
Mercury
Metaldehyde
Methionine
Metaclopromide
Metronidazole
Phenothiazine tranquilizers
Pyrethrin and pyrethroid insecticides
Pyriminil (Vacor)
Rotenone
Selegiline (L-deprenyl)Sertraline
Toluene
Tricyclic antidepressants
Zinc phosphide

Agents presented in either the current edition or previous editions of this textbook are identified using either bold or italic text, respectively. See also Khan (2012).[95]

toxic syndrome. Some of these agents also attack multiple sites within the nervous system, leading to mixed clinical effects and signs. Some neurotoxicants with mixed effects will also impair sensory function.

A. Bromethalin

Rodenticides containing 0.01% bromethalin (N-methyl-2,4-dinitro-N-[2,4,6-tribromophenyl]-6-[trifluoromethyl] benzeneamine) have been marketed since 1985. Bromethalin and its primary N-demethylated metabolite, desmethylbromethalin, are effective uncouplers of oxidative phosphorylation. The uncoupling of oxidative phosphorylation results in inadequate adenosine triphosphate synthesis, leading to decreased sodium and potassium ion channel pump activity, which leads to cerebral edema and elevated cerebrospinal fluid pressure. The reported experimentally determined minimal lethal dose in the cat is 0.45 mg/kg with the dog being approximately five- to sixfold less sensitive. Minimal lethal doses seen in clinical cases reported to the ASPCA's National Animal Poison Control Center were 0.46 and 0.24 mg/kg in dogs and cats, respectively. Secondary poisoning of cats through the ingestion of bromethalin-poisoned rodents occurs rarely.

The onset and severity of clinical signs induced by bromethalin are dose-dependent. Ingesting extremely high doses of bromethalin (> LD_{50}) may result in an acute onset of CNS excitation, muscle tremors, and seizures. Bromethalin ingestion by dogs and cats, however, more commonly occurs at lower doses and results in a delayed (1–7 days after ingestion) progressive mixed CNS syndrome. This clinical syndrome is characterized by ataxia, anorexia, vocalization, hindlimb paralysis, moderate to severe CNS depression, fine-muscle tremors, and focal motor or generalized seizures. Severely affected animals develop both hindlimb and forelimb paresis, which progresses to paralysis with extensor muscle rigidity, decerebrate posture, loss of deep pain, upper motor neuron bladder paralysis, and patellar hyperreflexia. Less commonly observed clinical signs include vocalization, behavioral changes ("dementia"), anisocoria, positional nystagmus, opisthotonus, and death. In this "low-dose" syndrome clinical signs generally develop within 2–7 days of ingestion; however, delays of up to 2 wks may occur. With mild poisoning, clinical signs usually resolve within 1–2 wks of the onset of clinical signs, although signs can persist for up to 4–6 wks in some animals.

Bromethalin may be detected in fresh frozen fat, liver, kidney, and brain tissue from lethally poisoned animals that died shortly after ingestion. Bromethalin has also been detected in formalin fixed liver samples obtained from a deceased human patient. Diagnostic alterations in routine serum electrolytes and chemistries are not anticipated. A small increase in CSF pressure may be noted; however, this increase is not as severe as that observed with other causes of cerebral edema (e.g. hydrocephalus). Although not specific for bromethalin toxicosis, EEG abnormalities commonly occur in bromethalin-poisoned animals. These may include spike and spike-and-wave activity (indicative of an irritative or seizure focus), marked voltage depression (indicative of cerebral hypoxia), and abnormal high-voltage slow-wave activities (associated with cerebral edema formation). A CT scan of the head of a lethally poisoned human patient showed hypodensities affecting the white matter diffusely, suggesting brain edema that was predominantly affecting the white matter. Bromethalin-induced lesions are generally confined to the CNS. Gross evidence of cerebral edema may occur but is relatively mild. Histopathologic changes in lethally poisoned animals include spongy degeneration of cerebrum, cerebellum, brain stem, spinal cord, and optic nerve white matter due to myelin edema. Ultrastructural findings include the separation of myelin lamellae at the interperiod lines, resulting in apparent intramyelinic edema and pronounced cytosolic vacuolation of astrocytes and oligodendroglial cells. The myelin lesion is generally not associated with a leukocytic inflammatory response, gitter cell response, or axonal degeneration, and may therefore be reversible.

Treatments should include the repeated administration of activated charcoal and a saline cathartic to decrease bromethalin absorption. Smaller subsequent doses of both activated charcoal (0.5 to 1 gm/kg, PO) and an osmotic cathartic (sodium sulfate, 125 mg/kg, PO) should be given every 4–8 hrs for at least 2–3 days. Serum sodium levels should be periodically assessed since hypernatremia may develop in animals given activated charcoal. Dexamethasone, mannitol, and urea to prevent bromethalin-induced cerebral edema are often only marginally effective in the management of severe bromethalin poisoning in cats or dogs. Diazepam and/or phenobarbital may be used to control seizures and severe muscle tremors. Many animals recovering from bromethalin toxicosis exhibit prolonged anorexia and may require supplemental feeding to maintain caloric intake. Recumbent animals should be placed in padded cages to prevent the development of decubital ulcers.

The toxic syndrome induced by bromethalin in dogs and cats must be distinguished from other neurologic syndromes produced by trauma, neoplasia, cerebral vascular disorders, as well as infectious and other toxic agents. Similar clinical signs and white matter lesions (WMLs) may occur in hexachlorophene- or trialkyltin-poisoned animals.

B. Metronidazole

Metronidazole is used in veterinary medicine for the treatment of protozoal infections (e.g. giardiasis), trichomoniasis, *Helicobacter*-associated gastritis, inflammatory bowel disease, hepatoencephalopathy, and certain anaerobic infections. Metronidazole binds to neuronal RNA and inhibits protein synthesis thereby causing axonal degeneration. Dosages associated with adverse clinical signs in dogs have ranged from 67.3 to 129.0 mg/kg/day. Common side effects of oral metronidazole include lethargy, anorexia, vomiting, and diarrhea in dogs and cats and ptyalism (increased salivation) in cats. More severe signs including neurotoxicity are occasionally observed in humans, dogs, and cats following metronidazole treatment. These clinical signs usually begin 7–12 days following the induction of therapy. Metronidazole-induced seizures and peripheral neuropathies occasionally occur in humans. In dogs and cats, central vestibular and cerebellar dysfunctions resulting in ataxia, nystagmus (spontaneous and positional), head tilt, tremors, and seizures are commonly reported in animals with severe metronidazole toxicosis. An increase in CSF protein may be found in some dogs. Recovery usually occurs within 1 to 2 wks after the cessation of therapy. Well-demarcated and symmetric lesions, consisting of spongiform changes in neurons with pronounced cytoplasmic vacuolization, may be observed in vestibular and cochlear nuclei, cerebellar nuclei, rostral colliculus, and olivary nucleus and other brain regions. Treatment is purely supportive. Decontamination therapies are usually ineffective unless an acute overdose has occurred.

C. Antidepressants

Major depressive disorder affects approximately 16% of Americans at some point during their lifetime. Pharmacologic treatment strategies for this syndrome include the use of monoamine oxidase inhibitors (MAOIs), including isocarboxazid, phenelzine, and selegiline; selective serotonin reuptake inhibitors (SSRIs), including paroxetine and sertraline, fluoxetine; serotonin/norepinephrine reuptake inhibitors (SNRIs), including duloxetine, and venlafaxine; and tricyclic antidepressants (TCAs), including amitriptyline, clomipramine, and nortriptyline. It is critical that veterinarians identify the specific drug since the toxicity and effects of antidepressants vary widely between and within therapeutic classes. The following discussion highlights select representative examples of these major classes.

Selegiline is a selective, irreversible inhibitor of MOA-B and acts centrally to increase dopamine concentrations. Its main use is to treat Parkinson's disease in humans. It has also been used (at 0.5 to 1.0 mg/kg, PO, once daily for 60 days) to treat canine geriatric cognitive dysfunction. Ingesting selegiline and other MAOIs may cause either hypo- or hypertension, CNS depression, ataxia, restlessness, tachycardia, arrhythmias, coma, seizures, respiratory depression, fever, and shock. Oral selegiline undergoes extensive first-pass metabolism by the hepatic cytochrome P450 system. Desmethylselegiline, l-methamphetamine, and l-amphetamine are the main metabolites of selegiline. There is concern that these metabolites may contribute to cardiovascular side effects and neurotoxicity. The MAOIs are absorbed rapidly from the GI tract and clinical signs are usually seen within 1 or 2 hrs but can be delayed for 12–24 hrs. A dermal patch system for selegiline has been developed for use in humans for the treatment of Parkinson's disease and mood disorders. No lethal doses in dogs have been published for the MAOIs, but a review of the ASPCA's National Animal Poison Control Center database shows that dogs have exhibited tremors with oral doses as low as 5.5 mg/kg of phenelzine and 2.2 mg/kg of tranylcypromine. Dogs have been given selegiline orally at 2 mg/kg/day for 90 days without adverse effects being noted. Oral administration of selegiline to dogs at ≥ 2 mg/kg was associated with stereotypy and other behavioral effects. These adverse effects, most notably, were attributed to either increased phenylethylamine, due to MAO-B inhibition, and/or increased amphetamine.

The SSRIs fluoxetine, paroxetine, and sertraline are generally well absorbed from the GI tract and highly protein-bound. The half-lives of sertraline and fluoxetine in dogs are 26 and 20 hrs, respectively. Depending upon the drug, hepatic metabolism may become saturated, resulting in prolonged elimination half times. The most common adverse effects seen in humans on SSRIs was restless leg syndrome/akathisia, followed by dystonia, parkinsonism, and tardive dyskinesia-like states. Fluoxetine, the most commonly prescribed antidepressant during the 1980s and 1990s, was implicated in most of these cases. Sertraline is also associated with drug-induced liver injury. Clinical signs of an SSRI overdose in animals include CNS depression or agitation, vomiting, ataxia, tremors, seizures, hypertension, and tachycardia. Dogs given sertraline at 10–20 mg/kg (PO) developed mild anorexia and mydriasis, while increased salivation and muscle tremors were seen at 50 mg/kg. The minimum lethal oral dose of sertraline in dogs is reported as 80 mg/kg.

Serotonin toxicity, often referred to as serotonin syndrome, is a potentially life-threatening adverse drug reaction seen in humans following therapeutic SSRI drug use, intentional self-poisoning, or from adverse drug–drug interactions. Serotonin toxicity results from excess serotonergic agonism on the CNS and peripheral serotonergic receptors. The typical clinical features of serotonin toxicity in people are: (a) neuromuscular hyperactivity: tremor, clonus, myoclonus, and hyperreflexia; (b) autonomic hyperactivity: diaphoresis, fever, tachycardia, tachypnea, and mydriasis; and (c) altered mental status: agitation and confusion. Based on human experiences, the management of the acutely exposed or poisoned animal depends on GI tract decontamination with activated charcoal and the use of intravenous benzodiazepines for seizures and benzodiazepines and external cooling measures for hyperthermia associated with SSRI-induced serotonin syndrome. Metabolic acidosis may also occur and should be treated appropriately. The serotonergic receptor antagonist propranolol hydrochloride (0.02 mg/kg slowly IV; titrate up as needed) has been used to treat tachycardia. The nonspecific serotonin antagonist cyproheptadine hydrochloride (1.1 mg/kg orally) has also been used in dogs to reduce adverse clinical effects.

Venlafaxine is a bicyclic antidepressant that acts as a serotonin, norepinephrine, and dopamine reuptake inhibitor.

Venlafaxine has been used (2.5 mg/kg/day, PO) to manage juvenile canine narcolepsy and cataplexy. Both dogs and cats can be poisoned; however, cats may be more commonly affected. Muscle tremors have been reported in dogs consuming 10 mg/kg. Clinical signs generally appear within 1–8 hrs after ingestion. Common clinical signs seen in cats include tachypnea, tachycardia, ataxia, and agitation. The serotonin antagonist cyproheptadine (1.1 mg/kg orally or rectally up to three or four times a day), acepromazine, or chlorpromazine have been advocated for the treatment of agitation. Generally, the prognosis is good with close monitoring and treatment of signs. The elimination half-life of venlafaxine in dogs is approximately 2–4 hrs. Since venlafaxine is heavily glucuronidated it is likely that cats, a species with lower glucuronidation rates, would eliminate this drug more slowly.

The tricyclic antidepressant medications (TCAs)—which include amitriptyline, nortriptyline, protriptyline, amoxapine, desipramine, imipramine, and trimipramine—represent a commonly used class of human psychotherapeutic medications used for the treatment of endogenous depression, childhood enuresis, and certain phobic disorders. Clomipramine and several other TCAs have found increasing use in veterinary medicine for the treatment of canine narcoleptic hypersomnia syndrome, canine narcoleptic cataplexy syndrome, canine separation anxiety, feline urine marking, fear and anxiety syndromes, and neuropathic pain. Poisonings with the TCAs represent one of the most common life-threatening drug ingestion in human patients,and poisoning incidences in animals may well be rising.

Dependent on the specific TCA, the typical therapeutic TCA dose in animals and humans falls in the range of 2–4 mg/kg. In general, 15–20 mg/kg is thought to be a potentially lethal dose of TCAs in both human and veterinary patients. At therapeutic oral doses, the TCAs are rapidly absorbed. Massive ingestions may result in prolonged GI absorption due to TCA-induced anticholinergic effects that result in decreased intestinal motility. The TCAs are very lipid soluble, are highly protein bound, and primarily undergo liver metabolism through demethylation or hydroxylation followed by glucuronide conjugation. In humans, the TCAs have somewhat variable elimination half-lives ranging from 10 to 21 hrs.

The TCAs have pronounced toxic effects on the central nervous, parasympathetic, and cardiovascular systems. In addition to their atropine-like anticholinergic effects, TCAs also inhibit biogenic amine (serotonin, norepinephrine) uptake. Clinical signs of TCA poisoning in animals include hyperexcitability, vomiting, CNS depression, ataxia, mydriasis, muscle tremors, and occasionally seizures. Cardiac abnormalities should also be anticipated and may include hypotension, cardiac arrhythmias (e.g. sinus tachycardia, ventricular tachyarrhythmia), pulmonary edema, cardiac arrest, and death. Management protocols have been largely adopted from the human toxicology literature. Treatment of TCA poisoning involves the initiation of life-supportive measures (e.g. using diazepam for seizure control, ventilation support), GI tract decontamination (e.g. repeated administration of activated charcoal, gastric lavage; note that emetics are generally not recommended), and the intravenous use of sodium bicarbonate (2–3 mEq/kg) to control signs of acidosis, tachycardia, bradycardia, and other cardiac conductance abnormalities. Asymptomatic patients are unlikely to develop signs if the interval between ingestion and the initial call to a veterinarian is known to be greater than 6 hrs.

D. Metaldehyde

Metaldehyde toxicosis most commonly results from the ingestion of metaldehyde-based molluscicides. The approximate lethal dose of metaldehyde ranges from 100 to 360 mg/kg. The biochemical mechanism of action of metaldehyde is unknown; however, decreased brain serotonin, GABA, and noradrenalin occurs in metaldehyde poisoned animals. Metaldehyde ingestion can also produce systemic acidosis. Clinical signs of metaldehyde toxicosis often develop within 3 hrs of ingestion, and commonly include tachycardia, salivation, tremors, vomiting, hyperesthesia, seizures, severe hyperthermia, diarrhea, and CNS depression. Metaldehyde remains an important cause of seizures in dogs. Death from respiratory failure and metabolic acidosis may develop from 4 to 24 hrs after exposure. Delayed deaths due to liver failure may also occur 3–4 days following ingestion. Nonspecific histologic lesions in the liver, kidney, GI tract, lungs, and heart may be observed. Chemical analysis of frozen stomach contents, liver, and urine is available at some diagnostic laboratories. In addition to anticonvulsants and activated charcoal administration, fluid therapy to control acidosis is also recommended.

E. Carbon monoxide (CO)

Carbon monoxide is an odorless, colorless, and nonirritating gas with rapid systemic absorption. The amount of CO absorbed depends on ambient CO concentration, length of exposure, and physiologic parameters (e.g. minute ventilation, cardiac output). CO is produced by the partial oxidation of carbon-containing materials. In the outdoor environment, major sources of CO are motor vehicles and fires. In the indoor environment, sources include tobacco smoking, combustion engines, and combustion appliances, such as furnaces and gas stoves. CO interferes with the oxygenation of blood and the delivery of oxygen to tissues because it has about 245 times more affinity with hemoglobin than does oxygen. The formation of carboxyhemoglobin (COHb) reduces the oxygen-carrying capacity of blood and shifts the oxygen dissociation curve, reducing the release of oxygen to tissues. Hypoxemia and subsequent tissue hypoxia comprise one mechanism of CO toxicity. CO also binds to muscle myoglobin, cytochrome c oxidase, and cytochrome P-450, and many of the adverse effects of CO might be associated with those reactions.

The brain and cardiovascular system are the primary targets of CO toxicity. The adverse effects of CO exposures in people range from subtle vascular and neurologic changes to more serious conditions, such as loss of consciousness and death. Permanent brain injury occurs frequently in people with CO poisoning even when extensive treatment is used. The incidence varies from 3 to 23% in affected people. Delayed neuropsychological sequelae often presented one to three or more weeks after the initial CO exposure. This lag is unusual from other forms of cerebral hypoxia. CO-induced hypotension and impaired brain perfusion likely contribute to delayed neurologic effects. In people, the most frequent signs and symptoms of delayed neurotoxicity include delirium, amnesia, cognitive dysfunction, gait disturbance, Parkinson-like syndromes, CNS depression, and anxiety. Brain-imaging studies in people with acute or delayed CO-induced neurotoxicity demonstrate lesions in the globus pallidus and diffuse white matter changes. Neuropathological changes seen in CO-poisoned humans include leukoencephalomalacia with reactive astrogliosis, necrosis of neurons in the cerebral cortex, Purkinje cells, and basal nuclei.

There have been several experimental studies conducted in dogs and cats with CO exposure. In dogs, exposures to CO at 100 ppm for 2 hrs (resulting in COHb at 6.3–6.5%) increased the susceptibility to induced ventricular fibrillations. COHb concentrations at 13–15% increased the severity and extent of ischemic injury and the magnitude of ST-segment elevation in myocardially infarcted dogs. Preziosi *et al.* (1970) report that dogs exposed both intermittently (6 hrs per day, 5 days per week) and continuously at 50 and 100 ppm for 6 wks had abnormal electrocardiograms in the second week of exposure and continuing through the exposure period. Cardiovascular (e.g. right and left heart dilation and myocardial thinning) and CNS pathology (e.g. gliosis and thinning of the white matter in the central semi ovale) were observed in some dogs in all CO exposure groups. Cats exposed to CO developed oligodendroglial and astrocytic swelling in the white matter, degenerative axonal changes (Wallerian-like), disintegration and phagocytosis of myelin sheaths, and demyelination. Some of these studies used high CO concentrations (e.g. 0.3%) and examined the effect of cerebral artery ligation or nitrogen-induced hypoxia) on CNS lesion development.

An important risk factor for CO poisoning in animals is exposure to smoke and other combustion products. The veterinary literature contains several reports regarding the neurologic consequences of smoke inhalation. In some cases neurologic effects were attributed to CO exposure; however, smoke is a complex mixture that may contain cyanide and other potentially neurotoxic components. The rapid onset of coma, seizure, metabolic acidosis, tachycardia, and hypotension often suggests that cyanide poisoning is present. Neurologic signs of presumed CO toxicity reported in dogs and cats are time dependent and include ataxia, absent menace response, CNS depression, loss of consciousness, head tremors, twitching, seizures, and dementia. Both acute and delayed neurotoxic syndromes have been reported. Like people, lesions seen in dogs with acute CO poisoning are found in the pallidum, substantia nigra, and cerebellum. Neuropathologic lesions seen with delayed CO neurotoxicity in dogs include focal rarefaction in the central white matter of the frontal lobe, endothelial cell hypertrophy, astrogliosis, and laminar necrosis of pyramidal neurons n layers II and III of the cerebral cortex. Other clinical signs suggestive of smoke inhalation can also be seen, including burns, dyspnea, and shock.

A diagnosis of CO poisoning in animals is often based upon the history of exposure to smoke and ancillary findings. Measurement of COHb (and cyanoHAB) concentrations in acute cases can also prove diagnostic. The use of 100% O_2 and/or hyperbaric O_2 chambers is a mainstay of the treatment of people with CO poisoning. Oxygen therapy decreases the elimination half-life of CO. In humans breathing room air, the elimination half-life of CO is 320 min, whereas the elimination half-life of CO in humans breathing 100% O_2 reduced fourfold. Similar benefits are seen under hyperbaric conditions. Treatment of CO-poisoned dogs and cats should also include supplemental O_2 and supportive care. The treatment of people with smoke inhalation often also includes considering management of cyanide poisoning with either the deliberate production of methemoglobinemia (with IV sodium nitrite and sodium thiosulfate) or the intravenous administration of hydroxocobalamin. Hydroxocobalamin acts by combining with cyanide to form cyanocobalamin, which is then eliminated by the kidneys. In human medicine, cyanocobalamin has become the antidote of choice because of its efficacy and wider margin of safety and minimal side effects.

Emerging issues in neurotoxicology[5, 7, 13, 14, 26–28, 54, 72, 98, 106, 116, 137, 138, 143, 155, 156, 159, 160, 164, 166, 167, 176, 177, 180, 183]

A. Air pollution

There is mounting evidence that exposure to air pollution can cause systemic inflammation, neuroinflammation, neurodegeneration, neurotoxicity, and structural brain changes and cognitive deficits. Particulate matter of the fine (< 2.5 μm) and ultra-fine (< 100 nm) size can translocate to the brain and has been found in the olfactory bulb and frontal cortex of dogs resident in Mexico City. Dogs from Mexico City have WMLs in the frontal lobes that are appreciable by magnetic resonance imaging (MRI). Histologic changes seen in these dogs include loss of olfactory neurons in the nasal cavity and the presence of Aβ amyloid in neurons and blood vessels (capillaries and arterioles) in the olfactory bulb and frontal cortex. Although the exact mode of action for these neurologic effects remains unknown, one intriguing hypothesis is that exposure to high levels of ambient air pollution may induce oxidative stress, leading to neuroinflammation. It is important to note that Mexico City has higher urban exposures to particulate matter and ozone than most United States cities, so extrapolation of these results to other locales must be made with caution. The studies performed in Mexico City highlight the possible use of dogs as sentinels for human toxicological disease. A similar experience was found in the 1950s in the Japanese city of Minamata, where methylmercury poisoning in cats and humans occurred coincidentally.

B. Manganese

Manganese is an essential nutrient that is required for many physiological functions. As with iron and many other essential metals, homeostatic controls regulate the GI absorption and biliary excretion of manganese to ensure adequate and stable tissue concentrations of this metal. Under certain high-dose conditions, manganese-induced neurotoxicity can occur in humans and animals. Early manifestations of manganese poisoning in humans include fatigue, headache, muscle cramps, loss of appetite, apathy, insomnia, and diminished libido. As overexposure continues and the disease progresses, patients may develop prolonged muscle contractions (dystonia), decreased muscle movement (hypokinesia), rigidity, and muscle tremors. Structural changes in the globus pallidus of manganese-exposed humans indicate that this brain region is a sensitive target site for manganese accumulation and effects. People with chronic manganese neurotoxicity can resemble patients with Parkinson's disease; however, the substantia nigra is largely spared and dopamine levels remain generally unaffected during manganese neurotoxicity. Several mechanisms of manganese neurotoxicity have been proposed, including the disruption of mitochondrial metabolism, oxidative stress, iron homeostasis alterations, inflammation, altered glutamate, and dopamine metabolism, among others.

Most human cases of frank or subclinical manganese neurotoxicity are associated with occupational exposure following the inhalation of dusts or fumes during welding, battery production, or other industrial processes. There is also increasing evidence that decreased biliary excretion as may occur during hepatobiliary disease can also lead to increased manganese retention and accumulation in the globus pallidus. Manganese is highly paramagnetic and can be detected in the brain in vivo with MRI because it shortens the longitudinal relaxation time (T1) of tissues. Humans and rhesus monkeys exposed to high levels of manganese can develop a high signal on T1-weighted (T1-W) MRI scans of the globus pallidus. Elevated concentrations of manganese in basal ganglia structures have been measured in liver disease patients and are consistent with basal ganglia hyperintensive signals in T1-W MRIs. Human patients with advanced cirrhosis have been documented with a form of parkinsonism with clinical symptoms similar to manganese-induced parkinsonism.

These findings have led to the recent theory that manganese may contribute to the signs associated with hepatic encephalopathy. Associations exist between globus pallidus T1-W MRI hyperintensity and motor disturbances in people with hepatic encephalopathy suggesting that basal ganglia dysfunction and manganese accumulation is involved in the etiology of this disease. Hepatic encephalopathy represents a complex disease syndrome that results, in part, from interactions between ammonia and astrocytic stores of glutamine synthetase with additional contributions from pro-inflammatory cytokines, and oxidative stress. Both manganese and ammonia are readily taken up by astrocytes which are also cellular targets for these toxicants. Studies conducted in rodents suggest that the presence of increased brain manganese concentrations may also enhance ammonia and glutamine accumulation in the brain. Limited studies performed to date suggest that manganese accumulation also occurs in dogs and cats with portosystemic shunts. For example, dogs and cats with portosystemic shunts develop hyperintense focal areas in the lentiform nuclei on T1-W images. In dogs, manganese concentrations observed in the lentiform nuclei were four times higher than those seen in unaffected animals. Whether manganese plays a significant role in the etiology of hepatic encephalopathy in companion animals remains unknown but will likely be the subject of future work.

C. Synthetic cannabinoids

One challenge facing the medical profession is the introduction of products that can rapidly become disseminated in the community. One example is recreational synthetic cannabinoids, such as "Spice," "K2," "Blaze," and "Red X Dawn." Smokeable herbal products marketed as being "legal" and as providing a marijuana-like high have become popular, particularly among teenagers. These products were widely sold at a variety of retail outlets, in head shops, and over the Internet. Each of these products contained a "cannabinoid," that is a chemical compound structurally related to Δ9-tetrahydrocannabinol (THC) the primary psychoactive constituent of marijuana. Human case reports describe psychotic episodes (e.g. agitation, anxiety, hallucinations, unresponsiveness) in cannabinoid users that included effects similar to those seen with THC. Convulsions were also seen during synthetic cannabinoid toxicosis. Fortunately, the US Drug Enforcement Agency took rapid action to designate five synthetic cannabinoids as schedule I substances. To the author's knowledge no published case reports of "Spice" poisoning in dogs or cats has been reported; however, it is likely that exposures and toxicosis resulted from the ingestion (or inhalation) of these products.

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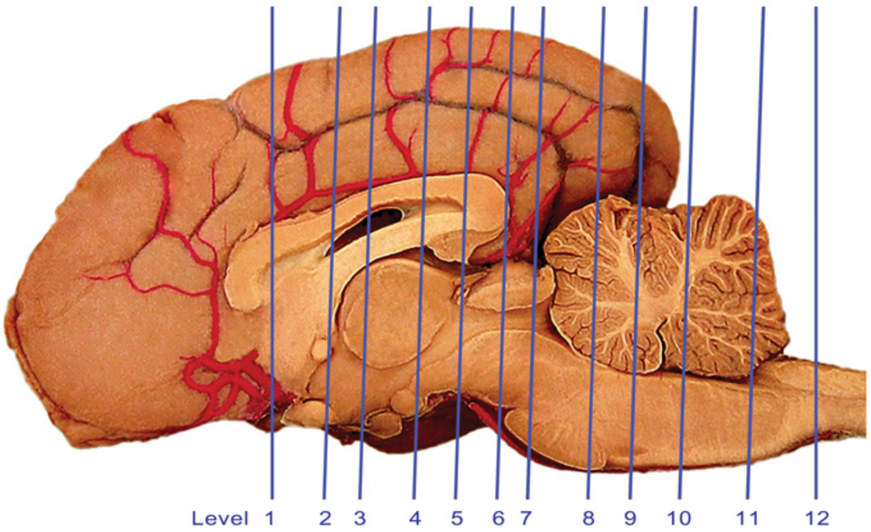
Canine Brain Atlas



Transection Levels Canine Half-Brain—Median View.
Atlas Images are from the University of Minnesota Veterinary Anatomy Web Site (http://vanat.cvm.umn.edu/brainsect/). Images were scanned by BrainMaps.org (BrainMaps.org) at the Center for Neuroscience. University of California. Davis.

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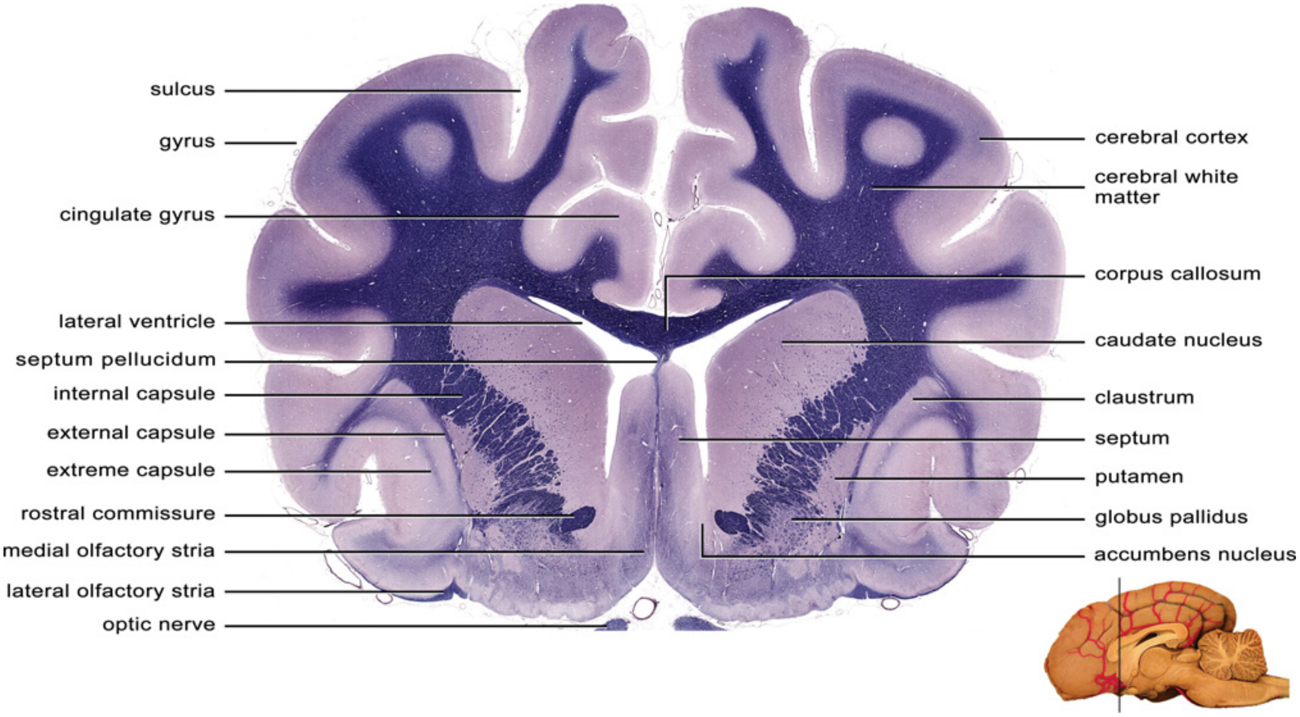
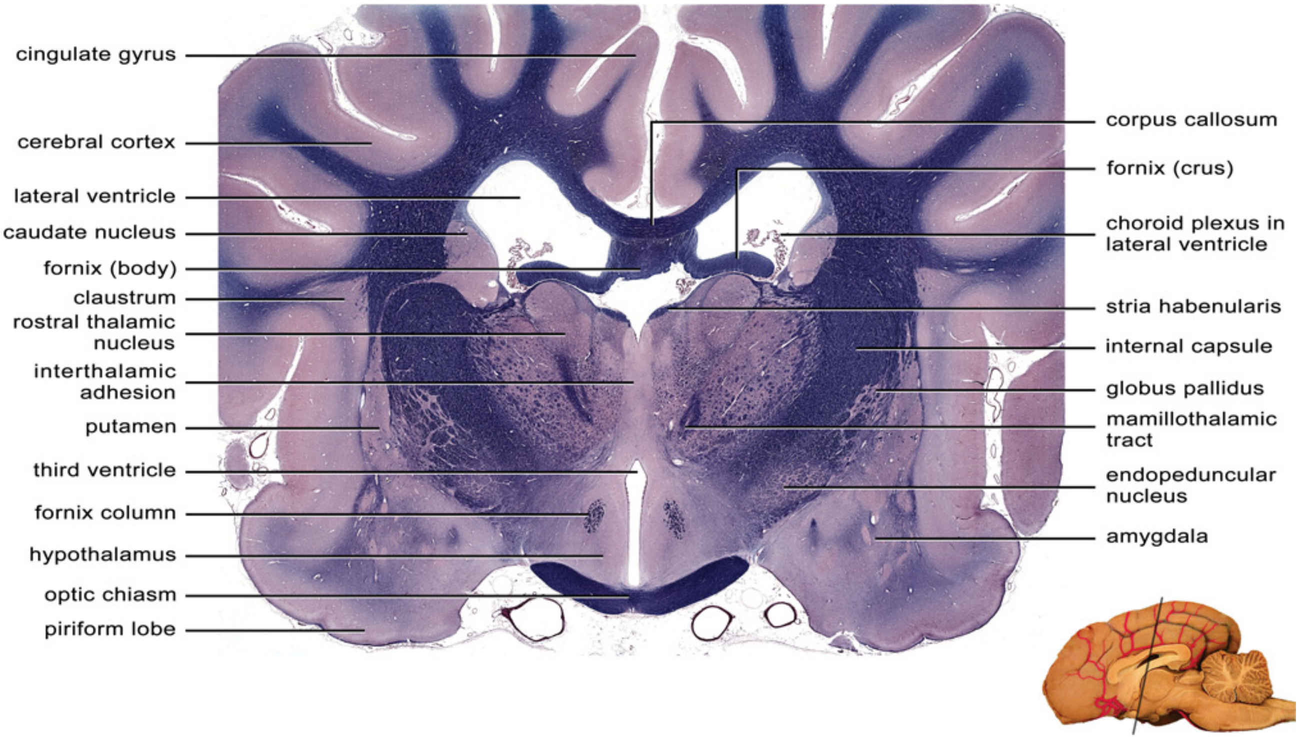
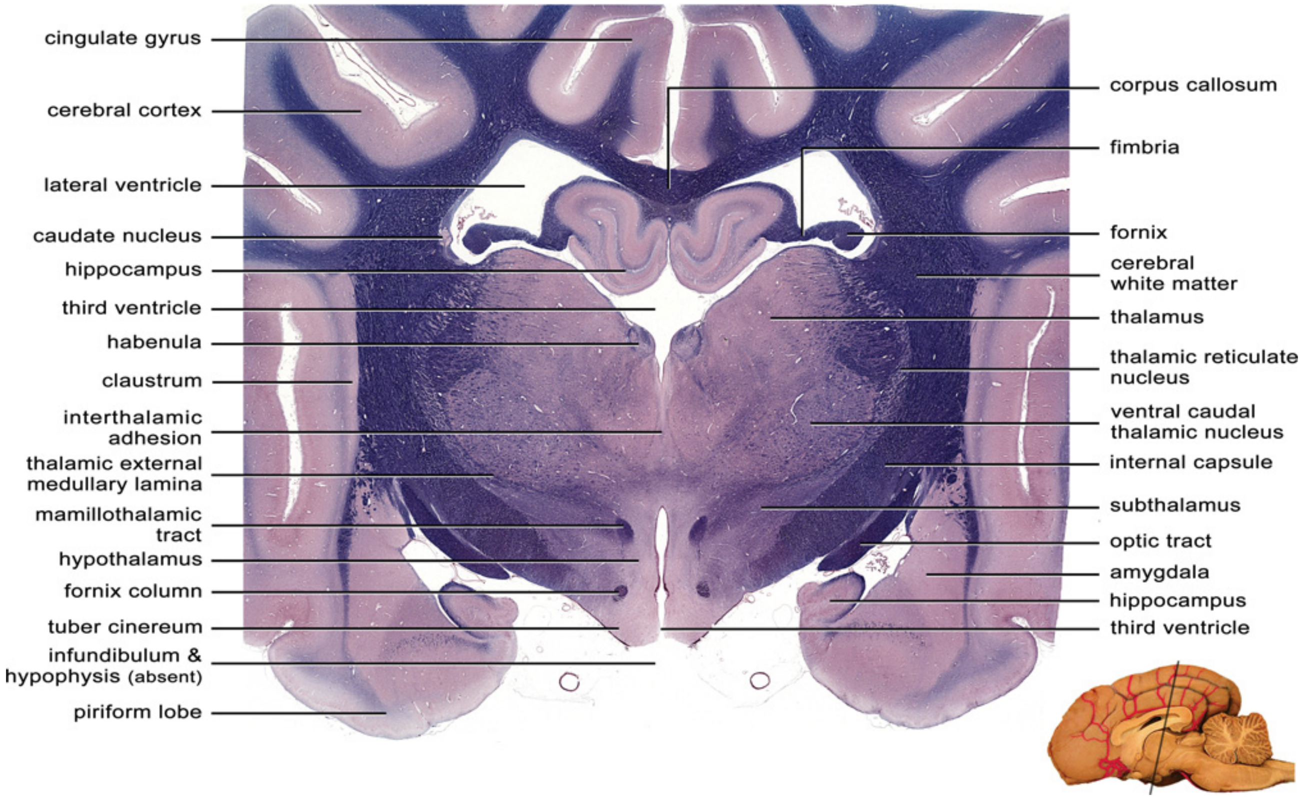

sulcus
gyrus
cingulate gyrus
lateral ventricle
septum pellucidum
internal capsule
external capsule
extreme capsule
rostral commissure
medial olfactory stria
lateral olfactory stria
optic nerve
cerebral cortex
cerebral white matter
corpus callosum
caudate nucleus
claustrum
septum
putamen
globus pallidus
accumbens nucleus

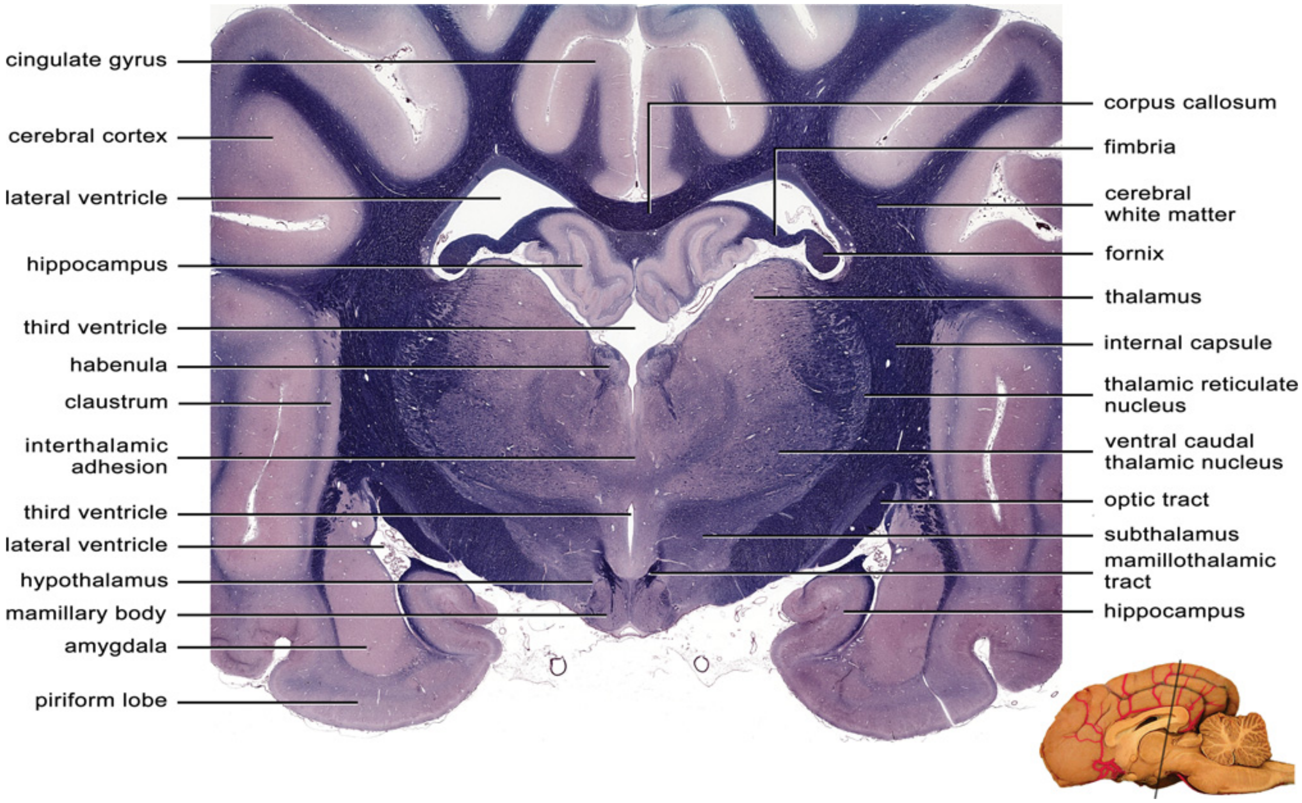
Level 1 Frontal Lobes (including: septum & basal nuclei).


cingulate gyrus
cerebral cortex
lateral ventricle
caudate nucleus
fornix (body)
claustrum
rostral thalamic nucleus
interthalamic adhesion
putamen
third ventricle
fornix column
hypothalamus
optic chiasm
piriform lobe
corpus callosum
fornix (crus)
choroid plexus in lateral ventricle
stria habenularis
internal capsule
globus pallidus
mamillothalamic tract
endopeduncular nucleus
amygdala

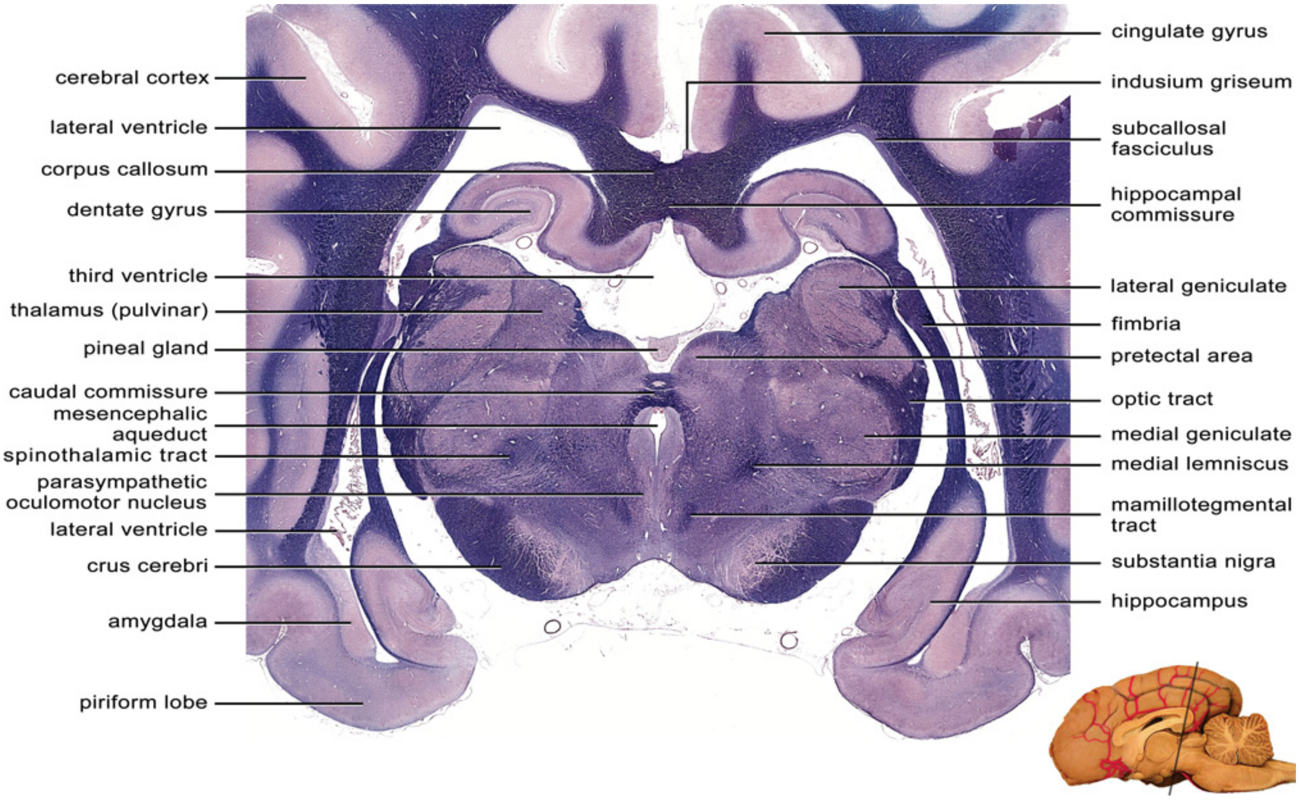
Level 2 Optic Chiasm (including: piriform lobe & basal nuclei).


cingulate gyrus
cerebral cortex
lateral ventricle
caudate nucleus
hippocampus
third ventricle
habenula
claustrum
interthalamic adhesion
thalamic external medullary lamina
mamillothalamic tract
hypothalamus
fornix column
tuber cinereum
infundibulum & hypophysis (absent)
piriform lobe
corpus callosum
fimbria
fornix
cerebral white matter
thalamus
thalamic reticulate nucleus
ventral caudal thalamic nucleus
internal capsule
subthalamus
optic tract
amygdala
hippocampus
third ventricle

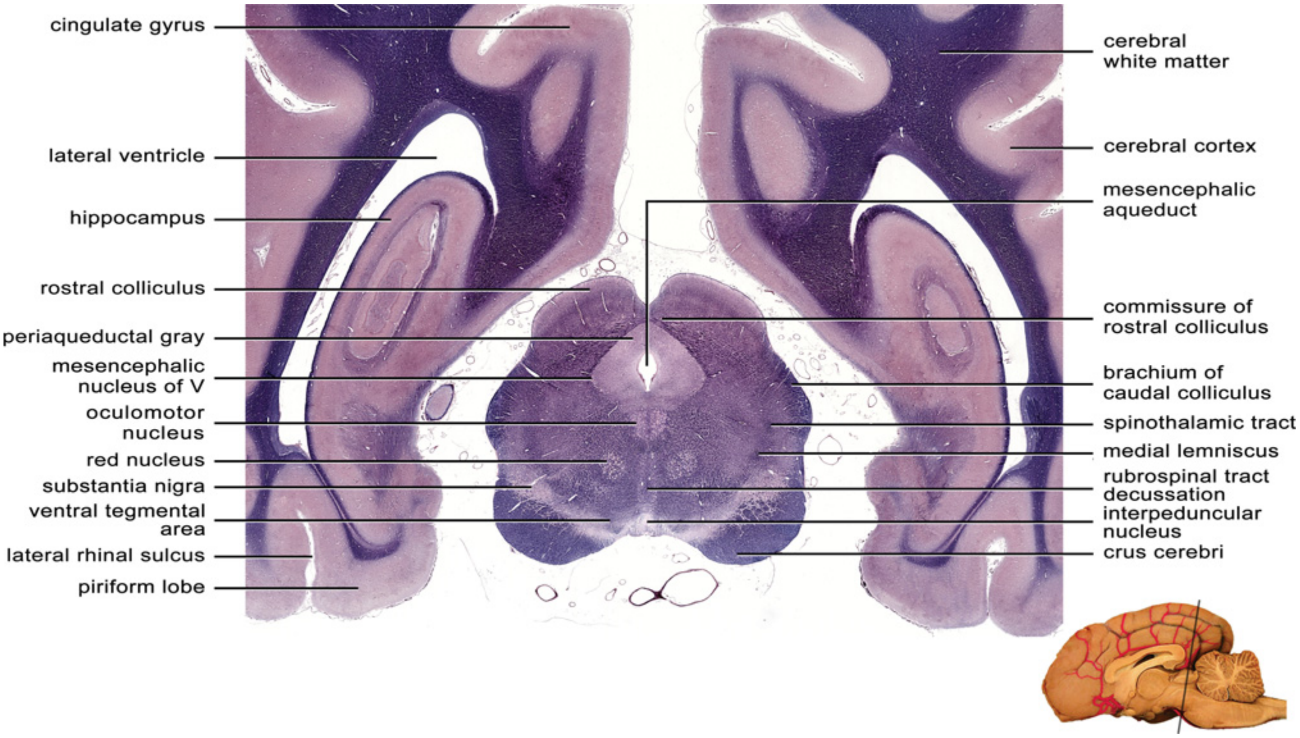
Level 3 Mid-Diencephalon (including: subthalamus & tuber cinereum).


cingulate gyrus
cerebral cortex
lateral ventricle
hippocampus
third ventricle
habenula
claustrum
interthalamic adhesion
third ventricle
lateral ventricle
hypothalamus
mamillary body
amygdala
piriform lobe
corpus callosum
fimbria
cerebral white matter
fornix
thalamus
internal capsule
thalamic reticulate nucleus
ventral caudal thalamic nucleus
optic tract
subthalamus
mamillothalamic tract
hippocampus

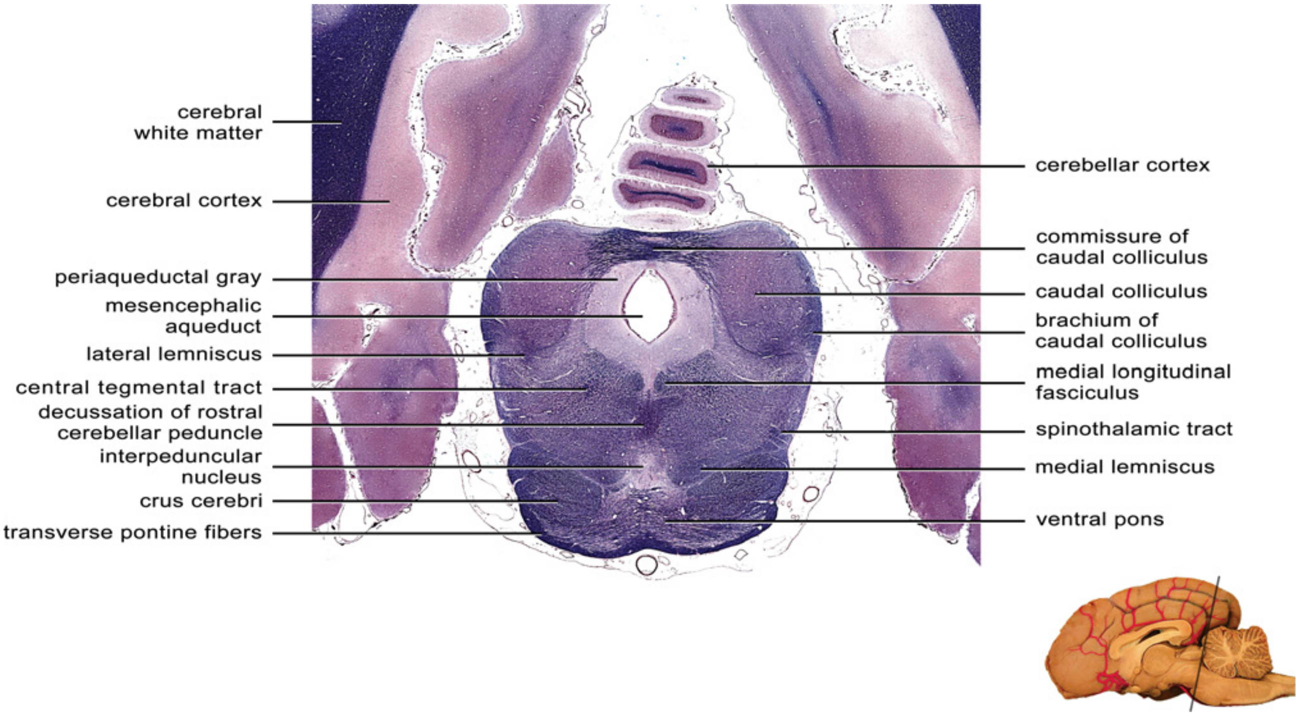
Level 4 Caudal Diencephalon (including: habenula & mamillary body).


cerebral cortex
lateral ventricle
corpus callosum
dentate gyrus
third ventricle
thalamus (pulvinar)
pineal gland
caudal commissure
mesencephalic aqueduct
spinothalamic tract
parasympathetic oculomotor nucleus
lateral ventricle
crus cerebri
amygdala
piriform lobe
cingulate gyrus
indusium griseum
subcallosal fasciculus
hippocampal commissure
lateral geniculate
fimbria
pretectal area
optic tract
medial geniculate
medial lemniscus
mamillotegmental tract
substantia nigra
hippocampus

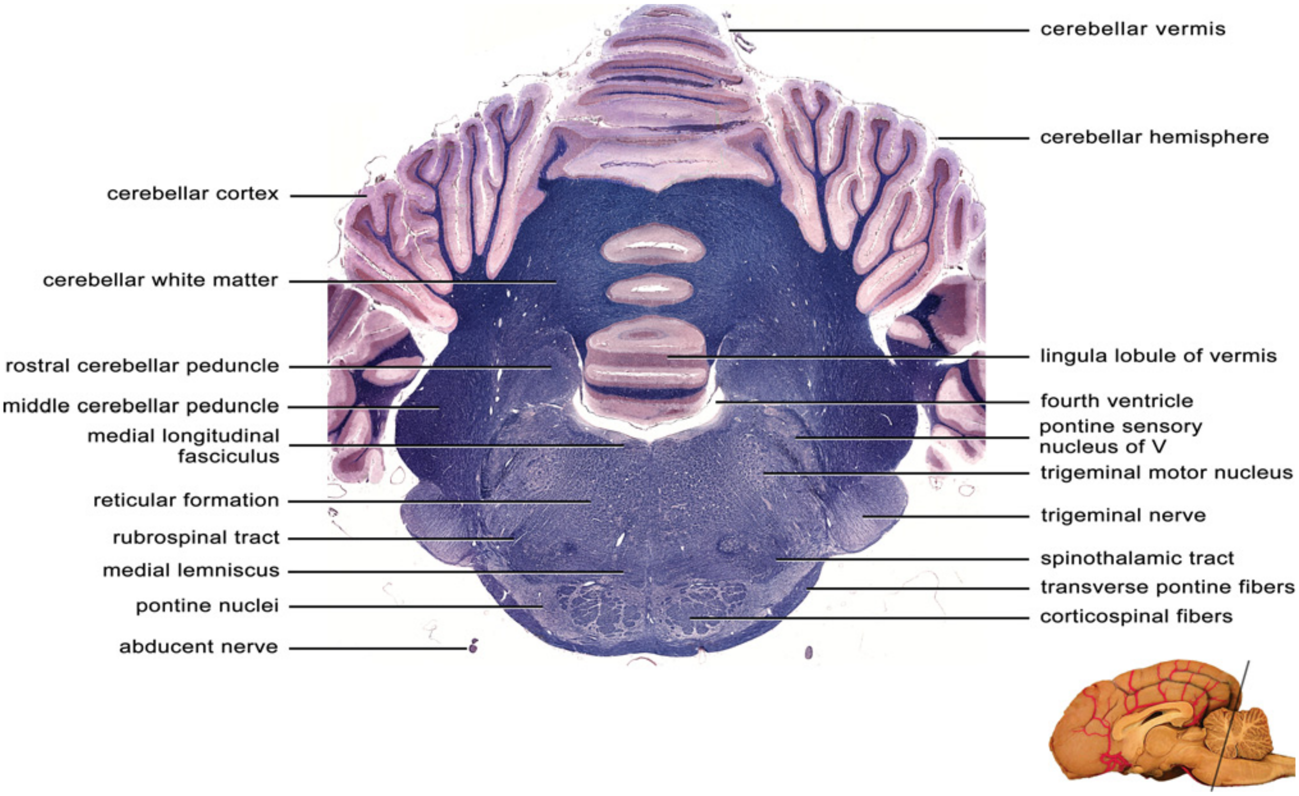
Level 5 Diencephalon-Midbrain (including: geniculate nuclei & pretectum).


cingulate gyrus
lateral ventricle
hippocampus
rostral colliculus
periaqueductal gray
mesencephalic nucleus of V
oculomotor nucleus
red nucleus
substantia nigra
ventral tegmental area
lateral rhinal sulcus
piriform lobe
cerebral white matter
cerebral cortex
mesencephalic aqueduct
commissure of rostral colliculus
brachium of caudal colliculus
spinothalamic tract
medial lemniscus
rubrospinal tract decussation
interpeduncular nucleus
crus cerebri

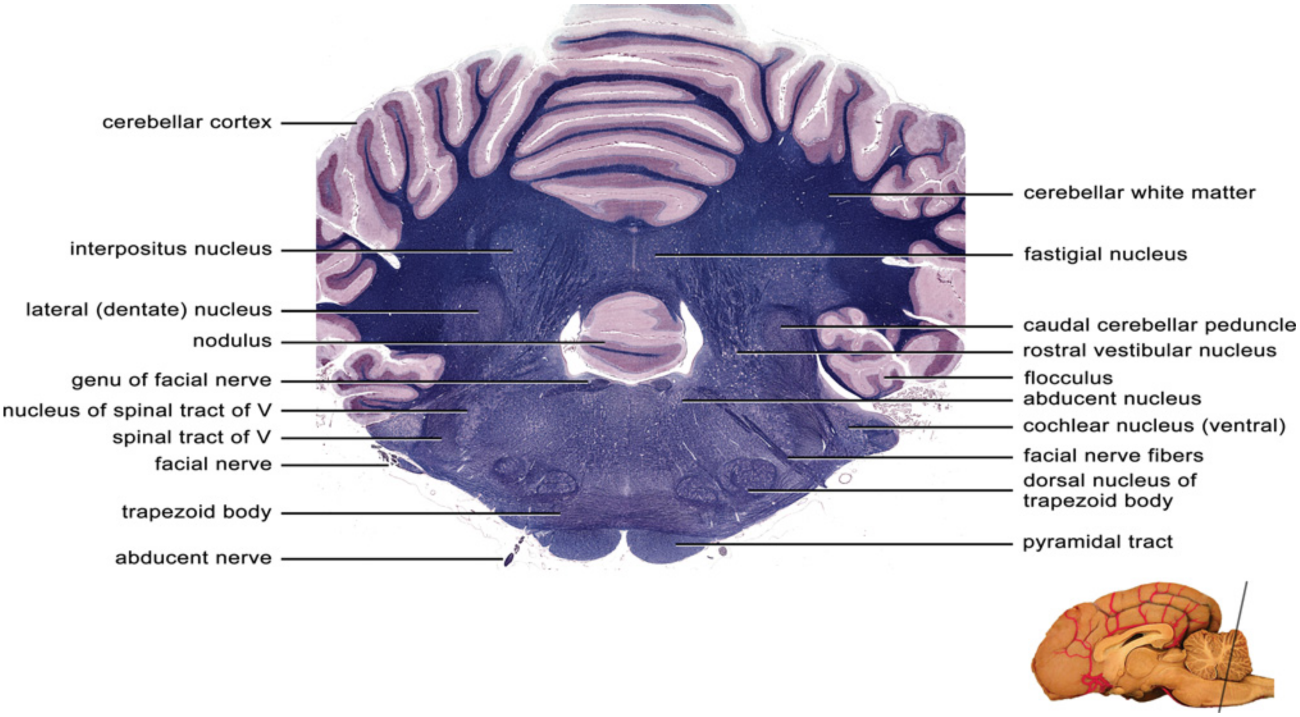
Level 6 Oculomotor Nucleus (including: rostral colliculus & red nucleus).


cerebral white matter
cerebral cortex
periaqueductal gray
mesencephalic aqueduct
lateral lemniscus
central tegmental tract
decussation of rostral cerebellar peduncle
interpeduncular nucleus
crus cerebri
transverse pontine fibers
cerebellar cortex
commissure of caudal colliculus
caudal colliculus
brachium of caudal colliculus
medial longitudinal fasciculus
spinothalamic tract
medial lemniscus
ventral pons

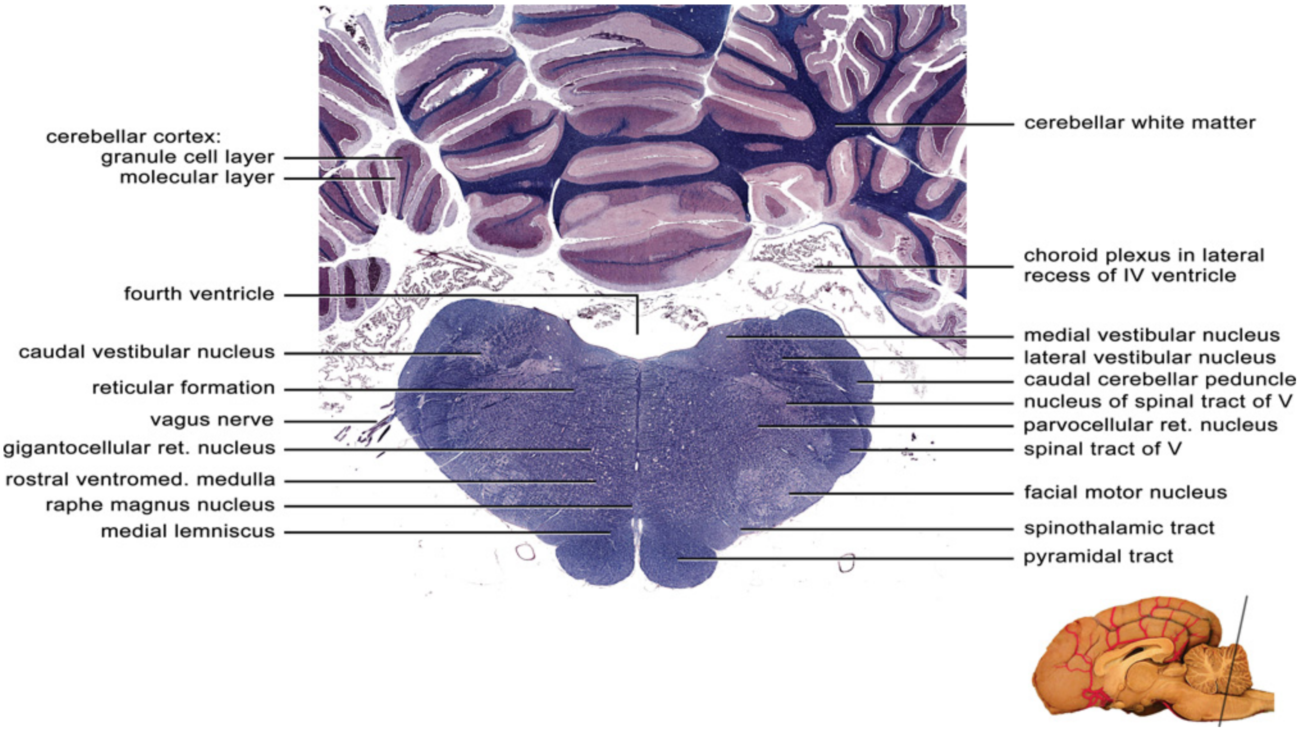
Level 7 Midbrain-Pons Juncture (including: caudal colliculus & ventral pons).


cerebellar vermis
cerebellar hemisphere
cerebellar cortex
cerebellar white matter
rostral cerebellar peduncle
middle cerebellar peduncle
medial longitudinal fasciculus
reticular formation
rubrospinal tract
medial lemniscus
pontine nuclei
abducent nerve
lingula lobule of vermis
fourth ventricle
pontine sensory nucleus of V
trigeminal motor nucleus
trigeminal nerve
spinothalamic tract
transverse pontine fibers
corticospinal fibers

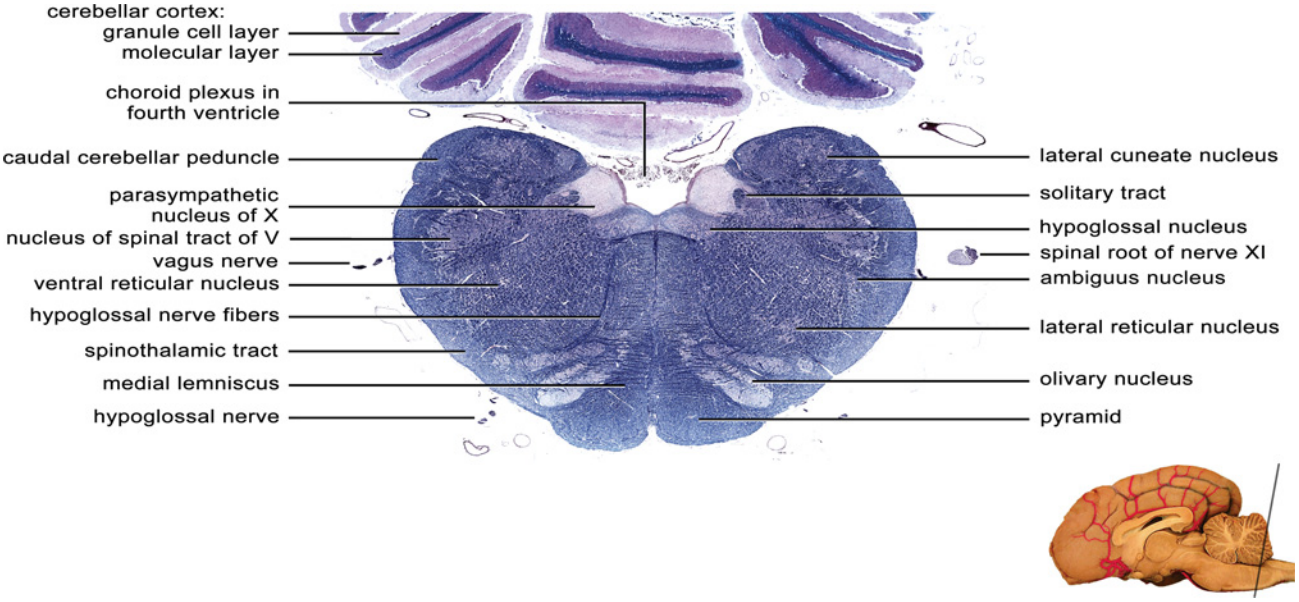
Level 8 Metencephalon (including: cerebellum & pons).


cerebellar cortex
interpositus nucleus
lateral (dentate) nucleus
nodulus
genu of facial nerve
nucleus of spinal tract of V
spinal tract of V
facial nerve
trapezoid body
abducent nerve
cerebellar white matter
fastigial nucleus
caudal cerebellar peduncle
rostral vestibular nucleus
flocculus
abducent nucleus
cochlear nucleus (ventral)
facial nerve fibers
dorsal nucleus of trapezoid body
pyramidal tract

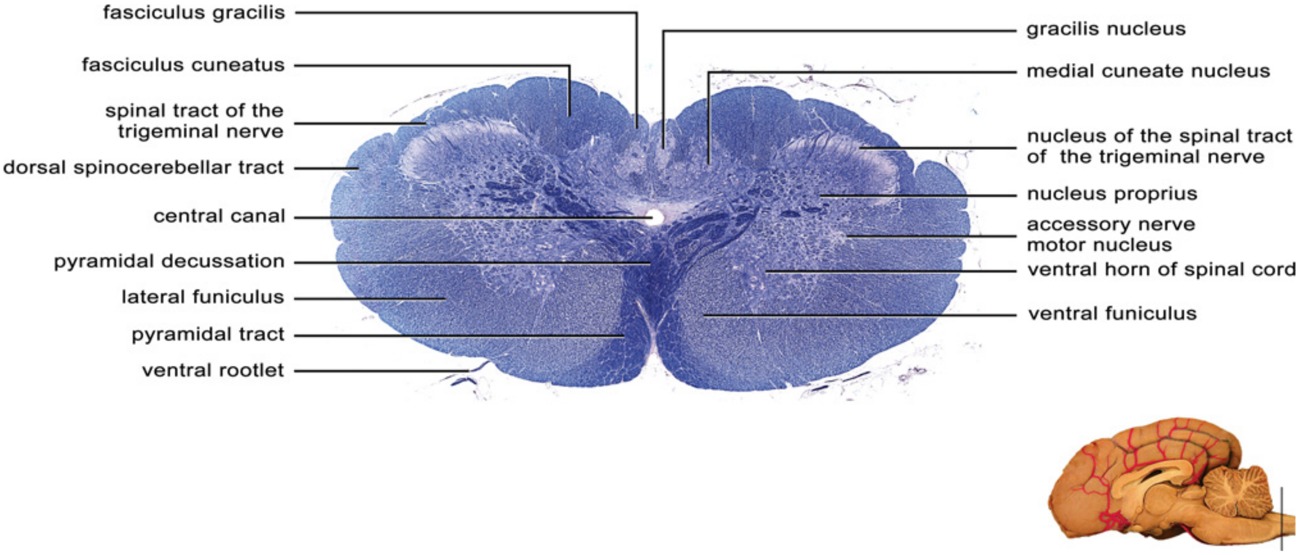
Level 9 Rostral Myelencephalon (including: cerebellum & trapezoid body).


cerebellar cortex:
granule cell layer
molecular layer
fourth ventricle
caudal vestibular nucleus
reticular formation
vagus nerve
gigantocellular ret. nucleus
rostral ventromed. medulla
raphe magnus nucleus
medial lemniscus
cerebellar white matter
choroid plexus in lateral recess of IV ventricle
medial vestibular nucleus
lateral vestibular nucleus
caudal cerebellar peduncle
nucleus of spinal tract of V
parvocellular ret. nucleus
spinal tract of V
facial motor nucleus
spinothalamic tract
pyramidal tract

Level 10 Mid-Myelencephalon (including: cerebellum & facial nucleus).


cerebellar cortex:
granule cell layer
molecular layer
choroid plexus in fourth ventricle
caudal cerebellar peduncle
parasympathetic nucleus of X
nucleus of spinal tract of V
vagus nerve
ventral reticular nucleus
hypoglossal nerve fibers
spinothalamic tract
medial lemniscus
hypoglossal nerve
lateral cuneate nucleus
solitary tract
hypoglossal nucleus
spinal root of nerve XI
ambiguus nucleus
lateral reticular nucleus
olivary nucleus
pyramid

Level 11 Hypoglossal Nucleus (including: solitary tract & olivary nucleus).


fasciculus gracilis
fasciculus cuneatus
spinal tract of the trigeminal nerve
dorsal spinocerebellar tract
central canal
pyramidal decussation
lateral funiculus
pyramidal tract
ventral rootlet
gracilis nucleus
medial cuneate nucleus
nucleus of the spinal tract of the trigeminal nerve
nucleus proprius
accessory nerve motor nucleus
ventral horn of spinal cord
ventral funiculus

Level 12 Brain-Spinal Cord (including: pyramidal decussation).

Canine Brain Atlas Glossary

Thomas F. Fletcher

A

abducent nerve [Levels 8, 9] The sixth cranial nerve. It exits the medulla oblongata and innervates the lateral rectus and retractor bulbi muscles of the eye. Note: "abducent" is derived from the Latin for "to lead away," referring to the lateral gaze for which the nerve is responsible.

abducent nucleus [Level 9] The nucleus consists of somatic efferent neuron cell bodies that innervate two of the seven extrinsic muscles of the carnivore eye. The neurons shift the gaze laterally (lateral rectus m.), and they retract the eyeball in order to protract the third eyelid (retractor bulbi m.). Note: "abducent" is derived from the Latin for "to lead away," referring to the lateral gaze for which the nerve is responsible.

accessory nerve motor nucleus [Level 12] This column of somatic efferent cell bodies is located in intermediate gray matter throughout most of the cervical spinal cord. Axons from the nucleus form the spinal root of the accessory nerve (XI) and ultimately innervate neck muscles (trapezius, omotransversarius, cleidocephalicus, mastoid part of the sternocephalicus).

accumbens nucleus [Level 1] Located at the base of the septum, the nucleus plays a role in pleasure, addiction, and processing reward stimuli. Dopamine and serotonin neurotransmitters are associated with neurons comprising the nucleus. Via a mesolimbic pathway, the nucleus connects with the ventral tegmental area of the midbrain, which contains neurons responsive to opiates, amphetamine, and alcohol. Note: "accumbens" is derived from the Latin word for "reclining."

amygdala [Levels 2–5] A collection of nuclei deep to the piriform lobe, the amygdala is involved in processing and remembering emotions, particularly fearful ones and those related to punishment. The amygdala is a basal nucleus of the telencephalon and a major component of the limbic system. It has reciprocal connections with other limbic components. Note: "amygdala" is from the Greek word for "almond."

B

basal nuclei (basal ganglia) [Levels 1, 2 captions] Refers to nuclei located deep within the white matter of the telencephalon, as opposed to surface gray matter (cerebral cortex). Basal nuclei include: caudate nucleus, nucleus accumbens, putamen, globus pallidus, amygdala, and claustrum. In addition, the subthalamic nucleus and substantia nigra are commonly referred to as basal nuclei because of their movement-related connections with certain telencephalic nuclei.

brachium of the caudal colliculus [Levels 6, 7] A band of auditory axons that run from the lateral lemniscus and caudal colliculus to the medial geniculate body. The axons convey conscious hearing from both ears, but predominantly from the contralateral ear. Note: *brachium* is the Latin word for "arm"; *colliculus* is the Latin word for "small hill."

C

caudal cerebellar peduncle [Levels 9–11] White matter connecting the cerebellum to the hindbrain and spinal cord. It contains cerebellar afferent input from the dorsal spinocerebellar tract (hindlimb), lateral cuneate nucleus (forelimb), olivary nucleus (climbing fibers), vestibular nuclei, and vestibular nerve. It conveys cerebellar efferents to vestibular nuclei and the reticular formation. Note: *peduncle* comes from the Latin word *pedunculus*, which means stemlike; like a stalk, the fiber bundle attaches the cerebellum to the brain stem.

caudal colliculus [Level 7] This functions as an auditory reflex center for head, eye, and ear orientation toward a sudden sound. It receives bilateral cochlear input via the lateral lemniscus. Note: *colliculus* is the Latin word for "small hill."

caudal commissure [Level 4] Nerve fibers that connect right and left pretectal areas in connection with the bilateral pupillary light reflex. Note: "commissure" is from the Latin word for "junction" (the term is used for fibers that cross the midline).

caudate nucleus [Levels 1–4] This basal nucleus is named for its long, narrow, arched tail. The caudate nucleus participates in voluntary movement circuits that are active during movement planning. Together the caudate nucleus and the putamen comprise the striate body, which facilitates movement by inhibiting the endopeduncular nucleus, which otherwise suppresses thalamic excitation of the motor area of the cerebral cortex. The striate body can inhibit movement by inhibiting the globus pallidus, which inhibits the endopeduncular nucleus. Note: *cauda* is the Latin word for "tail."

central canal [Level 12] This cavity within the spinal cord is derived from the embryonic neural cavity and lined by ependymal cells.

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central tegmental tract [Level 7] This bundle of axons carries information from the forebrain to the brain stem reticular formation. Also, it conveys information among nuclei of the reticular formation and from the red nucleus to the olivary nucleus. Note: "tegmentum", from the Latin word for "covering," is applied to midregions of the midbrain and pons.

cerebellar cortex [Levels 8–11] Refers to surface gray matter covering the cerebellum. Two of the three layers comprising the cortex are evident in the Atlas [Levels 10, 11]: a superficial molecular layer and a deep granule cell layer. The latter appears dark because it is densely populated with pachychromatic small neurons. Note: *cerebellum* is the Latin word for "small brain."

cerebellar hemispheres [Level 8] Refers to the paired cerebellar regions bilateral to the median vermis. Hemispheric cortex projects to the underlying lateral (dentate) nucleus in order to coordinate movement synergy. Note: *cerebellum* is the Latin word for "small brain."

cerebellar nuclei [Level 9] Located deep in the cerebellar white matter, three bilateral accumulations of neuron cell bodies form: fastigial, interpositus, and lateral (dentate) nuclei, from medial to lateral. Axons from the nuclei constitute cerebellar output to caudal and rostral cerebellar peduncles. Note: *cerebellum* is the Latin word for "small brain."

cerebellar vermis [Level 8] Refers to the (wormlike) median cerebellar region. It is divisible into 10 lobules. Cortex of the vermis projects to fastigial and interpositus cerebellar nuclei in connection with maintaining balance and appropriate muscle tone. Note: *vermis* is the Latin word for "worm."

cerebellar white matter [Levels 8–10] Refers to the internal accumulation of myelinated axons that run from cerebellar peduncles to cerebellar cortex and from cerebellar cortex to cerebellar nuclei. Note: *cerebellum* is the Latin word for "small brain."

cerebral cortex [Levels 7–11] Surface gray matter covering the telencephalon (cerebral hemispheres). Most of the cerebral cortex is isocortex (neocortex). This has six layers and is involved with detailed sensory perception, cognitive functions including learning and memory, and voluntary movement planning and initiation. Allocortex (fewer layers and older) covers the rhinencephalon (ventral telencephalon). Note: "cortex" comes from the Latin word for "bark" or "rind."

cerebral white matter [Levels 1, 3, 4, 6, 7] Refers to the internal accumulation of myelinated fibers that run from the thalamus to the cerebral cortex (corticopedal) and from the cortex to the basal nuclei, thalamus, and the brain stem (corticofugal). Also, there are fibers running within a cerebral hemisphere (association fibers) and between right and left hemispheres (commissural fibers). Note: *cerebrum* is the Latin word for "brain."

choroid plexus [Levels 2, 10, 11] The source of cerebrospinal fluid within a brain ventricle. It consists of epithelium covering highly vascular villi. Note: "choroid" is derived from the Greek word *khorion*; "plexus" is derived from Latin and means "to pleat."

cingulate gyrus [Levels 1–6] Located medially, dorsal to the corpus callosum, the cingulate gyrus is part of the limbic system and thus plays a role in processing emotions, including motivated learning and memory. It is involved with emotional response to pain and is a key brain structure associated with crying in mammals. It communicates with the thalamus and other areas of neocortex as well as with the rhinencephalon. Note: "cingulate" is derived from the Latin word for "girdle."

claustrum [Levels 1–4] A broad, narrow area of gray matter sandwiched between the white matter entities designated "external capsule" and "extreme capsule." The claustrum has broad connections with the cerebral cortex but its function is unclear. Note: "claustrum" is from the Latin word for "barrier."

cochlear nuclei [Level 9] Neurons comprising dorsal and ventral cochlear nuclei receive input from the cochlear nerve (VIII). The nuclei are positioned together, but the dorsal nucleus contributes to a surface elevation (acoustic tubercle). Neurons are tonotopically arranged within the nuclei. Axons from the nuclei initiate the auditory pathway within the brain. Note: "cochlear" is from the Latin for "snail shell."

commissure of the caudal colliculus [Level 7] The band of fibers that connects right and left caudal colliculi in the tectum (roof) of the midbrain. Note: "commissure" is from the Latin word for "junction"; *colliculus* is Latin for "small hill."

commissure of the rostral colliculus [Level 6] The band of fibers that connects right and left rostral colliculi in the tectum (roof) of the midbrain. Note: "commissure" is from the Latin word for "junction"; *colliculus* is Latin for "small hill."

corpus callosum [Levels 1—5] The band of commissural fibers that connects neocortex of right and left cerebral hemispheres, effectively making one integrated brain out of the two hemispheres. Note: *corpus* is the Latin word for "body"; *callosum* is the Latin word for "tough."

corticospinal fibers [Level 8] These fibers arise from cell bodies in the cerebral cortex (particularly motor and somatosensory neocortex) and terminate in the spinal cord. The fibers run in pyramids of the medulla oblongata (hence they are contained in the pyramidal tract). The fibers provide voluntary control of distal joints of the limbs, and they regulate traffic in ascending pathways.

crus cerebri [Levels 4–7] A midbrain bundle of corticospinal fibers coming from the internal capsule and going through the ventral pons to the pyramid of the medulla oblongata. The bundle also contains corticobulbar fibers to the substantia nigra, pontine nuclei, reticular formation, olivary nucleus, and cranial nerve nuclei. Note: "crus" is derived from the Latin word for "leg."

D

decussation of rostral cerebellar peduncle [Level 7] Axons originating from the interpositus nucleus or the lateral (dentate) nucleus of one side of the cerebellum cross the midline via this decussation in order to synapse, respectively, in the contralateral red nucleus and thalamus. Note: "decussation" is derived from the Latin word *decussare*, which means to divide crosswise, which itself comes from the Roman numeral for "ten," i.e. "X."

dentate gyrus [Level 5] The innermost gyrus of the hippocampus. In transverse sections, the gyrus appears to cap the deep edge of the hippocampus proper. In general, the dentate gyrus initially processes hippocampal input and sends its output to the hippocampus proper. The ability to distinguish among sensory patterns (pattern separation) is a particular role of this gyrus. The dentate gyrus is one of the few sites where the formation of new neurons (neurogenesis) is known to take place. Note: "dentate" is derived from a Latin word pertaining to "tooth," due to the shape of the gyrus when sectioned transversely.

dentate nucleus [Level 9] The dentate (lateral) nucleus of the cerebellum receives inhibitory input from cortical Purkinje cells located in the ipsilateral cerebellar hemisphere. Axons from the nucleus run through the rostral cerebellar peduncle and decussate in the midbrain. They impact the premotor cerebral cortex through the thalamus, via either a direct synapse or through a neuron in the red nucleus. Note: "dentate" is derived from a Latin word pertaining to "tooth," referring to the shape of the nucleus.

dorsal nucleus of trapezoid body [Level 9] Via fibers in the trapezoid body (from ventral cochlear nuclei), this nucleus receives input from both ears and is involved in sound localization. It is also a reflex center for middle ear muscles and the source of efferent axons found in the cochlear nerve. Note: "trapezoid" is derived originally from the Greek word for "table."

dorsal spinocerebellar tract [Level 12] This tract is formed by axons from the nucleus thoracicus of the spinal cord. The nucleus receives proprioceptive input from the pelvic limb. The tract enters the cerebellum via the caudal cerebellar peduncle. Note: "spino-" is derived from the Latin word for "backbone."

E

endopeduncular nucleus [Level 2] This basal nucleus may be regarded as the internal component of the globus pallidus (pallidum). It contains spontaneously active inhibitory neurons and its role in voluntary movement circuits is to suppress thalamic neurons that activate the motor cortex. Note: "endo-" is from the Greek word for "within"; "peduncular" is derived from the Latin word for "stemlike."

external capsule [Level 1] A thin white matter sheet that separates the putamen and globus pallidus from the claustrum. Note: the white matter appears to encapsulate the gray basal nuclei.

extreme capsule [Level 1] A layer of white matter positioned along the lateral margin of the claustrum, separating it from the cerebral cortex. Among the three white matter "capsules," it occupies the extreme lateral position. Note: the white matter appears to encapsulate the gray basal nuclei.

F

facial motor nucleus [Level 10] This nucleus is composed of somatic efferent neuron cell bodies that innervate muscles of facial expression via the facial nerve. Note: *nucleus* is from the Latin word for "kernel."

facial nerve [Level 9] Cranial nerve VII. It innervates muscles of facial expression (somatic efferent fibers); nasal and lacrimal glands, and mandibular and sublingual salivary glands (visceral efferent fibers); taste buds from the rostral two-thirds of the tongue (special visceral afferent); and sensation from the concave surface of the pinna of the ear (general somatic afferent). Note: "nerve" is derived from the Greek word for "sinew."

facial nerve fibers and genu [Level 9] Axons from the facial motor nucleus have an indirect course within the brain stem. From the nucleus, they run dorsally and rostrally, form a bend (genu) dorsal to the abducent nucleus, and then run ventrally and laterally to exit the brain stem. Note: *genu*, the Latin word for "knee," is applied to the bend made by the fibers.

fasciculus cuneatus [Level 12] This white matter bundle within the dorsal funiculus of the spinal cord conveys proprioception and discriminative touch from the thoracic limb to the medial cuneate nucleus (conscious pathway) and to the lateral cuneate nucleus (for relay to the cerebellum). The fasciculus is formed by cranial branches of primary afferent neurons. Note: *fasciculus* is the Latin word for "small bundle"; *cuneatus* is the Latin word for "wedge."

fasciculus gracilis [Level 12] A white matter bundle within the dorsal funiculus of the spinal cord that conveys discriminative touch from the pelvic limb to the gracilis nucleus as part of a conscious pathway. The fasciculus is formed by cranial branches of primary afferent neurons. Note: *fasciculus* is the Latin word for "small bundle"; *gracilis* is the Latin word for "slender."

fastigial nucleus [Level 9] This cerebellar nucleus receives inhibitory input from cortical Purkinje cells of the vermis. It sends axons through the caudal cerebellar peduncle to the reticular formation and vestibular nuclei to regulate muscle tone and maintain balance. Note: "fastigial" is derived from a Latin word referring to "gable peak" (roof of the IV ventricle).

fimbria [Levels 3–5] Refers to the white matter layer formed by axons from the hippocampus extending laterally to join the fornix. Note: *fimbria* is from the Latin word for "fringe."

flocculus [Level 9] Refers to a ventrolateral lobule of a cerebellar hemisphere. Together with the nodulus of the vermis, the two flocculi form the flocculonodular lobe of the cerebellum, which is closely associated with vestibular function. Note: *flocculus* is the Latin for word for "small tuft."

fornix [Levels 2–4] A white matter bundle composed of axons that come from the hippocampus (via the fimbria) and go to the septum or rostral thalamus or mamillary bodies. The fornix can be divided into regions [L2]: **crus**—lateral to the hippocampus; **body**—where right and left crura appear to join at the midline; and **column**—the bundle that runs to the mamillary body. Note: *fornix* is the Latin word for "arch" or "vaulted."

fourth ventricle [Levels 8, 10, 11] This hindbrain cavity is derived from the embryonic neural cavity. It is lined by ependyma, filled with cerebrospinal fluid, and covered by a thin roof that bilaterally gives rise to choroid plexuses. Rostrally, the ventricle communicates with the mesencephalic aqueduct. Caudally, the ventricle communicates with the central canal of the spinal cord. Bilaterally, the ventricle is open to the subarachnoid space via a lateral recess and aperture. Note: "ventricle" is derived from the Latin word for "small belly."

fourth ventricle lateral recess [Level 10] Bilateral extensions of the fourth ventricle leading to lateral apertures, by which cerebrospinal fluid exits the ventricular system in order to surround the brain and spinal cord.

frontal lobe [Level 1 captions] Refers to the rostral end of a cerebral hemisphere. The premotor area of the cerebral cortex (for planning and learning voluntary movement) is located in the frontal lobe. The frontal pole (prefrontal cortex) is associated with cognitive capacity, including the ability to plan and execute directed activities, choose better actions, and suppress impulsive and unacceptable behavior. In dogs, frontal lobe deficits are manifested by learning disability and incoherent, fleeting attention spans directed at any and every stimulus encountered.

G

gigantocellular reticular nucleus [Level 10] Composed of scattered large neurons, this nucleus gives rise to axons that descend to all levels of the spinal cord, impacting somatic, autonomic, and projection neurons. The neurons likely contribute axons to the medullary reticulospinal tract, which excites limb flexor muscles. Note: the term comes from the Latin word *reticulum*, which means "small net."

globus pallidus (pallidum) [Levels 1, 2] This basal nucleus is involved in voluntary movement circuits. The globus pallidus, which contains spontaneously active inhibitory neurons, sends inhibitory output to the endopeduncular nucleus and receives inhibitory input from the caudate nucleus and putamen (striate body). As a result the globus pallidus functions to facilitate desired movement (by disinhibition). Note: *globus pallidus* is Latin for "pale globe."

gracilis nucleus [Level 12] A relay nucleus in the discriminative touch conscious pathway from the pelvic limb. The nucleus receives cranial branches of primary afferent neurons that innervate, more or less, the caudal half of the body. Axons from the nucleus ascend in the contralateral medial lemniscus to the lateral portion of the ventral caudal nucleus of the thalamus. Note: "gracilis" comes from the Latin word for "slender."

gyrus [Level 1] Refers to an elevated ridge at the surface of the cerebrum or cerebellum. The elevation consists of gray matter cortex and underlying white matter. Note: "gyrus" comes from the Greek word for "ring."

H

habenula [Level 3] Refers to medial and lateral habenular nuclei, located lateral to the pineal body in the epithalamus of the diencephalon. The nuclei receive input from the septal region, rostral thalamus and hypothalamus, and spinal cord. Output is sent to the midbrain, including the interpeduncular nucleus and dopaminergic substantia nigra. Via inhibition of dopamine release, the habenula is involved in freezing movement, such as exhibited by prey animals in response to perceived threats. Note: "habenula" comes from the Latin word for "small rein."

hippocampal commissure [Level 5] Composed of nerve fibers crossing the midline between the right hippocampus and the left hippocampus. Note: "commissure" is derived from the Latin word for "junction" (the term is used for fibers that cross the midline).

hippocampus [Levels 3–6] Located medial to the lateral ventricle, the hippocampus is the oldest cerebral cortex. It is a component of the limbic system and it is essential for forming new memories, including spatial memory (how you got to your current location and how to return) and pattern completion (recollection of prior experiences invoked by sensory cues). Neurons of the hippocampus give rise to the fimbria and fornix. The hippocampus undergoes selective neuron loss as dogs age. Note: named for its appearance in cross section, the term "hippocampus" is derived from the Greek words for "sea horse."

hypoglossal nerve and nerve fibers [Level 11] These nerve fibers arise in the hypoglossal nucleus and run to the tongue to innervate intrinsic and extrinsic tongue muscles. Note: "hypoglossal" is from the Greek words for "under" and "tongue," referring to the course the nerve takes in innervating the tongue.

hypoglossal (motor) nucleus [Level 11] The nucleus is composed of somatic efferent neurons that, via the hypoglossal nerve, innervate intrinsic and extrinsic muscles of the tongue. In conjunction with the first cervical spinal nerve (ansa cervicalis), the nucleus also innervates sternohyoid and sternothyroid muscles. Note: "hypoglossal" is from the Greek words for "under" and "tongue," referring to the course the nerve takes in innervating the tongue.

hypophysis [Level 3] The hypophysis (pituitary gland) is attached via an infundibulum to the ventral surface of the tuber cinereum region of the hypothalamus. The hypophysis is absent in this brain atlas (it was lost during brain removal). Note: "hypophysis" comes from the Greek words for "undergrowth."

hypothalamus [Levels 2–4] Located ventrally and medially in the diencephalon, the hypothalamus is divisible into a number of regions, areas, and nuclei. Functionally, the hypothalamus is involved in expressing visceral and emotional behavior, controlling autonomic nuclei, and, via the pituitary gland, directing endocrine homeostasis. Note: "hypothalamus" comes from the Greek words for "under" and "thalamus."

I

indusium griseum [Level 5] This thin strip of gray matter, located dorsally on the corpus callosum, tucked ventral to the cingulate gyrus, is only remarkable for its anatomical oddity. Phylogenetically associated with the hippocampus, the indusium griseum is a caudal continuation of the slender supracallosal gyrus. Note: *indusium* is the Latin word for "tunic" and *griseum* for "gray."

infundibulum [Level 3] The infundibulum is a stalk that attaches the hypophysis (pituitary gland) to the ventral surface of the hypothalamus. It conveys axons and vessels from the hypothalamus to the hypophysis. The infundibulum is absent in this brain atlas; it was lost during brain removal. Note: "infundibulum," derived from Latin, means "funnel."

internal capsule [Levels 1–4] This white matter "capsule" is the largest and most medial of the three so-called capsules. It separates the putamen and globus pallidus from the caudate nucleus; further caudally, it separates the thalamus from the globus pallidus. The internal capsule consists of corticopedal axons that arise in the thalamus and corticoflugal axons that terminate in basal nuclei, thalamus, brain stem, or spinal cord. Note: the white matter was regarded as encapsulating gray matter by early anatomists.

interpeduncular nucleus [Levels 6, 7] The nucleus receives input from habenular nuclei and sends output to tegmental nuclei and midbrain raphe nuclei. Tegmental nuclei are concerned with visceral control and the raphe nuclei send serotoninergic projections to the forebrain, affecting mood and sleep status. Nuclear output decreases dopamine release, which leads to broad inhibition. The interpeduncular nucleus is named for its midline position between the right and left cerebral peduncles (the latter term is seldom used). Note: *inter-* is the Latin word for "between," and "peduncular" comes from the Latin word *pedunculus*, which means "stemlike."

interpositus nucleus [Level 9] This cerebellar nucleus sends axons into the rostral cerebellar peduncle. The axons decussate and terminate in the contralateral red nucleus in order to regulate the force and timing of activity of limb proximal musculature. Note: *inter-* is the Latin word for "between" and *posit* is the Latin word for "placed."

interthalamic adhesion [Levels 2–4] Refers to the midline site where the right thalamus contacts the left thalamus, obliterating the center of the third ventricle. It is not a site of significant right–left communication. Note: "thalamus" comes from the Greek word *thálamos,* which refers to part of the brain.

J K L

lateral (dentate) nucleus [Level 9] The lateral (dentate) nucleus of the cerebellum receives inhibitory input from cortical Purkinje cells located in the ipsilateral cerebellar hemisphere. Axons from the nucleus run through the rostral cerebellar peduncle and decussate in the midbrain. They impact the premotor cerebral cortex through the thalamus, via either a direct synapse or through a neuron in the red nucleus. Note: "dentate" is derived from a Latin word pertaining to "tooth," referring to the shape of the nucleus.

lateral cuneate nucleus [Level 11] Via fasciculus cuneatus, this nucleus receives cranial branches of proprioceptive primary afferent neurons from the thoracic limb. Axons from the nucleus run through the caudal cerebellar peduncle to the cerebellum. Note: "cuneate" is derived from the Latin word for "wedge."

lateral funiculus [Level 12] This is one of three major regions of spinal white matter. The lateral funiculus is bounded dorsally by the dorsolateral sulcus and ventrally by exiting ventral root fibers. The dorsal half of the lateral funiculus contains the principal voluntary movement tracts (rubrospinal and lateral corticospinal). Note: *funiculus* is the Latin word for "small rope."

lateral geniculate nucleus (body) [Level 5] This is a thalamic relay nucleus in the conscious visual pathway. The nucleus receives retinal input from the optic tract and sends axons through the internal capsule (optic radiation) to the primary visual cortex in the occipital lobe. The nucleus itself is capable of crude visual consciousness. Note: "geniculate" is derived from the Latin for "small knee," referring to the surface bulge produced by the nucleus.

lateral lemniscus [Level 7] This white matter tract is formed by trapezoid body axons ascending through the pons to the midbrain. The axons terminate in the caudal colliculus, or they continue in the brachium of the caudal colliculus. Axons comprising the lemniscus originate bilaterally from cochlear nuclei, although content from the contralateral ear is predominant. Note: "lemniscus" is derived from the Greek word for "fillet."

lateral reticular nucleus [Level 11] Located lateral to the olivary nucleus, the lateral reticular nucleus (also called the nucleus of the lateral funiculus) receives input from the rubrospinal tract and from the spinal cord. It sends output ipsilaterally to the cerebellum. Thus the nucleus appears to preprocess cerebellar input. Note: the term "reticular" is from the Latin word *reticulum*, which means "small net."

lateral rhinal sulcus [Level 6] Located laterally on each cerebral hemisphere, the sulcus separates the rhinencephalon (ventrally) from the neocortex (dorsally). The long sulcus is divided into rostral and caudal segments. Note: "rhinal" is derived from the Greek word for "nose"; "sulcus" comes from the Latin word for "furrow."

lateral ventricle [Levels 1–6] The cavity within each cerebral hemisphere. Derived from the embryonic neural cavity, each lateral ventricle is lined by ependyma and filled with cerebrospinal fluid produced locally by a choroid plexus within the ventricle. Each lateral ventricle communicates with the third ventricle via an interventricular foramen. Note: "ventricle" is from the Latin word for "small belly."

lingula lobule of vermis [Level 8] This is the most rostral of the 10 lobules comprising the cerebellar vermis. Note: *lingula* is the Latin word for "little tongue."

M

mamillary (mammillary) body [Level 4] The mamillary body (nuclei) is a significant component of the limbic system. The nuclei are involved in working memory (their damage results in "diencephalic amnesia"). The mamillary body receives input from the hippocampus and amygdala via the fornix. Axons from mamillary nuclei go to rostral thalamic nuclei and the midbrain tegmentum. Note: "mamillary" is derived from the Latin word for "small breast."

mamillotegmental tract [Level 5] Conveys output from the mamillary body to the midbrain tegmentum.

mamillothalamic tract [Levels 2–4] Conveys output from the mamillary body to rostral thalamic nuclei.

medial cuneate nucleus [Level 12] A relay nucleus in the kinesthesia and discriminative touch conscious pathway. The nucleus receives cranial branches of primary afferent neurons that innervate the thoracic limb. Axons from the nucleus ascend in the contralateral medial lemniscus to the thalamus (ventral caudal nucleus). Note: "cuneate" is derived from the Latin word for "wedge."

medial geniculate nucleus (body) [Level 5] This is a relay nucleus in the conscious auditory pathway, receiving input from the brachium of the caudal colliculus. Axons from the nucleus run through the internal capsule to the primary auditory cortex. By itself, the nucleus is capable of imprecise sound consciousness. Note: "geniculate" is derived from the Latin for "small knee," referring to the surface bulge produced by the nucleus.

medial lemniscus [Levels 5–11] Formed by axons from the contralateral gracilis nucleus and medial cuneate nucleus, the tract conveys conscious discriminative touch and kinesthesia to the lateral part of the ventral caudal nucleus of the thalamus. Note: "lemniscus" is derived from the Greek word for "fillet."

medial longitudinal fasciculus [Levels 7, 8] This tract connects nuclei of extrinsic eye muscles and conveys output from vestibular nuclei for reflex control of eye muscles. The fasciculus extends caudally into the cervical spinal cord for vestibular reflex control of neck muscles. Note: *fasciculus* is the Latin word for "small bundle."

mesencephalic aqueduct [Levels 5–7] A canal within the midbrain that connects between the third ventricle rostrally with the fourth ventricle caudally. It is not a ventricle since it lacks a choroid plexus. Note: "cephalic" is derived from the Greek word for "head."

mesencephalic nucleus of V [Level 6] This trigeminal nucleus is composed of cell bodies of primary afferent neurons that convey proprioceptive information from the jaw. The neurons send axons to the motor nucleus of the trigeminal nerve. Note: "trigeminal" is derived from the Latin word *tres* and the Greek word *treis*, both meaning "three," and the Latin word *geminus* for "twin."

middle cerebellar peduncle [Level 8] The peduncle consists entirely of afferent fibers from pontine nuclei. Information from the cerebral cortex is conveyed to the cerebellum via pontine nuclei. Note: "peduncle" comes from the Latin word *pedunculus*, which means "stemlike."

N

nodulus [Level 9] This is the most caudal of the 10 lobules comprising the cerebellar vermis. Together with bilateral flocculi, the nodulus forms the flocculonodular lobe, which is closely associated with vestibular function. Note: *nodulus* is the Latin word for "small knot."

nucleus ambiguus [Level 10] Contains somatic efferent neurons that send axons through the glossopharyngeal (IX) and vagus (X) cranial nerves to innervate the striated muscle of the pharynx, larynx, and esophagus. The nucleus also contains parasympathetic preganglionic neurons that inhibit heart rate and constrict bronchioles. Note: *ambiguus* is the Latin word for "doubtful" (the nucleus appears ambiguous because its cell density is sparse).

nucleus proprius [Level 12] Refers to the collection of neuron cell bodies that occupy the bulk of the dorsal horn of the spinal cord. The cell bodies belong to interneurons and ascending pathway projection neurons. Note: *proprius* is the Latin word for "belonging to."

nucleus of the spinal tract of V [Levels 9–12] This trigeminal nucleus runs the length of the medulla oblongata, overlapping with the substantia gelatinosa in the spinal cord. The nucleus is composed of cell bodies of interneurons and ascending pathway projection neurons activated by pain and temperature axons comprising the spinal tract of the trigeminal nerve. Note: "trigeminal" is derived from the Latin word *tres* and the Greek word *treis*, both meaning "three," and the Latin word *geminus* for "twin."

O

oculomotor nucleus [Level 6] The nucleus is composed of somatic efferent neuron cell bodies that innervate four of the seven extrinsic muscles of the carnivore eye. The neurons shift the gaze dorsally, medially, and ventrally, and they rotate the eyeball (ventral eye region toward the nose). Note: *oculus* is the Latin word for "eye."

olfactory stria [Level 1] An olfactory stria (tract) conveys axons from the olfactory bulb to another location within the rhinencephalon. Three tracts are recognized: the **lateral olfactory stria** is the conscious olfactory pathway to the piriform lobe; the **medial olfactory stria** conveys olfactory information to the septum; (not shown, an intermediate olfactory stria communicates with the contralateral olfactory bulb via the rostral commissure). Note: *stria* is the Latin word for "furrow"; "olfactory" comes from the Latin for "to smell."

olivary nucleus [Level 11] The nucleus is remarkable for its distinctive appearance in transverse section and as the source of the climbing fibers found on Purkinje cells of the cerebellar cortex. Since the nucleus receives motor directive input from both the cerebral cortex and red nucleus as well as proprioceptive input from the spinal cord, it serves as an integrative center for preprocessing input to the cerebellum. Note: *oliva* is the Latin word for "olive."

optic chiasm (chiasma) [Level 2] Axons of the optic nerve travel through the optic chiasm to reach the optic tract. In dogs, about 75% of optic nerve fibers decussate in the chiasm to reach the contralateral optic tract (cat: 63%; horse: 90%). Note: *khiasma* is the Greek word for "cross-shape."

optic nerve [Level 1] The collection of axons that originate from ganglion cells of the retina and go to the optic chiasm. The "nerve" is actually a CNS tract enclosed in meninges (both the retina and optic nerve are embryological outgrowths of the diencephalon). Note: "optic" comes originally from the Greek word *optikos*, which means "seen."

optic tract [Levels 3–5] The tract is composed of axons from retinal ganglion cells. The axons come from both eyes, more so from the contralateral eye. The axons travel through both optic nerves and the optic chiasm to reach the optic tract. The tract begins at the optic chiasm and conveys axons (contralateral visual field per eye) to the lateral geniculate nucleus (conscious vision) and, via the brachium of the rostral colliculus, to visual reflex sites (rostral colliculus and pretectum). Note: "optic" comes originally from the Greek word *optikos*, which means "seen."

P

parasympathetic nucleus of vagus [Level 11] Contains visceral efferent preganglionic neurons that send axons into the vagus nerve to innervate terminal ganglia in thoracic and abdominal viscera. Note: *vagus* is the Latin word for "wandering."

parasympathetic oculomotor nucleus [Level 4] Contains visceral efferent preganglionic neurons that, via postganglionic neurons in the ciliary ganglion, innervate intrinsic muscles of the iris (pupil constriction) and ciliary body (accommodation to near vision). Note: "Edinger-Westphal nucleus" is an older term for this nucleus.

parvocellular reticular nucleus [Level 10] The term "parvocellular" refers to small neurons. This reticular nucleus receives spinal tract input and contains interneurons that project to other reticular nuclei. Along with other reticular nuclei, the nucleus is involved with visceral regulation and has a role in the expiration phase of breathing. Note: *parvus* is a Latin word for "small."

periaqueductal gray matter (PAG) [Levels 6, 7] Refers to the gray matter surrounding the mesencephalic aqueduct (central gray substance). It is the origin of an intrinsic analgesia system that indirectly releases serotonin and noradrenaline into the dorsal horn of the spinal cord to block transmission of ascending pathways. Neurons in the PAG are responsive to endorphins and opiates.

pineal gland (body) [Level 4] The pineal endocrine gland contains pinealocytes that secrete melatonin in response to light/dark cycles (darkness stimulates and light inhibits melatonin production). Melatonin promotes sleep. Also the gland is involved in sexual development, seasonal breeding, and hibernation. Light affects the pineal gland via a pathway that includes: light-sensitive ganglion cells in the retina, optic tract axons to hypothalamic nuclei, sympathetic preganglionic neurons in the spinal cord, and postganglionic neurons in the cranial cervical ganglion. Note: "pineal" is derived from the Latin word for "pinecone."

piriform lobe [Levels 2–6] The piriform lobe is located within the rhinencephalon and associated with conscious olfaction. It receives olfactory input from the olfactory bulb via the lateral olfactory stria. The lobe consists of a rostral flat part and a caudal swollen part. The amygdala and the ventral tip of the hippocampus are deep to the caudal part. Note: "piriform" is derived from the Latin for "pear-shaped."

pons [Level 8 caption] Refers to the brain-stem component of the metencephalon (cerebellum being the other metencephalon component). The ventral region of the pons appears anatomically distinct and features transverse pontine fibers, whose surface appearance gives the region its name. Note: *pons* is the Latin word for "bridge."

pontine nuclei [Level 8] Located within the ventral pons, the dispersed pontine nuclei relay information from the cerebral cortex motor area to the cerebellum. The nuclei receive their input from collateral branches of axons traveling through the pons from the crus cerebri. Axons from pontine nuclei decussate and, as transverse pontine fibers, they proceed to form the middle cerebellar peduncle. Note: "pontine" is derived from the Latin word for "bridge" (*pons*).

pontine sensory nucleus of V [Level 8] This trigeminal nucleus consists of cell bodies of interneurons and ascending pathway projection neurons that are activated by tactile and proprioceptive input from the face. The nucleus gives rise to conscious pathways for facial discriminative touch and also jaw kinesthesia. Note: "trigeminal" is derived from the Latin word *tres* and the Greek word *treis*, both meaning "three," and the Latin word *geminus* for "twin."

pretectal area (pretectum) [Level 5] Situated rostral to the tectum of the midbrain, the pretectum is concerned with the pupillary light reflex. Input is from the optic tract (via the brachium of the rostral colliculus). Output from pretectal nuclei goes to the parasympathetic oculomotor nucleus. Right and left sides are connected via the caudal commissure. (The pretectum is also involved with REM sleep activity.) Note: "tectum" comes from the Latin word for "roof."

putamen [Levels 1, 2] The putamen and the caudate nucleus are basal nuclei that comprise the striate body. The putamen participates in voluntary movement circuits that are active during movement execution (following movement planning). The striate body suppresses movement by inhibiting the endopeduncular nucleus, which prevents thalamic excitation of the motor area of the cerebral cortex. The striate body facilitates movement by inhibiting the globus pallidus, which inhibits the endopeduncular nucleus. Note: *putamen* is the Latin word for "remaining after pruning."

pyramid [Level 11] Refers to white matter, located ventromedially in the medulla oblongata, which is more or less pyramid-shaped in transverse section. The pyramids contain corticospinal and corticobulbar fibers that collectively constitute the pyramidal tract (named for its location in the pyramid). Note: "pyramid" is derived from the Greek word *puramis*.

pyramidal decussation [Level 12] At the junction of the brain and spinal cord, most of the corticospinal fibers in the pyramidal tract cross to the contralateral side (decussate) and then descend in the dorsal half of the lateral funiculus as the lateral corticospinal tract. A minority of fibers (ventral corticospinal tract) continue to descend in the ventral funiculus; they cross before terminating in the spinal cord. Note: "decussation" is derived from the Latin word *decussare*, which means to divide crosswise, which itself comes from the Roman numeral for "ten," i.e. "X."

pyramidal tract [Levels 9, 10] This tract contains axons from cell bodies located in the cerebral cortex. The axons traverse: internal capsule, crus cerebri, pons, and, in the medulla oblongata, they run in the pyramid (which gives the tract its name). The axons terminate in cranial nerve nuclei (corticobulbar fibers) or in the spinal cord (corticospinal fibers). Via the tract, the motor area of cerebral cortex (upper motor neurons) has direct input to interneurons and efferent neurons (lower motor neurons). The pyramidal tract controls voluntary movement of mainly distal muscles of a limb. The tract also contains axons from somatosensory cortex. These axons regulate sensory pathway activity by influencing excitation of second-order projection neurons. Note: "pyramid" is derived from the Greek word *puramis*.

Q R

raphe magnus nucleus [Level 10] This reticular nucleus is one of several serotonergic nuclei situated along the seam separating right and left halves of the brain stem reticular formation. Axons from raphe magnus nucleus descend into the spinal cord and release serotonin in order to inhibit synaptic transmission in ascending pain pathways. Note: "raphe" is derived from the Greek word for "seam."

red nucleus [Level 6] From rostral to caudal, the red nucleus contains small, medium, and large neurons. Large neurons give rise to rubrospinal tract axons that constitute the principal tract for voluntary control of limb proximal musculature. Axons of medium-size neurons terminate in the cervical spinal cord to control head movement. The small neurons project to the thalamus and to the olivary nucleus. The red nucleus receives input from the cerebral motor cortex and from cerebellar nuclei (interpositus to large neurons and dentate to small neurons). Note: iron content in the neurons of this nucleus gives it a red appearance, particularly in primates.

reticular formation [Levels 8, 10] Anatomically, the term refers to the network of intermixed gray and white matter that forms a background for prominent nuclei and white matter in the brain stem. Functionally, various nuclei of the reticular formation have important roles, including alerting the cerebral cortex to maintain wakefulness; regulating visceral functions (micturition, heart rate, respiration, etc.); and producing movement via medullary and pontine reticulospinal tracts. The latter is spontaneously active and generates muscle tone in limb extensor muscles. Note: "reticular" is from the Latin word *reticulum*, which means "small net."

rostral cerebellar peduncle [Level 8] This peduncle is composed predominantly of efferent fibers from interpositus and dentate cerebellar nuclei. The axons go to the red nucleus and thalamus and are the means by which the cerebellum regulates ongoing movement. Note: "peduncle" comes from the Latin word *pedunculus*, which means "stemlike."

rostral colliculus [Level 6] This is a control center for eye movement and a visual reflex center (for head, ear, eye orientation toward sudden light). Bilateral retinal input arrives via the optic tract and brachium of the rostral colliculus, terminating superficially in the colliculus. The deepest neurons of the colliculus receive auditory and spinal input. Intermediate neurons give rise to tectobulbar and tectospinal tracts that produce orientation reflexes for both vision and sound (caudal colliculus). Note: *colliculus* is the Latin word for "small hill."

rostral commissure [Level 1] Nerve fibers that connect right and left sides of the rhinencephalon. The rostral limb of the commissure links bilateral olfactory bulbs via intermediate olfactory striae. The amygdala is linked bilaterally via the caudal limb of the commissure. Note: "commissure" is from the Latin word for "junction" (the term is used for fibers that cross the midline).

rostral ventromedial medulla [Level 10] This region of the medulla oblongata is involved in pain modulation, among other roles. Part of the brain's intrinsic analgesia circuit, it receives input from the periaqueductal gray and sends axons into the spinal cord to inhibit second-order projection neurons of pain pathways. The region is known to contain opioid-sensitive neurons. Note: "rostral" is derived from the Latin word for "beak"; "medulla" is from the Latin word for "marrow."

rubrospinal tract [Level 8] Originating from neurons of the red nucleus, the rubrospinal tract immediately decussates and then descends through the brain stem and through the dorsal half of the lateral funiculus of the spinal cord. Axons from medium-size neurons terminate in the cervical spinal cord and produce head movement. Axons from large neurons constitute the principal tract for quadruped gait and voluntary movement involving limb proximal musculature. Note: "rubro-" is derived from the Latin word for "red."

rubrospinal tract decussation [Level 6] The rubrospinal tract immediately decussates before descending through the brain stem and spinal cord. Note: "decussation" is derived from the Latin word *decussare*, which means to divide crosswise, which itself comes from the Roman numeral for "ten," i.e. "X."

S

septum [Level 1] The septum (septal area; septal nuclei) forms the medial wall of the rostral end of the lateral ventricle (ventral to the thin septum pellucidum). A major component of the limbic system, the septum is a known reward center. It receives input from the medial olfactory stria and has reciprocal connections with the hippocampus, amygdala, hypothalamus, habenula, and the cingulate gyrus. Note: "septum" is derived from the Latin word for "enclose."

septum pellucidum [Level 1] This thin layer is part of the medial wall of the lateral ventricle. It is more or less evident between the septum and corpus callosum. Note: "pellucidum" is derived from the Latin word for "shine through."

solitary tract [Level 11] This tract is composed of axons from primary general visceral afferent neurons innervating the pharynx, middle ear, and larynx (glossopharyngeal and vagus nerves). Rostrally, the tract also contains taste fibers, i.e. special visceral afferent fibers from facial, glossopharyngeal, and vagus nerves. Axons of the tract terminate in the adjacent nucleus of the solitary tract. Note: the tract is named for its solitary profile, surrounded by gray matter in transverse section.

spinal root of nerve XI [Level 11] The root is composed of somatic efferent axons from the motor nucleus of the accessory nerve. The spinal root is formed by nerve fibers that emerge periodically from the midlateral surface of the cervical spinal cord. After joining the bulbar root of the accessory nerve (temporarily), the spinal root fibers continue in the accessory nerve to innervate neck muscles (trapezius, omotransversarius, cleidocephalicus components, the mastoid part of sternocephalicus).

spinal tract of V [Levels 9–12] The spinal tract of the trigeminal nerve is composed of facial pain and temperature axons. The axons are from the primary general somatic afferent component of the trigeminal nerve. Note: "trigeminal" is derived from the Latin word *tres* and the Greek word *treis*, both meaning "three," and the Latin word *geminus* for "twin."

spinothalamic tract [Levels 4–8, 10, 11] The spinothalamic tract is composed of second-order axons of a three-neuron pathway conveying conscious pain and temperature sensation. The axons arise from second-order projection neurons located in the dorsal horn of the spinal cord (marginal nucleus and nucleus proprius). The axons decussate in the spinal cord and ascend, in the lateral funiculus and through the brain stem, to terminate in the lateral portion of the ventral caudal nucleus of the thalamus.

stria habenularis [Level 2] Conveys axons from the septal region, rostral thalamus, and rostral hypothalamus to habenular nuclei. Note: *stria* is the Latin word for "furrow"; *habenula* is the Latin word for "small rein"; -*aris* is the Latin word for "of the."

substantia nigra [Levels 5, 6] This gray matter has compact and reticulated divisions, each with a different role. In general, the substantia nigra interacts with the basal nuclei circuits concerned with movement. In particular, the dorsal compact region sends dopamine projections to the caudate nucleus and putamen to neuromodulate basal nuclei circuits. The net effect is movement facilitation. Parkinson's disease results from the loss of dopamine neurons in the substantia nigra. Ventrally, the reticulated substantia nigra contains spontaneously active inhibitory neurons controlled by basal nuclei. The axons project to the tectum to control eye movement (saccades). Note: *nigra* is the Latin word for "black." In primates, the compact neurons are pigmented.

subthalamus [Level 3] Located ventral to the thalamus and lateral to the hypothalamus, the subthalamus consists of several nuclei and fiber zones. Functionally, the subthalamus participates in basal nuclei circuits concerned with movement. In response to cortical input, the subthalamus suppresses unwanted movements by exciting the inhibitory neurons of endopeduncular nucleus. Premature movements result from damage to the subthalamus and, because it generates bursts of neuronal activity, the subthalamus may play a pacemaker role in rhythmic movements. (In primates, subthalamic lesions produce hemiballismus.) Note: "thalamus" is derived from the Greek word for "inner chamber."

sulcus [Level 1] Refers to a surface groove located on the cerebrum, cerebellum, or spinal cord. In the cerebral cortex, sulci demarcate gyri; in the cerebellum, they demarcate folia. Note: "sulcus" comes from the Latin word for "furrow."

T

thalamus [Levels 2–4] The thalamus is the source of all input to the cerebral neocortex. Close to three dozen nuclei are included within the thalamus. The following components are labeled in the brain atlas:

rostral thalamic nucleus [L 2] is concerned with affective behavior; it has connections with the hippocampus and cingulate gyrus.

thalamic external medullary vellum [L 3] is white matter separating groups of thalamic nuclei (an internal medullary vellum is also present).

thalamic pulvinar nucleus [L 4] is the most caudal thalamic nucleus (except for geniculate nuclei). Damage to it is associated with visual attention deficits.

thalamic reticulate nucleus [L 4] is the thalamic nucleus that does not project to the cerebral cortex. Located lateral to the external medullary vellum, it contains inhibitory neurons that receive input from the cerebral cortex and send output to the thalamus.

ventral caudal thalamic nucleus [L 3, 4] relays information from conscious pathways (e.g. spinothalamic tract and medial lemniscus) to the primary somatosensory area of the cerebral cortex. The lateral part of the nucleus deals with spinal input; the medial part relays trigeminal information. Taste is most medial in the nucleus.

third ventricle [Levels 2–4] A narrow chamber within the diencephalons, derived from the embryonic neural cavity. It is lined by ependyma, filled with cerebrospinal fluid, and covered by a thin roof to which bilateral choroid plexuses are attached. Rostrally, the ventricle communicates bilaterally with lateral ventricles (via intervertebral foramina); caudally, the ventricle communicates with the mesencephalic aqueduct. The center of the ventricle is obliterated by the interthalamic adhesion. Note: "ventricle" is derived from the Latin for "small belly."

transverse pontine fibers [Levels 7, 8] Situated superficially on the ventral surface of the pons, the fibers arise from contralateral pontine nuclei and proceed to form the middle cerebellar peduncle. They convey information to the cerebellum from motor areas of the cerebral cortex. Note: "pontine" is derived from the Latin word *pons*, which means "bridge."

trapezoid body [Level 9] Associated with hearing, it is composed of bilateral axons from ventral cochlear nuclei along with ventral nuclei of the trapezoid body (diffuse gray matter among the fibers). The axons ascend as lateral lemniscus fibers; some of the axons synapse in dorsal or ventral nuclei of the trapezoid body. Note: "trapezoid" is derived from the Greek word for "table."

trigeminal motor nucleus [Level 8] The nucleus is composed of somatic efferent neuron cell bodies that innervate jaw muscles for mastication, plus mylohyoideus and tensor tympani muscles. Note: "trigeminal" is derived from the Latin word *tres* and the Greek word *treis*, both meaning "three," and the Latin word *geminus* for "twin."

trigeminal nerve [Level 8] Cranial nerve V. It innervates muscles of mastication (somatic efferent fibers) and conveys sensation from the face (general somatic afferent). Within the cranial cavity, distal to the trigeminal ganglion, the nerve divides into three branches: ophthalmic, maxillary, and mandibular. Note: "trigeminal" is derived from the Latin word *tres* and the Greek word *treis*, both meaning "three," and the Latin word *geminus* for "twin."

tuber cinereum [Level 3] Refers to a swollen area on the ventral surface of the hypothalamus that gives rise to the infundibulum and hypophysis. Neurons in this region produce releasing factors that, via the hypothalamic hypophyseal portal system, regulate hormone secretion by the adenohypophysis. Note: *tuber* is the Latin word for "swelling," and "cinereum," derived from the Latin word for "ashen color," pertains to gray matter.

U V

vagus nerve [Levels 10, 11] Cranial nerve X. It innervates muscles of the larynx, pharynx, and esophagus (somatic efferent fibers from nucleus ambiguus) and thoracic and abdominal viscera (visceral efferent fibers from the parasympathetic nucleus of the vagus). The vagus nerve conveys general visceral afferent fibers and special visceral afferents (pharyngeal taste) to the solitary tract. The vagus also innervates the external auditory canal (general somatic afferent fibers). Note: *vagus* is the Latin word for "wandering."

ventral funiculus [Level 12] One of three major bilateral regions of spinal white matter, "ventral funiculus" refers to white matter located medial and ventral to the ventral gray horn. The funiculus contains the fibers responsible for driving extensor muscle tone and standing (pontine reticulospinal and lateral vestibulospinal tracts). Note: *funiculus* is the Latin word for "small rope."

ventral horn of spinal cord [Level 12] Refers to the profile of the ventral column of spinal gray matter when seen in transection. The ventral gray matter contains motor nuclei (alpha and gamma neurons and interneurons). Note: *venter* is the Latin word for "belly."

ventral pons [Levels 7, 8] Refers to the anatomically distinct ventral region of the pons division of the brain stem. Corticospinal/corticobulbar fibers conveying motor commands run longitudinally through the ventral pons and send collateral branches to pontine nuclei. The nuclei give rise to transverse pontine fibers that decussate and become the middle cerebellar peduncle. Note: *pons* is the Latin word for "bridge."

ventral reticular nucleus [Level 11] This nucleus is related to the parvocellular reticular nucleus. The rostral end of the nucleus plays a role controlling inspiratory breathing (ventral respiratory group). Note: "reticular" is from the Latin word *reticulum*, which means "small net."

ventral tegmental area [Level 6] Located in the midbrain, lateral to the interpeduncular nucleus, this area contains neurons with dopamine and serotonin neuromodulators, and it is a target of agents such as cocaine. The area is part of a pleasure/reward circuit, connecting with the accumbens nucleus. Note: "tegmentum" is derived from the Latin word for "covering" and is applied to midregions of the midbrain and pons.

vestibular nuclei [Levels 9, 10] These nuclei generate vestibular reflexes. They receive vestibular input both directly from the vestibular nerve and indirectly from the flocculonodular lobe of the cerebellum. They send output to extrinsic eye muscle nuclei and to neck muscle nuclei (via the medial longitudinal fasciculus) and to limb muscle nuclei (via the lateral vestibulospinal tract). There are four nuclei: **rostral** [L 9] and **caudal**, **lateral**, and **medial** [L 10]. The lateral vestibular nucleus gives rise to the lateral vestibulospinal tract. Note: "vestibular" comes from the Latin word for "entrance court"; parts of the vestibular apparatus are housed in a bone chamber called the "vestibule."

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