WHAT DO I DO NOW?

PERIPHERAL NERVE AND MUSCLE DISEASE

JEFFREY A. COHEN
JUSTIN MOWCHUN
JON GRUDEM



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Peripheral Nerve and Muscle Disease

"Drs. Cohen, Mowchun, and Grudem have written a concise and informative case-based text covering the most important issues in neuromuscular practice. All readers, no matter their level of expertise, will come away with new insights and information. The material is presented in an organized and engaging manner that can be read with ease in its entirety or consulted as stand alone topics in the context of particular clinical issues. For any medical practitioner with a neuromuscular patient, this textbook provides excellent general guidance for the question, 'What do I do now?'"

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—John D. England, MD, The Grace Benson Professor and Head, Department of Neurology, LSUHSC School of Medicine, New Orleans, LA

What Do I Do Now?

SERIES CO-EDITORS-IN-CHIEF

Lawrence C. Newman, MD
Director of the Headache Institute
Department of Neurology
St. Luke's-Roosevelt Hospital Center
New York, NY

Morris Levin, MD
Codirector of the Dartmouth Headache Center
Director of the Dartmouth Neurology Residency Training Program
Section of Neurology
Dartmouth Hitchcock Medical Center
Lebanon, NH

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Peripheral Nerve and Muscle Disease

Jeffrey A. Cohen, MD
Section of Neurology
Dartmouth Hitchcock Medical Center
Lebanon, NH

Justin Mowchun, MD
Section of Neurology
Dartmouth Hitchcock Medical Center
Lebanon, NH

Jon Grudem, MD
Section of Neurology
Dartmouth Hitchcock Medical Center
Lebanon, NH

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Dedication

I would like to thank all my students, residents, and fellows who continue to educate me. In addition, I am always appreciative of the support of Renee and Jason.

J. A. C.

To Rand, who inspired a career change, as well as Jackie, Alyson, and Zachary, who have been so supportive throughout my medical education.

J. M. G.

To the attending neurologists at Dartmouth, who teach with enthusiasm and humility, and to my lovely wife Carrie for all her support.

J. M.

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Preface

Many of us, on a daily if not regular basis, encounter clinical problems while consulting on neuromuscular cases. We may not always know the "correct" answer, but we may often ask colleagues for their advice and opinion. But what do you do when you are the only person on call?

The 27 cases that comprise *Peripheral Nerve and Muscle Disease* come from our own experience. We have incorporated mistakes and miscues that occurred in our own diagnosis and treatment in the hope that you might better learn from our experience. The book is divided into three sections. The first section, "Neuropathy," describes, for example, cases that are the result of poisoning, either therapeutic or malicious; surgical procedures, like bariatric surgery, that can result in peripheral neuropathy; and peripheral neuropathy that can be the result of genetic disorders, such as the hereditary neuropathies. The second section, "Myopathy," presents issues that can be a bane to the clinician: how to approach the patient with cramps, the dilemma of fatigue in a healthy young man, and how to categorize and understand the limb-girdle muscular dystrophies. The final section, "Neuromuscular Junction and Autonomic Neuropathy," discusses the approach to diagnosis and management of the difficult myasthenic patient and how to approach the patient with autonomic neuropathy and the pitfalls in their diagnosis and treatment.

We hope you will find this book practical and readable. It is meant to be read by any level of neurologist, the adventuresome medical student, or primary care physician in any order you like. Each case is short but also "real-life." What would you do now?

Finally, having taken my neuromuscular boards (J.C.) recently, I regretted not having this book for my studying. Please enjoy reading the cases, and we hope you will share our excitement of learning.

J. C., Hanover, NH
J. G., Lebanon, NH
J. M., Enfield, NH

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Jon, Justin, and I are very grateful to Mo Levin and Larry Newman for asking us to do this volume in the What Do I Do Now? series. Mo has been a trusted colleague and friend since my start at Dartmouth. He is a great sounding board for both difficult clinical and administrative issues which I have faced. He is also a terrific writer and his editing is always perfect.

I want to thank Justin Mowchun and Jon Grudem for doing such a prompt and excellent job on their chapters. They are very skilled neurologists, competent way beyond their years.

Craig Panner and David D'Addona were very supportive and gently nudged us toward our goal. Their assistance was always appreciated.

My students, residents, and fellows have always taught me the most: a sense of humility and the excitement of sharing an important clinical "pearl."

Finally, my family had to put up with me during this project: Renee is a superb teacher in her own right, and Jason is an extreme kayaker and soaring enthusiast who teaches me every day about risk and life.

Jeffrey Allen Cohen, MD
Hanover, NH

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SECTION I

Neuropathy

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1 Small Fiber Neuropathy

A 38-year-old female complains of a 2.5-year history of pain and paresthesias. She initially experienced these symptoms in her entire right leg. Over the first year, the pain subsided but left her with waxing and waning paresthesias. Within several months of onset, she noticed tingling sensations in her left leg from the popliteal fossa distally. The paresthesias have been accompanied by burning dysesthetic pain. About 14 months prior to this encounter, she began to experience paresthesias in the dorsal aspect of her hands, which have extended up to the mid-forearm and later to the shoulders and upper cervical region. In recent months, these symptoms have extended to the mandibular and maxillary divisions of the trigeminal nerve bilaterally. Her past medical history was significant for irritable bowel syndrome, migraine with aura, as well as long-standing problems with esophageal reflux and spasms.

On her initial examination, her vital signs were unremarkable. Her reflexes were symmetrically brisk but without pathological spread, and her toes were downgoing to plantar stimulation. On sensory exam, she had decreased sensation to temperature and vibratory stimulation in the right distal leg in a length-dependent pattern. Pinprick exhibited a length-dependent gradient of sensory loss in the lower and right upper extremities. She also had diminished pinprick and temperature sensations in the maxillary and mandibular divisions bilaterally.

Other basic tests including a complete blood count, electrolytes, and sedimentation rate were all normal. Magnetic resonance imaging of the brain and cervical spine were normal. Finally, nerve conduction velocity (NCV) testing was normal. Her primary care physician asks for help in sorting out whether or not her complex symptoms are psychogenic.

What do you do now?

This patient presents with a compelling story for peripheral neuropathy, yet NCV testing was normal, as were the more objective motor and reflex portions of the exam. The bedside sensory exam can be difficult to quantify and interpret. Of necessity, it is subjective from the patient's point of view, but to a large extent, it is subjective from the examiner's point of view as well. When patients present with vague symptoms, lack objective findings on exam, and have a negative initial work-up, it can be easy to ascribe these symptoms to a "hypervigilant" patient or suggest a somatization syndrome.

With any test, an understanding of its operating characteristics, including sensitivity and specificity for a given indication, is critical to proper interpretation. In most peripheral neuropathies NCV is an excellent test to help narrow the differential. The test does have significant limitations however. For example, since the only fibers effectively tested with NCV are the large-diameter heavily myelinated fibers, it has a very low sensitivity for detecting conditions that preferentially affect only small fibers. Additional testing is therefore necessary.

Features consistent with small fiber neuropathy (SFN) typically include dysesthesias, loss of pain and temperature sensation, and sometimes autonomic dysfunction. While small fiber neuropathy is typified by a length dependent pattern, small fiber neuronopathies, which affect the dorsal root ganglion, are not. For the purpose of this discussion, I will use the two terms interchangeably. Features that are notably lacking in SFN include proprioceptive loss in the toes, vibration loss above the ankles, generalized areflexia, distal wasting, and weakness. Patients with SFN often experience "positive" symptoms including pain and dysesthesias, though this is not universal. The pain is described as burning, prickling, or shooting and is more prominent at night. Even bed sheets can produce painful sensations. Calf cramps and restless leg syndrome without a positive family history are commonly seen. Negative symptoms include numbness, tightness, and cold sensations. Signs and symptoms are usually length-dependent but can be patchy and asymmetrical as in this case, suggesting a ganglionopathy. In variants of SFN where the clinical manifestations are multifocal or diffuse, patients may experience a plateau and slow recovery, though symptom fluctuations may persist. Autonomic features can present with hypo- or hyperhidrosis, diarrhea or constipation, urinary incontinence or retention, gastroparesis, sicca syndrome, blurry vision, facial flushing, orthostatic intolerance, or sexual

dysfunction. Spontaneous exacerbations and remissions can be seen, and many patients complain of severe incapacitating fatigue.

The diagnosis requires a high index of suspicion, a compatible history and examination, and confirmation with specialized testing. Unfortunately, there is no gold standard for the diagnosis of SFN. Several approaches have been suggested, and many clinicians use complementary tests. Many tests, such as quantitative sensory testing and current perception threshold testing, require active patient participation and may not localize well. That is, abnormalities can suggest damage anywhere from the sensory end organs to the sensory cortex. In our clinic, we typically rely on the more objective skin punch biopsy with specific staining and quantitation of intraepidermal nerve fiber density. Once restricted to only a few major centers, this is now readily available as a "send-out lab". It is important to consistently use a reputable laboratory as preparation and quantification standards vary. One sample is typically taken from 10 cm above the lateral malleolus and another more proximal site. Of necessity, the laboratory will dictate the specific biopsy sites since the results will be compared to standardized data. Two or three biopsy sites also allow for demonstration of the length-dependent nature of many of these neuropathies. Newer techniques with thinner sections may allow better quantification of dermal autonomic adnexa, especially sweat glands. Quantitation of epidermal nerve fibers has a positive predictive value of 75% and a negative predictive value of 90% with a diagnostic efficiency of 88% for patients with sensory neuropathies. Sural nerve biopsies are rarely used in the diagnosis of SFN unless amyloid or an inflammatory etiology is suspected. In addition to the biopsy, one may use sympathetic skin response. This test assesses sudomotor function as a reflex change in sweat-related potential in response to stimuli such as a small electric shock or a deep breath. Unfortunately, both sensitivity and specificity for this test are fairly low and the test can be abnormal with pathology from the cerebral cortex to the sweat glands. In the quantitative sudomotor axon reflex test (QSART), axons in the skin are activated locally via acetylcholine iontophoresis. This produces a quantifiable sweat response at the skin surface. The sensitivity of QSART for SFN ranges 59%–80%. It can also be used serially to monitor for disease progression. The parasympathetic, cardiovagal axis is assessed by measuring heart rate variation during deep breathing and Valsalva maneuvers.

While awaiting confirmation of the diagnosis, a search for an etiology should begin. Diabetes is the most common cause in cases where a clear diagnosis is made. More recently, impaired glucose tolerance has been strongly associated with neuropathies, especially small fiber variants; and a 2-hour oral glucose tolerance test should be considered even for patients without other signs of diabetes. A history of heavy alcohol use may implicate alcoholic neuropathy, which tends to preferentially affect smaller fibers early in the course, although this is commonly in the context of malnutrition. Inflammatory autoimmune etiologies are entertained if presentation follows an illness or is rapidly progressing. In these cases a lumbar puncture should be done to look for albuminocytological dissociation. Most cases of SFN will not require a lumbar puncture.

Findings might include a positive antinuclear antibodies test, possibly leading to a diagnosis of systemic lupus erythematosus or Sjögren syndrome. Vasculitis, mitochondrial antibodies, or autoimmune thyroid disease can cause SFN as well. History about environmental toxins should be sought, though most of these neuropathies affect mainly large fibers. One exception to this is metronidazole. Human immunodeficiency virus can cause both large and small fiber neuropathy and should be tested for in most of these patients. Hyperlipidemia, especially with markedly elevated triglycerides, is a potentially treatable cause of SFN, so a fasting lipid panel should be obtained. Some have also implicated celiac disease as an etiology for SFN. While this patient had some gastrointestinal disturbance, antigliadin antibodies and tissue transglutaminase were negative. A careful family history can document the familial "burning feet neuropathy." It is important to remember that familial amyloidosis needs to be excluded before accepting this diagnosis. The same skin punch biopsy sample used to assess intraepidermal nerve fiber density is also stained with Congo red, producing an apple green birefringence in patients with amyloid angiopathy.

Serum and urine protein electrophoresis with quantitative immunoglobulins should be done early in these patients, and if monoclonal gammopathy is present, this increases the pretest probability of amyloid, considerably. In these cases, a biopsy of the sural nerve, abdominal fat pad, or rectum is required, even if the skin punch was negative for amyloid. If dry eyes and dry mouth are present, with or without autonomic symptoms, one should strongly consider Sjögren syndrome.

Patients with SFN require treatment of the underlying disorder and management of symptoms, most frequently this means neuropathic pain. Medications will reduce pain by only modest amounts. Useful drug classes include tricyclics, anticonvulsants including gabapentin, and transdermal lidocaine. Tricyclic antidepressant doses should be increased every 3 days or so until either unacceptable symptoms arise or clinical goals are achieved. Opiates are reserved for refractory cases. These medications can be used as monotherapy or in combination. If the area being treated is small, topical preparations can be compounded. We work closely with a local pharmacy to customize topical compounds that may include various amounts of gabapentin, ketamine, lidocaine, and clonazepam. Transdermal delivery routes

TABLE 1-1 Investigations to Consider in the Evaluation of Small Fiber Neuropathy (SFN)

	Test
Patients with suspected SFN:	EMG, NCV, skin punch biopsy, and autonomic testing B_{12} (MMA and homocysteine if less than 300-400, especially if autonomic symptoms are present) Folate TSH SPEP and UPEP OGTT Fasting lipids CBC ANA ESR/CRP B_6
If the above are negative:	HIV Anti-gliadin antibodies
Sjögren's suspected:	Anti-SS A and B antibodies Lip biopsy Schirmer test
If the above are negative:	Rectal or fat pad biopsy for amyloid

EMG, electromyography; NCV, nerve conduction velocity; MMA, methylmalonic acid; TSH, thyroid-stimulating hormone; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis; OGTT, oral glucose tolerance test; CBC, complete blood count; ANA, antinuclear antibodies; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; HIV, human immunodeficiency virus; SS, Sjögren syndrome.

can occasionally be more effective and allow lower total doses. Finally, it is critical that pain medications be prescribed "scheduled" and not "as needed." This provides a more constant degree of pain control throughout the day and limits the possibility of escalating doses and addiction (Table 1–1).

KEY POINTS TO REMEMBER

- **Diabetes and impaired glucose tolerance are associated with peripheral neuropathies including SFN. Levels of hemoglobin A_{1C} and fasting glucose may no longer be adequate for evaluation in these patients. Careful consideration should be given to a 2-hour oral glucose tolerance test.**
- **Routine NCV studies evaluate only the largest, fastest myelinated fibers and are expected to be unremarkable in SFN.**
- **Autonomic testing involves multiple complementary tests and helps to document the efferent manifestations of SFN.**
- **Pain medications should be prescribed scheduled, not "as needed." This reduces total medication use, enhances pain relief, and limits addictive potential.**
- **Elevated triglycerides can be a treatable cause of SFN and therefore should not be missed.**

Further Reading

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2 Multifocal Motor Neuropathy

A 35-year-old right-handed male with no significant past medical history presents with a 3-month history of worsening left-hand weakness. He complains of difficulty with grip. The patient is a systems analyst and has had some problems typing with his left hand. He notes mild, intermittent tingling on the lateral aspect of the left hand but denies pain. He denies problems with cognition, speech, swallowing, and vision changes. On further questioning he does mention slight weakness of the right foot for the last week. He denies back pain or recent trauma. Family history is significant for rheumatoid arthritis in his mother. He does not smoke or drink and denies toxin exposure. Neurological exam is significant for 4/5 strength of left thumb abduction, pincer grip of left thumb, and left grip strength (although only the thumb and first two finger flexors are weak). Right ankle dorsiflexion is 4+/5, but otherwise strength is normal in the lower extremities. Tone is normal. There are minimal fasciculations and mild wasting of the left abductor pollicis brevis. Reflexes, sensation, coordination, and gait are normal.

What do you do now?

This patient's neurological exam of the upper extremity is consistent with median nerve injury. The common initial thought in a young man is that he has developed carpal tunnel syndrome (CTS). However, CTS is usually associated with pain, as well as nocturnal paresthesias and sensory loss. It also would not cause weakness of the long thumb flexor and deep medial finger flexors, as median nerve innervation to these muscles is proximal to the carpal tunnel. Another important observation is fasciculations in his left hand, and when associated with weakness this raises a red flag for early motor neuron disease (MND). He also has mild right ankle dorsiflexion weakness, which is concerning for additional muscle involvement characteristic of MND. However, there are several features on his examination that are atypical for this diagnosis: minimal atrophy in the context of significant muscle weakness, median nerve involvement but sparing of ulnar nerve muscles, lack of bulbar findings, lack of upper motor neuron signs, and younger age. The patient may have multifocal motor neuropathy (MMN), which typically presents with these features; also, it is more common in men and in patients under the age of 50. Usually, MMN leads to progressive individual motor nerve involvement (most common are ulnar, median, radial, and peroneal), without objective sensory loss, which is followed by further individual nerve demyelination months to years later. Of note, radial lesions often involve the terminal motor branches of the posterior interosseous nerve that leads to mainly third- and fourth-finger extensor weakness. Patients with MMN may have cramps and fasciculations.

As the patient has a family history of rheumatological disease, mononeuritis multiplex secondary to an undiagnosed rheumatological condition or primary vasculitic neuropathy may be considered. However vasculitis typically leads to a painful neuropathy due to microinfarction of the nerve. There is no history of systemic symptoms to suggest toxin-induced or paraneoplastic neuropathy. One should keep in mind that paraneoplastic neuropathy can present asymmetrically, rarely with predominantly motor complaints (typically associated with lymphoma).

The most important test for this patient is electromyography/nerve conduction study (EMG/NCS) to confirm a neuropathy and rule out diffuse anterior horn pathology. An NCS must be obtained to evaluate for conduction block of the median nerve proximal to the wrist. This location is not typically prone to compression (in contrast to the carpal tunnel) and very

suggestive of MMN. Conduction block in this case would be defined as a compound motor action potential (CMAP) amplitude drop by 50% or higher at elbow stimulation compared to wrist stimulation. Most experts feel that a CMAP amplitude drop of 20%–49% is equivocal. Keep in mind that MMN does not always show clear conduction block. There are cases where conduction block is not seen early or where the patient presents later in the course, when extensive axonal damage has occurred. The sensory nerve action potentials are not affected in MND (exception is Kennedy's disease) and are normal to mildly abnormal in MMN.

With respect to laboratory studies, an anti-GM_1 antibody must be sent. However, a negative result does not rule out MMN as the sensitivity is only 30%–70%. It is also important to remember that the anti-GM_1 antibody may be highly positive in 15% of MND patients and 5% of immune neuropathies other than MMN (see Table 2–1).

A common question is whether our patient should have a lumbar puncture. A lumbar puncture is not required to make the diagnosis of MMN if the clinical picture fits, and NCS indicate conduction block at a location not prone to compressive neuropathy. However, there are atypical presentations of MMN. Some patients may have more proximal weakness and/or more symmetrical weakness, as typically seen in chronic inflammatory demyelinating polyneuropathy (CIDP). As in MMN, occasionally CIDP can lack sensory findings on examination, and it is often unclear how to interpret mild sensory abnormalities on NCS. Also, one does not want to miss the diagnosis of vasculitic neuropathy or neoplastic infiltration of spinal roots. Therefore, a lumbar puncture can be very helpful in atypical cases. In MMN the cell count and protein are often normal, or if the protein is elevated, it is not usually higher than 70 (while in CIDP the protein level is often higher than 100). Vasculitis, sarcoidosis, neoplastic infiltration, and

TABLE 2-1 Utility and Limits of GM_1 Antibody Testing for Diagnosis of Multifocal Motor Neuropathy (MMN)

MMN–antibodies present in 30%–70% of cases
MND–antibodies present in <15% of cases
CIDP and other immune neuropathies–antibodies rarely present (<5%)

MND, motor neuron disease; CIDP, chronic inflammatory demyelinating polyneuropathy.

paraneoplastic neuropathy are often associated with high protein and/or high cell count. In MND cerebrospinal fluid studies are usually normal (except for mild protein elevation in some cases). A lumbar puncture is not needed for this patient if the lab work and EMG/NCS support the diagnosis of MMN, even if the GM_1 antibody is negative.

With respect to imaging, magnetic resonance imaging (MRI) of the lumbar spine/plexus could have initially been considered in this patient because of new mild weakness of ankle dorsiflexion. An MRI would help to rule out a lumbar radiculopathy/plexopathy as a result of a structural lesion (e.g., herniated disk, malignancy). Of note, MRI may show increased signal in the proximal plexus of a patient with MMN if he or she has clinical involvement of that region. If the patient's MRI does not show a significant structural lesion and the lower extremity EMG/NCS is unremarkable, the leg weakness is likely the result of peroneal nerve injury secondary to MMN (but too early to be detected on EMG/NCS). Sural nerve biopsy is usually indicated only to obtain supportive evidence of an inflammatory etiology (e.g., vasculitis, sarcoidosis) or amyloidosis.

First-line treatment of MMN is intravenous immunoglobulin (IVIG) 0.4 mg/kg over 5 days, and initial improvement can be dramatic. Many patients achieve complete recovery within 1 week of treatment. Almost 80% of patients respond to IVIG, which has been confirmed in several small randomized placebo-controlled trials. The pathogenesis of MMN is not clear but is believed to be immune-mediated, and IVIG modulates this process. Periodic infusions every 4–8 weeks are typically required to maintain benefits. In contrast to CIDP, steroids and plasmapheresis are ineffective and steroids may actually worsen MMN. If a patient becomes refractory or nonresponsive to IVIG, there are limited data on alternative treatments; but there are patients who have improved with azathioprine, high-dose cyclophosphamide, or rituximab. With respect to mycophenolate mofetil, the data are more conclusive as a recent randomized controlled showed that it did not alter the disease course or allow significant reduction in IVIG doses. For prognosis it is important to decipher MMN and MND early because the outcome is typically good for MMN but very poor for MND. Most patients with MMN can ambulate late in their course; however, loss of upper limb dexterity and strength may limit many activities.

KEY POINTS TO REMEMBER

- MMN typically leads to progressive individual motor nerve involvement (most common are ulnar, median, radial, and peroneal), without objective sensory loss.
- A negative GM_1 antibody does not rule out MMN as the sensitivity is only 30%–70%.
- A lumbar puncture is not required to make the diagnosis of MMN if the clinical picture fits, and NCS indicate conduction block at a location not typically prone to compressive neuropathy.

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3 Diagnosis of Amyotrophic Lateral Sclerosis

A 54-year-old surgeon stops you in the hall to ask you about his weak right hand. He tells you that his hand often tires during a long procedure and his usually excellent dexterity seems impaired. He spoke to a surgical colleague, who assured him it was probably an overuse syndrome or carpal tunnel syndrome (CTS). He would like your opinion. You examine him over your lunch break.

On examination, the cranial nerves are intact. He has atrophy and 4/5 weakness of the right abductor pollicus brevis (APB) and first dorsal interosseous (FDI) muscles. Reflexes in the upper and lower extremities are very brisk. Toes are neutral. Sensory examination is normal. There is no Tinel's or Plalen's sign. Upon questioning, he has cramps and spasms of the hand. There is a history of prior neck trauma related to an automobile accident at age 25. There are no bowel and bladder symptoms.

What do you do now?

Considering the pattern of the patient's weakness, CTS would be unlikely, the FDI being weak (Table 3–1). The FDI is usually innervated by the ulnar nerve (although there may be rare anatomical variants). The lack of median nerve sensory symptoms and signs—numbness, tingling, and sensory abnormalities in the first three digits and half of digit four—makes CTS unlikely as well. Finally, patients with CTS usually complain of nocturnal paresthesias. Additional history can include proximal arm or shoulder pain. A positive Tinel's or Phalen's sign usually helps confirm the diagnosis. Nerve conduction studies (NCS) are usually very sensitive for CTS. In fact, abnormalities of median nerve conduction may be present in individuals who have no complaints of CTS. It should be noted that CTS is associated with occupation (e.g., weavers, meat cutters), hypothyroidism, acromegaly, Colles' fracture of the wrist, pregnancy, amyloidosis, and diabetes.

WHAT ARE OTHER CONSIDERATIONS IN OUR PATIENT?

With the history of prior neck trauma, consideration should be given to a cervical spine or spinal cord pathology. With the prior neck trauma, the patient may have developed a cervical myeloradiculopathy due to degenerative arthritic changes of the cervical spine. The C5–C6 and C6–C7 levels are the most commonly involved levels. Our patient has weakness and atrophy of the right APB and FDI muscles, which suggests C8–T1 involvement. C8–T1 is an unusual level for a cervical myeloradiculopathy. Our patient's brisk reflexes are consistent with upper motor neuron findings, which would occur in a cervical myelopathy, although there are no sensory level or bowel and bladder complaints. Therefore, this picture would be

TABLE 3-1 Features of Carpal Tunnel Syndrome

Nocturnal paresthesias
Sensory symptoms and signs first 3.5 digits
Weakness APB and opponens muscles
NCS almost always demonstrate sensory abnormalities
Proximal arm pain
Associated with pregnancy, occupation, hypothyroidism, wrist fracture, amyloidosis, acromegaly, inflammatory arthritis, diabetes

APB, abductor pollicus brevis; NCS, nerve conduction studies.

unusual for a cervical myeloradiculopathy. There is also the possibility of a syrinx of the cervical cord. This may have occurred as a result of the neck injury and cervical cord trauma. The lack of sensory symptoms would be unusual for syrinx. The cape-like distribution of sensory loss associated with anesthesia and the resultant traumatic damage to the fingers is the classic presentation of syringomyelia.

WHAT WOULD YOU DO NEXT?

As discussed above, imaging of the cervical spine would be indicated. Magnetic resonance imaging (MRI) scanning would be preferred since we are considering a syrinx or damage of the cervical spinal cord in our differential. The patient's MRI shows C5–C6 osteophytic disk changes; there is no significant cervical stenosis. There is slight foraminal narrowing at that level; the cervical cord appears normal.

It would be helpful to perform NCS. The NCS would be able to ascertain the presence of CTS or an ulnar neuropathy. In addition, another diagnostic consideration not yet discussed would be multifocal motor neuropathy (MMN) (Table 3–2), which usually involves distal muscles resulting in weakness, atrophy, and fasciculations of these muscles. Sensory symptoms and signs are usually absent or minimal. Reflexes may be present. On NCS there is conduction block. On electromyography (EMG) there can be active denervation, neuropathic motor units, reduced motor recruitment patterns, and fasciculations in the involved muscles. GM_1 antibody testing may be positive in 60% of MMN patients. Initial treatment involves the use of human immunoglobulin.

An EMG examination would be helpful as noted in the diagnosis of MMN and importantly to see if other muscles are involved, that is, if more diffuse pathology of anterior horn cells or their axons are present.

THE NCS AND EMG STUDIES

The NCS results showed low-amplitude median and ulnar compound muscle action potentials (CMAPs) with normal median and ulnar sensory studies. Peroneal motor nerve and sural nerve conduction studies were normal (Table 3–3).

TABLE 3-2 Multifocal Motor Neuropathy (MMN) versus Amyotrophic Lateral Sclerosis (ALS)

	MMN	ALS
Distribution	Usually involves distal upper extremity, not a specific nerve	Involves proximal and distal muscles of upper and lower extremities
Sensory Findings	Few if any	None
Atrophy	Yes	Yes
Fasciculations	Present but not diffuse	More prominent and diffuse
Cranial Nerve Involvement	No	Yes
UMN Signs	No	Yes
Conduction Block	Yes	No
GM_1 Antibodies	Yes	No
Respiratory Function Affected	No	Yes

UMN, upper motor neuron; NCS, nerve conduction studies.

TABLE 3-3 Patient's Nerve Conduction Study and Electromyographic (EMG) Findings

Motor Nerve Conduction

Nerve and Site	Latency	Amplitude	Conduction Velocity
Peroneal.L			
Ankle	4.8 ms	2.1 mV	–
Fibula (head)	13.1 ms	2.1 mV	39 m/s
Ulnar.L			
Wrist	3.6 ms	3.3 mV	–
Below elbow	7.5 ms	3.3 mV	48 m/s
Median.L			
Wrist	4.1 ms	4.2 mV	–
Elbow	9.7 ms	4.2 mV	44 m/s

F-Wave Studies

Nerve	F-Latency
Peroneal.L	54.0
Ulnar.L	32.5
Median.L	32.8

Sensory Nerve Conduction

Nerve and Site	Peak Latency	Amplitude	Conduction Velocity
Sural.L			
Lower leg	3.8 ms	10 μV	42 m/s
Median.L			
Digit II	3.1 ms	10 μV	52 m/s
Mid-palm	2.2 ms	51 μV	54 m/s
Ulnar.L			
Digit V	3.0 ms	10 μV	50 m/s

Needle EMG Examination

	Spontaneous Activity			Volitional MUAPs			
Muscle	Fibs	+ Wave	Fasc	Polyphasic	Amplitude	Duration	Recruitment
FDI.R	2+	2+	1+	0	INC	INC	70%
APB.R	2+	2+	1+	0	INC	INC	70%
Deltoid.R	1+	1+	0	0	INC	INC	80%
Biceps.R	1+	1+	0	0	INC	INC	80%
FDI.L	1+	1+	0	0	INC	INC	80%
Deltoid.L	1+	1+	0	0	INC	INC	80%
Tib. Ant.R	1+	1+	0	0	INC	INC	80%

MUAP, muscle action potential; APB, abductor pollicus brevis; FDI, first dorsal interosseus.

The EMG demonstrated active denervation and occasional fasciculation potentials in the right APB and FDI muscles with neuropathic motor unit potentials and reduced motor recruitment patterns. Would you test other muscles? Yes. As discussed, it would be important to ascertain if there was a more diffuse process. There was active denervation in the right biceps, right deltoid, left FDI, left deltoid, and right anterior tibialis muscles; there were also neuropathic motor units and reduced motor recruitment patterns.

The NCS and EMG findings with the relatively unremarkable MRI suggest a diffuse process affecting anterior horn cells. In the context of the brisk reflexes (upper neuron findings), this suggests a process affecting lower motor neurons and upper motor neurons without significant sensory findings or sphincteric problems. The most likely diagnosis is amyotrophic lateral sclerosis (ALS).

The most common type of the motor neuron diseases is ALS. The motor neuron diseases include primary lateral sclerosis (PLS), which is the pure upper motor neuron variant; progressive muscular atrophy (PMA), the pure lower motor neuron variant; bulbar palsy, a distribution of purely cranial nerve weakness, though it is unclear if this is really a unique classification; and familial ALS. The spinal muscular atrophies may also be considered in the group of motor neuron diseases; although they have different characteristics. Depending on the series, 10%–20% of ALS cases are familial. Approximately 20% of these familial cases have a mutation on chromosome 21q that encodes a superoxide dismutase (SOD1). The knowledge of the genetics of familial ALS is continually evolving.

Sporadic ALS (Table 3–4) is most common in individuals aged 50–70 years but is seen in patients from their twenties into their eighties or older. There are reports of ALS clusters. There may be an association of ALS and military service;, recently a study outlining those who served in Operation Desert Storm, was published. There are reports of associations with trauma,

TABLE 3-4 Amyotrophic Lateral Sclerosis Features

Men more than women
Clusters
Peak at 50–70 years
Asymmetrical
Upper and lower motor neuron findings
Cramps
Fasciculations
Lack of pain early
Respiratory insufficiency begins nocturnally
Emotional lability
Lack of bowel and bladder involvement
Paucity of sensory findings

athletics, thin body stature, dairy products, toxin exposure, and pets. The reasons for these associations are not clear.

Usually, ALS presents with asymmetrical weakness of a distal extremity (e.g. a foot drop or weakness of the hand). It is a disorder of both the upper and lower motor neurons. There is no significant sensory deficit or pain. In ALS bowel and bladder functions are maintained until late in the course of the illness, where there may be incontinence due to the inability to ambulate or move. Cognitive impairment in the form of frontotemporal dementia can occur. The lower motor neuron findings in ALS include atrophy, fasciculations, absent reflexes, weakness, and cramps. Fasciculations and atrophy of the tongue are very suggestive of ALS. Examination by EMG demonstrates this lower motor neuron involvement: recording denervation (fibrillations and positive sharp waves), fasciculations, neuropathic motor units, and decreased motor recruitment. The upper motor neuron findings include increased tone, increased reflexes, pathological reflexes, (extensor toe signs, Hoffmann sign, palmomental reflex) weakness, and decreased rapid alternating movements. Patients can have emotional lability when there is corticobulbar involvement. This can be manifested as laughing or crying when the situation would not normally provoke such an emotional response from the patient. Crying is usually more common than laughter. As the disease progresses, significant weight loss occurs as the result of pronounced chewing and swallowing problems, as well as loss of muscle mass. Speech becomes more difficult, and anarthria may ensue. Respiratory insufficiency due to diaphragmatic and accessory muscle weakness is usual.

The diagnosis is usually not difficult as ALS progresses. Diagnosis can be difficult if only corticobulbar symptoms and signs are present. The EMG is usually not clear in this situation. If the patient's symptoms and signs do not include cranial nerve involvement, MRI scanning of the cervical or thoracic cord is essential, depending on the localization.

To assist in confirming the diagnosis, NCS and EMG are performed. The NCS velocities are usually normal. If there is significant loss of anterior horn cells and muscle atrophy, the CMAP will be decreased. The EMG examination documents widespread active denervation, fasciculations, neuropathic muscle action potentials, and decreased voluntary recruitment. These changes should be present in three extremities or the cranial musculature and two extremities for a definitive diagnosis.

A very difficult meeting with the patient ensued after the diagnosis of ALS was made. The patient obtained three other neurological consultations, which affirmed the diagnosis.

Chapter 4 addresses the ethical issues and the management of the ALS patient.

KEY POINTS TO REMEMBER

- ALS is the most common type of the motor neuron diseases, which include PLS (upper motor neuron signs), PMA (lower motor neuron signs), and bulbar palsy. It is most common in individuals aged 50–70 years.
- Between 10% and 20% of ALS cases are familial. Approximately 20% of these familial cases have a mutation of chromosome 21q that encodes a superoxide dismutase (SOD1).
- Usually, ALS presents as asymmetrical weakness of a distal extremity. There are upper and lower motor neuron findings, with no significant sensory findings. Bowel and bladder functions are maintained until late in the illness.
- The EMG demonstrates active denervation in a diffuse distribution. Motor NCS are normal unless there is extensive atrophy. Sensory NCS are normal.
- If there are no neurological signs above the level of the neck, appropriate neuroimaging of the spine should be performed.
- Emotional lability can occur with corticobulbar involvement.

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4 Amyotrophic Lateral Sclerosis Ethical Issues and Management

A family practice physician calls you for advice. He has a 50-year-old patient with progressive speech and swallowing problems who went to a neurologist at a large tertiary center and was given a diagnosis of amyotrophic lateral sclerosis (ALS). The patient saw another neurologist, who said he was not sure of the diagnosis. The family physician is worried because the patient's family feels his behavior has become stranger over the last 3 months. The patient is missing appointments (he is an accountant), looks disheveled, and has been in computer chat rooms for extended periods of time. You tell the family physician you would be happy to see the patient.

The patient arrives 30 minutes late and tells your receptionist he got lost. The patient is unshaven and his clothing is dirty. He has trouble giving you a cogent history of his illness. He seems very surprised and angry when you ask about the diagnosis of ALS he was given at the tertiary care center. He emphatically tells you, "I do not have ALS." During the neurological examination the patient is very uncooperative. His speech is dysarthric.

There are decreased rapid alternating movements of the tongue and mild facial weakness. There is atrophy of the intrinsic hand muscles bilaterally. He has brisk reflexes, bilateral extensor toes, a snout reflex, and grasp reflexes. After you finish the neurological examination, you ask about performing an electromyographic (EMG) examination. The patient angrily tells you, "The EMG infected me and made me sick." He runs out of your office. The family calls you and asks what to do.

What do you do now?

This is a very difficult situation. It is imperative to review the patient's prior work-up. Fortunately, the patient left a packet of medical records addressed to you with your receptionist. The patient had an EMG, which demonstrated active denervation in three extremities as well as the cranial musculature. His brain magnetic resonance imaging was reported to be normal. Laboratory examinations were normal, including B_{12} levels, thyroid studies, and Venereal Disease Research Laboratory and human immunodeficiency virus (HIV) testing. It is important to ascertain that there is not another cause for the patient's cognitive problems. It is certainly possible that ALS can coexist with another condition which is causing the patient's cognitive problems.

It appears that the patient has a diagnosis of ALS with features of frontotemporal dementia (FTD) (Table 4–1). It was thought that cognitive impairment was rare in ALS. It is now recognized that FTD can coexist with ALS. The frequency of FTD in a Scandinavian series was approximately 2%–6% of cases. There is a similar frequency in the United States. It is not clear whether ALS with FTD is part of a spectrum of disease or a distinct clinical entity. The course of ALS with FTD is usually more rapid. Patients with FTD exhibit personality changes and lack of appropriate social behavior, such as our patient. Early, there may be impulsive behavior. In ALS with FTD, bulbar symptoms are usually prominent. As a result, recognition and treatment of these problems by the neurologist are essential. The cognitive problems of FTD may precede the motor symptoms. In FTD, memory problems are less prominent than the personality and social behavioral abnormalities. Positron emission tomography (PET) in

TABLE 4-1 Features of Frontotemporal Dementia

Apathy
Disinhibition
Dietary changes
Compulsions
Social withdrawal
Depression
Perseverations
Diminished word output
Frontal/executive dysfunction

ALS–FTD patients demonstrates hypometabolism in the frontal lobes, sparing the temporal lobes.

The patient's safety is of prime importance. The patient's behavior suggests that his judgment is impaired and his safety may be jeopardized. It would be important to have a frank discussion with the patient and the family to discuss safety, employment, and self-determination issues. The patient and family come to your office. The patient is quite agitated; he keeps repeating that nothing is wrong with him and leaves your office. You receive a number of rambling e-mails from the patient in the ensuing week.

This case is an extreme example of the difficulty in caring for a patient who has cognitive impairment. As noted above, the most likely diagnosis of our patient is ALS– FTD. When reviewing records, it is important to ascertain that appropriate testing has been done and that the nerve conduction studies/EMG "make sense" and are performed by a competent electromyographer.

Discussing the diagnosis of ALS is never easy. It is important to be honest with the patient and family but also to not overwhelm the patient with too much information. Giving realistic hope is important. Discussing patients who have survived for a longer period, the availability of ALS clinics where multiple services are available, and the possibility of enrollment in research trials can help in your breaking of the news. We have had the experience of patients not being able to "remember" their diagnosis or relating that they were never told they had ALS. This is in the context of no cognitive impairment but rather a possible psychological defense mechanism.

In this patient, we would like to initiate a treatment plan. The first issue is the patient's competence. It would be important to discuss this frankly with the patient's family. As a result of the patient's cognitive impairment, the family will need to establish a mechanism for appropriate medical decisions to be made for the patient.

The approach to caring for the ALS patient involves comprehensive care (Table 4–2). If an ALS clinic exists near the patient, referral should be considered. Most clinics offer a multidisciplinary approach. This includes respiratory therapy, nutrition, speech therapy, occupational therapy, physical therapy, social work, and nursing.

TABLE 4-2 Management of Amyotrophic Lateral Sclerosis

Pseudobulbar symptoms	SSRIs, amitriptyline
Salivation	Amitriptyline, botulinum toxin
Respiratory	PFT, PSG, BiPap
Gastrointestinal	Weights, dietitian evaluation, PEG
Spasticity	Baclofen, tizanidine
Depression	Counseling, SSRIs
End-of-life issues	Palliative care
Speech	Speech and swallowing evaluation/therapy
OT	Adaptive devices, strengthening
PT	Adaptive devices, safety, strengthening, pain

SSRI, selective serotonin reuptake inhibitor; PFT, pulmonary function test; PSG, polysomnography; BiPAP, bilevel positive airway pressure; PEG, percutaneous endosocpic gastrostomy; OT, occupational therapy; PT, physical therapy.

Respiratory function in ALS needs to be evaluated at the initial diagnosis and monitored. As noted by others, there is no "one best test." Usually, pulmonary function testing (PFT) is performed. The critical indicator of impending respiratory problems is a forced vital capacity (FVC) <50% of predicted. It is important to remember that nocturnal respiratory insufficiency can occur with relatively "normal" PFTs. In this situation there are symptoms of sleep apnea such as frequent awakenings, sore throat, headache upon awakening, and sleepiness. Overnight polysomnography (PSG) can be very useful. This nocturnal respiratory insufficiency precedes daytime symptoms. With an abnormal PSG that suggests oxygen desaturation, the use of a bilevel positive airway pressure (BiPAP) apparatus at night can improve the patient's alertness, fatigue, and mood. The PFT can be difficult to perform in patients with facial weakness. Despite measures to help sealing around the mouth, erroneous results may occur. Noninvasive ventilatory procedures can be expanded from night use to use during the day as needed. We are not enthused about the use of tracheostomy and mechanical ventilation, although a few of our patients have decided on that course of treatment. In this situation we have tried to counsel our patients about the

expense and the need for 24-hour care and support. It is important to discuss with all patients the discomfort and anxiety which will occur with increasing respiratory insufficiency. The patient should be reassured that with the prudent use of medications, such as opioids and anxiolytics these problems can be humanely managed.

Nutritional consultation and support by a dietitian are essential. Regular weights should be recorded. The caloric needs of the ALS patient are increased over baseline. Rapid weight loss that cannot be slowed by dietary changes or additional supplementation should raise the question of performing a percutaneous endoscopic gastrostomy (PEG). As pointed out in a practice parameter of the American Academy of Neurology, PEG is preferably performed when the patient has a FVC >50% of predicted.

Additional care involves the use of medications for spasticity, such as baclofen or tizanidine. Cramps can be treated with tonic water, which contains quinine; if worried about the sugar content, diet tonic water can be used. Quinine can still be obtained through Canadian pharmacies. Excessive salivation is best treated with small doses of amitriptyline. We have found atropine to cause significant side effects in treating excessive salivation. Botulinum injections into the salivary glands may be indicated if other measures do not work. Ultrasound guidance can improve the results. Depression and anxiety issues should be addressed. Psychiatric consultation can be very useful. Emotional lability occurs in ALS when the corticobulbar tracts are affected. This usually results in events that are not that sad or happy making the patient spontaneously cry or laugh. Usually, patients do not feel that sad or happy. It is felt to be the result of a "disinhibition" of the emotional response. The treatment of emotional lability with amitriptyline or serotonin reuptake inhibitors such as fluoxetine is usually very effective. The effect of riluzole increasing survival is modest, but the effect on secondary improvement measures is not significant.

Finally, it is very important to engage the patient and family in end-of-life issues. We find that the palliative care consultant can be very helpful in assisting the patient and the family in facing these very important and difficult decisions.

In our patient's case, the family continued to call about patient care issues. We repetitively tried to set up appointments; the patient canceled.

KEY POINTS TO REMEMBER

- Cognitive impairment can occur in ALS in the form of FTD; behavioral and personality disorders, not memory loss, predominate in FTD.
- A PET scan can be helpful in ascertaining the diagnosis of ALS–FTD.
- It is important when giving the diagnosis of ALS to a patient to break the news gently and to give hope.
- Symptoms of respiratory insufficiency can occur insidiously; nocturnal oxygen desaturation precedes daytime symptoms; performing a PSG is very useful.
- Nutrition status should be carefully monitored and weights checked regularly. A PEG should be placed when the FVC is still >50%.

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5 Arsenic Neuropathy

A 45-year-old geologist comes to your office. He is very concerned that he is being exposed to chemicals at work. He does mainly fieldwork but says that the office has a number of chemicals which are haphazardly stored in a building where he has a desk. He is unsure what the specific chemicals are, but he has heard that a previous geologist became ill a few years ago and is now on medical disability. He complains of abdominal pain and very painful feet and hands. The patient denies any significant past medical history, and he is unsure of the family history; his parents both had problems with alcohol consumption, and his father may have had foot problems. He is not taking any medications, although he takes an energy supplement which he ordered online. The patient is vague about his alcohol consumption. The patient appears very anxious. His vital signs are pulse 95 beats per minute and blood pressure 140/90. On physical examination the patient has sweaty palms, which are erythematous. Neurological examination demonstrates a sensorimotor peripheral neuropathy to the modalities of pin, temperature, and vibration in the lower extremities

and involving the fingers in the upper extremities. Reflexes were absent. The patient has high arches. You would like to do further diagnostic testing that day, but the patient abruptly leaves because he must get back to work.

What do you do now?

You would like to obtain more information about the workplace chemicals. The Occupational Safety and Health Administration requires employers to disclose the chemicals which are stored at a place of employment and their toxicity to the workers. The patient speaks with his union representative, and you receive by fax a list of chemicals which are stored in the building; none appears to be neurotoxic. The patient calls you back and relates that he is concerned because of a dispute he is having with a fellow employee and he feels this person may be poisoning him. The patient agrees to come in for further testing. What would you do now?

You decide that electromyography (EMG) and nerve conduction studies (NCS) are a helpful first step to document and characterize the peripheral neuropathy. The studies demonstrate an axonal peripheral neuropathy. The EMG demonstrates active denervation in the distal muscles (Table 5–1). After the study, you reexamine the patient and note that he has transverse bands across his nails (Fig. 5–1) as well as some depigmented areas on his trunk. The palms and ankles still appear red and swollen. What would these signs point to? The areas of depigmentation and nail changes suggest arsenic poisoning. The abnormalities of NCS suggest an axonal peripheral neuropathy, which is also consistent with an arsenic peripheral neuropathy. It is reported that early in the course of arsenic peripheral neuropathy there may be a proximal demyelinating picture. This could be confused with Guillain-Barré syndrome (GBS). As in most heavy metal poisonings, it is common



FIGURE 5-1 Mees' lines.

TABLE 5-1 Patient's Nerve Conduction Study Findings

Motor Nerve Conduction

Nerve and Site	Latency	Amplitude	ConductionVelocity
Peroneal.R			
Ankle	5.6 ms	0.4 mV	
Fibula (head)	13.2 ms	0.4 mV	38 m/s
Tibial.R			
Ankle	5.2 ms	0.7 mV	
Popliteal fossa	14.7 ms	0.9 mV	39 m/s

F-Wave Studies

Nerve	F-Latency
Peroneal.R	54.6
Tibial.R	52.6

Sensory Nerve Conduction

Nerve and Site	Peak Latency	Amplitude	Conduction Velocity
Sural.R			
Lower leg	3.6 ms	6 μV	38 m/s

Needle EMG Examination

	Spontaneous Activity				Volitional MUAPs		
Muscle	Fibs	+ Wave	Fasc	Polyphasic	Amplitude	Duration	Recruitment
Tib. Ant.L	1+	1+	0	0	INC	INC	70%
Gastroc.L	0	0	0	0	INC	INC	70%

to have systemic symptoms such as nausea, vomiting, malaise, and weight loss. These symptoms can be confused with a gastroenteritis and subsequent GBS. Arsenic neuropathy (Table 5–2) usually begins between 10 days and 3 weeks after ingestion. This would be similar to the time course for GBS after gastroenteritis. In arsenic neuropathy cerebrospinal fluid studies usually demonstrate elevated protein without cells, although there have been isolated reports of pleocytosis. If we suspect arsenic poisoning, what testing should we pursue? Blood levels of arsenic are usually insensitive because it is cleared very quickly. Urine levels may still be elevated several months after a single high dose of arsenic. Importantly, arsenic is bound to the keratin of

TABLE 5-2 Features of Arsenic Poisoning

Gastrointestinal symptoms
Malaise
Severe pain distal extremities
Stocking glove sensory loss with distal weakness
Can rarely look like Guillain-Barré syndrome
Skin changes
Mee's lines
Alcohol may worsen
Axonal neuropathy
Urine levels, hair and nail analysis
Most cases are suicides or homicides

growing skin, hair, and nails and, because of the slow turnover of these tissues, it may be detected months or years later. In our case the patient's elusive history of alcohol consumption may be very important due to the pathophysiology of arsenic poisoning. Arsenic inhibits a number of enzyme systems, including pyruvate dehydrogenase. It is interesting that pyruvate dehydrogenase also requires thiamine pyrophosphate, which is inhibited by a deficiency of thiamine. Therefore, in individuals with an excessive consumption of alcohol, arsenic may be more toxic. It is always important to remember that it can be very difficult to obtain an accurate alcohol consumption history. Our patient's elusiveness and family history suggest that he may have excessive alcohol consumption. The sural nerve pathology in arsenic is usually a demyelinative process affecting all fiber diameters. The treatment of arsenic poisoning first requires the removal of the source of arsenic exposure. In this case it appears that there is not an exposure issue at work since the chemicals in proximity were not neurotoxic and arsenic was not one of the chemicals. In addition to removal of the arsenic, there have been two advocated treatment modalities: British antilewisite (BAL) and D-penicillamine. Reports suggest that BAL is not effective for peripheral neuropathy. It must be given parenterally and has a number of side effects. Therefore, it is felt that BAL is probably not indicated for the treatment of arsenic peripheral neuropathy. D-Penicillamine increases the rate of arsenic excretion. Again, there is no clear indication that D-penicillamine reverses the neuropathy associated with arsenic. It also has side effects.

Therefore, it is recommended that when it is used urinary excretion of arsenic be monitored after baseline levels of excretion are measured. The prognosis of arsenic neuropathy is related to removing the source of arsenic and supportive rehabilitative measures. Also, medications that help with pain control are an important facet of treatment.

It may be helpful to briefly review three other metals associated with peripheral neuropathy: lead, mercury, and thallium.

Lead is a less common cause of peripheral neuropathy due to public health measures and increased awareness of its toxicity. Lead affects the central nervous system of children and the peripheral nervous system of adults. It causes a motor neuropathy predominantly affecting the upper limbs. Radial innervated muscles are most affected, causing a wrist drop. Sensory symptoms are a minor feature. Other systemic features include weight loss, anorexia, fatigue, abdominal pain, constipation, and lead lines on the gums. Basophilic stippling and anemia are common. Blood lead concentrations may be used as a screening test, although free erythrocyte protoporphyrin may be a more accurate indicator of chronic exposure.

Mercury causes both central and peripheral nervous system signs. The term "mad as a hatter" comes from mercury salts being used in the manufacture of felt hats. Most information on mercury poisoning comes from the ingestion of inorganic mercury. There are personality and behavioral changes, weight loss, fatigue, tremor, and peripheral neuropathy. Occasional poisoning may be the result of children playing with old mercury thermometers, switches, and monometers. Methylmercury has a high affinity for central nerve system tissue and, as a result, urinary levels may be normal. With organic and metallic mercury, urinary levels can be used.

Thallium is a rare cause of peripheral neuropathy. The cardinal feature is hair loss. Many of the peripheral neuropathy features are similar to those of arsenic, although there are autonomic features. A recent case of radiation poisoning of an ex-Russian spy was initially thought to be thallium poisoning.

The patient related a dispute with a coworker. The patient returns to your office to discuss the results of the arsenic testing, which disclosed elevated urinary and hair arsenic levels. The patient is very hesitant to discuss his problem at work. You suggest that this may be a law enforcement situation which needs to be investigated. The patient begins to cry, and he tells you there is no angry coworker; rather, his wife and he have been fighting

over the last year. You strongly suggest that the patient have his wife return with him to discuss this matter. The patient never returns your call; you try his home telephone number, but it is disconnected; at work you are told he left. You contact your risk management office.

This case points out a number of additional considerations. Arsenic in the past had been used as a pesticide; it is also used as a wood preservative. However, most recent arsenic poisonings are the result of suicides or homicides. Arsenic can be easily mixed into sugar. It has been our experience that most of the poisonings occur in a rural environment. The spouse is usually the suspected person, and rarely does the poisoned party wish to pursue contacting the police.

KEY POINTS TO REMEMBER

- **The clinical picture of arsenic neuropathy can appear similar to GBS.**
- **Mees' lines, depigmented areas, and erythematous swollen hands and feet are all suggestive of arsenic poisoning.**
- **Blood levels of arsenic are not useful due to quick transit. Hair and nail samples are more useful.**
- **The neuropathy is a painful axonal peripheral neuropathy.**
- **Most arsenic exposures are due to suicide or homicide.**
- **D-Penicillamine may be used to increase urinary excretion; its efficacy in arsenic neuropathy is unclear.**

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6 Diagnosis of Guillain-Barré Syndrome

A 48-year-old male presents to the emergency department with a 4-day history of progressive weakness and pain. He first noted difficulty walking up the stairs at work. That evening, when carrying grocery bags to his car, they felt unusually heavy. He and his wife finally went to the emergency department because he was having trouble with walking and balance. He also describes "deep, aching" pain in his neck and shoulders, which he has never experienced before. Ibuprofen and tramadol have not provided relief. He has chronic moderate back pain since a car accident 3 years earlier but feels his back has been "acting up a lot more" in the last week. He describes constant tingling of his feet and hands for about 1 week and mentions a little difficulty swallowing for the last day. Past medical history is significant for hypertension, hyperlipidemia, and chronic back pain. Medications include simvastatin, aspirin, and lisinopril. He takes tramadol and ibuprofen as needed for back pain. He does not smoke or drink alcohol, denies illicit drug use, and denies toxin exposure. Review of systems is negative except for mild urinary hesitancy, and he denies

recent illness. Vital signs and general exam are normal. On neurological exam, mental status and cranial nerves are intact. Power is 3/5 proximally and 4+/5 distally. Tone is normal. Reflexes are trace throughout. Sensory examination shows mild vibratory sense loss distally but otherwise is unremarkable. Cerebellar testing is not interpretable in the context of weakness. Gait is ataxic with a slightly wide base (he requires one-person assist), and Romberg is negative. The labs (complete blood count, basic metabolic panel, international normalized ratio, liver function test, vitamin B12, thyroid stimulating hormone, urinalysis), chest X-ray, and electrocardiogram ordered by the emergency room physician are reviewed and are remarkable for a potassium of 3.0.

What do you do now?

Acute diffuse symmetric weakness is concerning for spinal cord pathology (a neurological emergency). However, the patient denies significant bowel or bladder complaints, and a sensory level is absent on exam, which reduces the suspicion of a spinal cord lesion. Guillain-Barré syndrome (GBS, acute inflammatory demyelinating polyneuropathy, or AIDP, being the most common form) becomes higher on the differential. This man's weakness, associated with trace reflexes, is also consistent with GBS. However, a myelopathy can also lead to these exam findings early after injury (spinal shock), which can complicate the picture. Also difficult to localize is the mild bowel/bladder dysfunction, which may be seen in myelopathy or in GBS secondary to autonomic neuropathy. However, note that early severe bowel/bladder involvement is atypical for GBS. The patient's worsening pain may suggest spine pathology, but severe back, neck, or interscapular pain is also common in GBS (and often an early feature). The patient's predominant proximal weakness can be a distraction and suggest myopathy or neuromuscular junction disease. However, the recent paresthesias and mild sensory examination findings would be inconsistent with these presentations but would be common early features of GBS. Predominant proximal weakness is also a common (and often overlooked) feature of GBS. The patient's history suggests ascending weakness which is classic for GBS, but it is important to remember that 10% of GBS cases present with a descending pattern, often starting with bifacial and bulbar weakness. There are uncommon variants of GBS besides AIDP. The primary axonal forms make up 5%–10% of cases; acute axonal motor neuropathy and acute sensorimotor axonal neuropathy are often preceded by *Campylobacter jejuni* infection. Reflexes may be preserved in axonal forms, which can lead to diagnostic confusion. Ophthalmoplegia, areflexia, and ataxia (from proprioceptive loss) suggest the Miller-Fisher variant of GBS. Our patient had normal extraocular movements, and his ataxia was secondary to weakness rather than proprioceptive loss (as joint position sense was intact). The pharyngeal–cervical brachial variant leads to acute symmetric arm weakness, dysphagia, and at times facial weakness; but interestingly leg strength and reflexes are mainly intact. There is a paraparesis GBS variant that affects only the legs. The rare pure sensory variant leads to sensory ataxia, areflexia, and minimal to no weakness. Acute pandysautonomia with hypo-/areflexia but normal strength has also been described.

As the hospital admission is arranged, should this patient have urgent magnetic resonance imaging (MRI) of the cervical/thoracic spine, a lumbar puncture, or both? As described above, this patient's presentation is not suggestive of myelopathy but very compelling for GBS. A lumbar puncture must be done with minimal delay as early treatment with intravenous immunoglobulin (IVIG) is very important if the patient does have GBS. A nonurgent MRI of the entire spine with gadolinium could also be considered as nerve roots often enhance on MRI in inflammatory radiculoneuropathies which include GBS. Another important factor in this case is that the emergency room physician presented the case to the neurologist as weakness caused by hypokalemia. However, keep in mind that a potassium level must be critically low to lead to significant weakness (a hypokalemia periodic paralysis picture).

A lumbar puncture must be performed. Although cerebrospinal fluid (CSF) albuminocytological dissociation (high protein and low cells) is classic for GBS, a normal protein level is seen in the first week in one-third of patients. About 10% of cases never have elevated CSF protein. If the patient's CSF cell count is higher than 10 (especially if higher than 50), the suspicion would be raised for an infectious etiology or a vasculitis that can mimic the autoimmune GBS. In presentations with significant CSF pleocytosis, strongly consider CSF studies for West Nile virus, Lyme, Syphilis, Tuberculosis, Herpes Simplex virus, Varicella Zoster virus, and Cytomegalovirus. Always obtain human immunodeficiency virus (HIV) antibodies in cases with significant CSF pleocytosis. More extensive vasculitis investigations would also need to be considered (anti double stranded DNA, extractable nuclear antigens, hepatitis serologies, C and P antineutrophil cytoplasmic autoantibodies, rheumatoid factor, complement levels, cryoglobulins). Although an aggressive vasculitis of the peripheral nervous system typically presents with painful asymmetric weakness, occasionally it may mimic the rapid progressive symmetric weakness of GBS, when nerve involvement is confluent. Cytology and flow cytometry may be considered as lymphoma or other aggressive malignancies (i.e., meningitis carcinomatosis) may occasionally mimic GBS. Oligoclonal bands (and IGG index) may be elevated in GBS and in other inflammatory disorders of the central nervous system.

Extra blood work may also be ordered for this patient, which includes: erythrocyte sedimentation rate and C-reactive protein (may be nonspecifically

elevated in GBS or can be seen in vasculitis, infection, and malignancy), antinuclear antibodies (may be elevated in vasculitis or GBS), HIV antibodies (HIV commonly mimics GBS), serum/urine protein electrophoresis (may be a marker for lymphoma), angiotensin-converting enzyme level (sarcoidosis can rarely mimic GBS), creatine kinase (often moderately elevated in GBS but a more helpful test if suspicious for acute/subacute myopathies), immunoglobulin A level (deficiency is an IVIG contraindication). Ganglioside antibodies such as anti-GD_{1a} are not recommended as they have limited clinical utility and are typically used in research settings only. The exception is the GQ_{1b} antibody, which should be obtained if the Miller Fisher variant of GBS is suspected (sensitivity is 90%–95%, but can also be seen in Bickerstaff encephalitis and the pharyngeal–cervical–brachial GBS variant). These antibodies are immune responses to myelin (associated with AIDP) and axonal membranes (associated with axonal forms of GBS). A final point on differential diagnosis is that toxin exposure (e.g., thallium, arsenic, lead), acute intermittent porphyria, or paraneoplastic neuropathy can rarely present as an acute progressive symmetric polyneuropathy; however, the history, physical examination, and initial investigations did not raise suspicion for these conditions.

Although not required urgently for the diagnosis of GBS (in contrast to lumbar puncture), electromyography/nerve conduction studies (EMG/NCS) are very helpful in confirming GBS and other polyradiculoneuropathies. This can also give prognostic information. Note that EMG/NCS abnormalities are often subtle early in the course of GBS. However, the most common early findings to support the diagnosis of AIDP are prolonged/absent F waves (and H-reflexes), secondary to early proximal nerve root demyelination (see Table 6–1). Other helpful early findings are abnormal or absent sensory nerve action potentials (SNAPs) in the upper extremities, with present sural SNAPs. This is known as "sural sparing." The EMG shows impaired motor recruitment early in GBS. Conduction block, impaired distal latencies and conduction velocities, reduced distal compound motor action potentials (CMAPs), and active denervation may be seen about 1–2 weeks or more after disease onset. The EMG/NCS may also confirm the axonal variant of GBS. This is usually apparent at least 1–2 weeks after disease onset (time is needed for wallerian degeneration to occur). As mentioned previously, the axonal variant caries a worse prognosis.

TABLE 6-1 Early Nerve Conduction Study/Electromyographic Findings in Guillain-Barré Syndrome

1. Absent H reflex
2. Absent or prolonged F waves
3. Low-amplitude/absent upper extremity SNAP with normal sural SNAP
4. Slowed conduction velocities and prolonged distal latencies
5. Conduction Block
6. Reduced recruitment on EMG

SNAP, sensory nerve action potential.

KEY POINTS TO REMEMBER

- **Predominant proximal weakness is a common and often overlooked feature of GBS.**
- **Although ascending weakness is the classic pattern for GBS, 10% of cases present with a descending pattern, often starting with bifacial and bulbar weakness.**
- **Although CSF albuminocytological dissociation is classic for GBS, a normal protein level is seen in the first week in one-third of patients.**
- **If the CSF cell count is higher than 10 (especially if higher than 50), suspicion is raised for an infectious etiology or a vasculitis that can mimic GBS.**
- **Studies such as EMG/NCS are very helpful in confirming GBS, but EMG/NCS abnormalities may be subtle early in the course of illness.**

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7 Management of Guillain-Barré Syndrome

A 30-year-old male is transferred from a local emergency department with a presumptive diagnosis of Guillain-Barré syndrome (GBS). He has a 4-day history of progressive upper and lower extremity weakness. He notes severe back pain but denies any other complaints. A lumbar puncture as well as magnetic resonance imaging (MRI) of the entire spine were done prior to transfer. The spinal fluid showed a protein of 120, four nucleated cells, and glucose of 40. You review the MRI and agree with the radiology report that it is normal. Physical exam is significant for 3/5 strength in the lower extremities, 4/5 strength in the upper extremities, absent reflexes, and unsteady gait. He has normal vital signs, mental status, and sensory exam. You agree with the diagnosis of GBS.

What do you do now?

Pulmonary status must be assessed carefully. Clinical features that indicate respiratory muscle weakness and the need for possible intubation include tachycardia, tachypnea, use of accessory respiratory muscles, and diaphoresis. Although this patient's cardiorespiratory status appears within normal limits, he (as most patients with suspected GBS) must be admitted to the neurological special care unit/intensive care unit (ICU). This is because pulmonary decompensation can occur very rapidly in GBS. However, patients who are mildly affected, with minimal weakness, may be admitted to the general ward (but closely monitored). There are several factors to note on admission that are associated with increased risk of respiratory failure. These factors are the inability to stand, inability to lift elbows or head, inability to cough, elevated liver function tests, and duration of symptoms from onset to admission of less than 1 week. This patient met the last criterion. Four or more of these findings leads to mechanical ventilation in >85% of patients. Pulmonary function tests (PFTs) should be checked every 4 hours. The orders (see Table 7–1) should include that the house officer be notified if the negative inspiratory force is <30 cmH_2O, forced vital capacity (FVC) <20 ml/kg, or FVC drop >30% of baseline. These are indicators for probable intubation even if the patient shows no clinical signs of respiratory distress. All patients must be placed on telemetry, and blood pressure should be checked every 4 hours because of the risk of autonomic dysfunction (tachy-/bradycardia, hyper-/hypotension, orthostatic hypotension).

TABLE 7-1 Important Orders for Guillain-Barré Syndrome Management

Admit to neurology special care unit or intensive care unit
PFTs every 4–6 hours initially (follow NIF and FVC)
Telemetry
Frequent blood pressure monitoring (e.g., every 4 hours initially)
IVIG (2g/kg IV over 3–5 days)
DVT prophylaxis
Bowel/bladder care
Pain management
Physical, occupational, and speech therapy consults
Nutrition consult

PFT, pulmonary function test; NIF, negative inspiratory force; FVC, forced vital capacity; IVIG, intravenous immunoglobulin; DVT, deep venous thrombosis.

Intravenous immunoglobulin (IVIG) 2 g/kg over 3–5 days must be ordered on admission for this patient. It is the treatment of choice for GBS as it is less complicated to administer than plasma exchange and has been shown in randomized controlled trials to have similar efficacy. Recovery speed is increased by about 50% with IVIG or plasma exchange. There is no benefit of steroid treatment for GBS. Contraindications to IVIG are advanced renal failure, uncontrolled hypertension, and immunoglobulin (IGA) deficiency. A patient with low IGA levels will develop antibodies after the first dose of IVIG, and a second dose will lead to anaphylaxis. Common complications of IVIG include infusion reactions (10%), headache, myalgias, chills (pretreat with acetaminophen and/or ibuprofen), and rash (pretreat with diphenhydramine [Benadryl]). Rare complications of IVIG include aseptic meningitis, pulmonary edema, and acute renal failure. In elderly patients or those with mild renal insufficiency, follow renal function daily. Other rare IVIG complications are hyperviscosity syndromes that lead to coronary thrombosis, acute ischemic stroke, deep vein thrombosis (DVT), or retinal vein occlusion. If the patient has a history of thrombosis, IVIG must be used with caution, if at all. Of note, distribution of IVIG over 5 days lowers the risk of complications, in contrast to shorter durations of therapy, and should be used in higher-risk and elderly patients. However, younger and lower-risk patients, like this patient, may be considered for a 3- or 4-day division of the IVIG total dose. As for plasma exchange, complications that must be considered are problems with intravenous access, sepsis, and hypotension (autonomic neuropathy can exacerbate the latter complication).

Other factors to address on the patient's admission are DVT prophylaxis, bowel/bladder care (ileus and urinary retention may be develop in GBS secondary to dysautonomia), physical/occupational/speech therapy consults, nutrition, and pain control. The patient presented with severe pain, and although nonsteroidal anti-inflammatory drugs (NSAIDs) can be ordered as first-line treatment, there should be opioids available as the pain can be refractory to NSAIDs. Gabapentin can also be helpful for GBS-related pain.

A typical response to IVIG is that the patient's weakness will stabilize within a few days of treatment, and strength slowly improves over the hospital stay. Patients who are clinically stable (with stable PFTs) may be transferred

to the general neurology floor in a few days. There are no clear rules with respect to PFT frequency for GBS; however, it is reasonable to change the PFT order from every 4 hours to every 8 or 12 hours when the patient begins to improve (i.e., can walk with assistance, lift arms and head up, resolution of dysphagia). If the PFTs remain stable, they can be discontinued in a few days. Discontinuation of telemetry can also be addressed in this manner.

The prognosis of GBS is good for many patients, if managed properly. About 80% of patients make a complete recovery or have only mild deficits. However, even with the development of immunotherapies like IVIG, about 10% of patients have a prolonged course with incomplete recovery. Five percent of patients die despite ICU care. Factors associated with poor prognosis are need for ventilatory support, older age, rapid onset (<7 days prior to presentation), preceding diarrheal illness, and axonal features on electromyography/nerve conduction studies (EMG/NCS). These include active denervation and distal motor amplitude reduction of <20% normal on follow-up EMG/NCS (2–5 weeks post-GBS onset). Relapses occur in about 10% of patients with GBS, and treatment should include another course of IVIG or perhaps plasmapheresis if the patient did not respond well to IVIG in the past. Alternative diagnoses, such as human immunodeficiency virus (HIV) polyradiculoneuropathy (that did not seroconvert on the first presentation), must be reconsidered.

If a patient with a history of GBS asks about the influenza vaccine, should he or she get one? Vaccination risk in patients who have had GBS is not known, and decisions must be made on a case-by-case basis. However, vaccinations are often not recommended for 1 year after disease onset. A vaccine is typically avoided in the future if it was given within 6 weeks of GBS onset. It is important to note that the Centers for Disease Control does not make recommendations on these issues because of lack of reliable data.

KEY POINTS TO REMEMBER

- **Factors on admission that are associated with increased risk of respiratory failure in GBS are inability to stand, lift elbows, lift head, or cough; elevated liver function tests; and less than 1-week duration of symptoms from onset to admission.**

- In GBS, PFTs must be monitored regularly as abnormal results may be indicators for intubation, even if the patient shows no clinical signs of respiratory distress.
- Patients with GBS must be placed on telemetry, and blood pressure should be monitored carefully because of the risk of autonomic dysfunction.
- First-line treatment for GBS is IVIG as it is less complicated to administer than plasma exchange and has been shown in randomized controlled trials to have similar efficacy.
- There is no role for steroids in GBS treatment.

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8 Chemotherapy-Induced Peripheral Neuropathy

A hematology colleague calls you about a 35-year-old artist who is human immunodeficiency virus (HIV)–positive. The patient is receiving high-activity antiretroviral therapy (HAART), a triple therapy which inhibits both reverse transcriptase and protease. These enzymes are critical for viral replication and assembly. The patient has done very well on his last testing. Recently, he was diagnosed with lymphoma and underwent CHOP therapy: cyclophosphamide, hydroxydaunomycin (doxorubicin, Adriamycin), vincristine (Oncovin), and prednisone. Sometimes CHOP is used in conjunction with immunotherapy such as rituximab. The patient is complaining of numbness, tingling, and severe pain in his fingertips and toes. In addition, he feels his hands are clumsy. Of worry to his physician, the patient appears to have developed a Bell's palsy. The hematologist is quite concerned because the symptoms are getting worse despite the cessation of therapy.

What do you do now?

This patient has a number of factors that could be related to his peripheral neuropathy symptoms. These would include chemotherapy-induced peripheral neuropathy, HIV-related peripheral neuropathy, and a paraneoplastic syndrome of peripheral neuropathy. As a result, we should review these possibilities. At first glance, the patient's Bell's palsy does not seem to be related to a peripheral neuropathy. It would be helpful to ask the referring physician questions concerning the patient's facial weakness to ascertain if this is a Bell's palsy. A Bell's palsy may include problems with taste, weakness of the frontalis muscle, severe eye closure weakness, hearing disturbance, tearing, and initially retro-orbital pain.

As noted, the patient's chemotherapy regimen includes vincristine. Vincristine is used commonly in association with other agents in the CHOP protocol for lymphoma. Damage to microtubules is the mechanism of vincristine-induced peripheral neuropathy. It binds to microtubules and interferes with microtubular assembly. There is disordered orientation of the microtubules and disorganization and fragmentation of the smooth endoplasmic reticulum. These structural alterations account for impaired axoplasmic transport, which plays a role in axonal degeneration and the peripheral neuropathy. As it was recognized that vincristine caused a peripheral neuropathy, doses of vincristine used in chemotherapy have been reduced. Vincristine causes a sensorimotor peripheral neuropathy with autonomic features, ankle jerks are usually absent after treatment, and half of patients lose all of their reflexes. The peripheral neuropathy usual involves distal pain and temperature loss. Large fiber function, such as joint position sense and vibration sensibility, is usually spared. It is important to note that the sensory symptoms may first occur in the fingers. Motor weakness is less common in the context of the present dosages of vincristine, but cramps may occur. The pattern of weakness when it does occur usually involves extensor muscles of the fingers and hands and distal foot muscles. Rarely, cranial nerves may be affected, including the facial nerve. Autonomic symptoms commonly include erectile dysfunction, distention, bloating, constipation, and difficulty with urination. Orthostatic hypotension is rare. Abdominal pain may be a feature of this autonomic neuropathy. Nerve conduction studies demonstrate axonal features in both sensory and motor nerves, loss of amplitude of the compound muscle action potentials, and sensory nerve action potentials. Recovery usually occurs once the vincris-

tine is ended. Paresthesias and weakness usually improve within 3 months. Mild symptoms may persist for as long as 3 years after treatment termination. A finding of "coasting" also has been reported in vincristine peripheral neuropathy. This means that the peripheral neuropathy continues to worsen for a time period despite cessation of therapy.

Other common chemotherapeutic agents which cause a peripheral neuropathy are the taxanes and platins (Table 8–1). Taxanes cause primarily a sensory neuropathy with mild motor symptoms. There is a stocking glove sensory loss. Perioral numbness may occur. Coasting may be common. Neuropathy improves over months, but there is often incomplete recovery. Platins affect the dorsal root ganglia. They produce a large fiber sensory neuropathy. There is a specific symptom of cold-induced laryngopharyngeal pain. In addition, there may be ototoxicity and Lhermitte's sign. There is coasting as well, and severe neuropathy patients make a poor recovery.

A number of neuromuscular complications are associated with HIV (Table 8–2). Early in the course of HIV, often before diagnosis is made, autoimmune processes predominate. This can include inflammatory demyelinating polyradiculoneuropathy (both acute and chronic), inflammatory myopathy, sensory ataxia, and facial nerve palsy. Before HAART, the retrovirals used were related to both myopathy and peripheral neuropathy. There are reports that HAART may actually decrease the frequency of peripheral neuropathy. As HIV progresses, there are a number of different peripheral nerve and muscle clinical pictures. In intermediate stages of HIV infection,

TABLE 8-1 Features of Chemotherapy-Induced Peripheral Neuropathy

Vincristine	Microtubules disrupted, distal pain and temperature loss, fingers may be affected first, cranial nerves rarely, recovery, rare coasting
Taxanes	Stocking glove sensory loss, perioral numbness, coasting common, improves, often incomplete recovery
Platins	Affect dorsal root ganglia, large fiber sensory neuropathy, cold-induced laryngopharyngeal pain, ototoxicity, Lhermitte's sign, coasting, possibly a poor recovery

TABLE 8-2 **Temporal Course of Neuromuscular Complications in HIV**

Early (Autoimmune)
Inflammatory demyelinating polyradiculoneuropathy (both acute and chronic)
Inflammatory myopathy
Sensory ataxia
Facial nerve palsy
Intermediate
Mononeuropathy multiplex
Later Stages
Wasting myopathy
Autonomic neuropathy
Painful distal symmetric peripheral neuropathy
Polyradiculoneuropathies

mononeuropathy multiplex may occur. The cause is not clearly known but may be related to cytomegalovirus (CMV) infection, cryoglobulins, direct HIV infection, or herpes simplex or herpes zoster infection. In the later stages of HIV, a wasting myopathy, autonomic neuropathy, a painful distal symmetric polyneuropathy (DSN), and polyradiculoneuropathies are seen. There are a number of factors which contribute to the painful DSN. These include a direct effect of HIV, infection by other viruses (herpes zoster or CMV), vitamin deficiency, malnutrition and weight loss, drug therapy, and other illness such as hepatitis.

Our patient's HIV load is undetectable, and he had herpes zoster once involving his trunk. His diagnosis was made 3 years ago, when he was asymptomatic; he had wanted just to check his HIV status due to a new partner.

Finally, we should discuss the patient's lymphoma and the possibility of a neoplastic or paraneoplastic syndrome. It is estimated that the nervous system is involved in 10%–25% of cases of lymphoma (Table 8–3). These complications include the effects of local deposits on the brain, spinal cord, and cranial and peripheral nerves. In addition, there are disorders whose cause is not well known, including encephalomyelitis, cerebellar degeneration, peripheral neuropathy, inflammatory myopathy, and progressive multifocal leukoencephalopathy. Finally, due to therapy and the disease process,

TABLE 8-3 Neurological Complications of Lymphoma

Local deposits or compression on brain, spinal cord, and peripheral nerves
Encephalomyelitis
Cerebellar degeneration
Peripheral neuropathy (chemotherapy and other causes)
Inflammatory myopathy
Progressive multifocal leukoencephalopathy
Opportunistic infections
Subacute motor neuropathy

opportunistic infections such as herpes zoster and cryptococcus can occur. Cranial nerves can be affected by compression; mental nerve involvement with chin numbness may be a presenting sign of lymphoma. Compression of the cauda equina and roots by tumor deposits or vertebral collapse is not uncommon. Individual plexus or peripheral nerves may be directly involved by tumor. Symmetric peripheral nerve involvement as a manifestation of paraneoplastic syndrome is much rarer. Paraneoplastic syndromes of acute and chronic demyelinating polyradiculoneuropathy are more common in lymphoma. Cerebrospinal fluid protein is elevated, and nerve conduction studies demonstrate a segmental demyelination. There is a relatively specific paraneoplastic syndrome in lymphoma. This is a subacute motor neuropathy. The cerebrospinal fluid is normal, and the clinical examination and electromyography demonstrate lower motor neuron findings.

The patient is seen the following day. He does not appear ill. On neurological examination he has weakness of the right frontalis, orbicularis oculi, and oris muscles. He does not recognize taste well on the right anterior two-thirds of his tongue. There is some slight weakness of the finger extensors and toe extensors bilaterally. Reflexes are absent. There is sensory loss of pin and temperature to wrists and ankles. Joint position sense and vibration sensibilities are normal. We perform nerve conduction studies, and an axonal sensorimotor polyneuropathy is present. On electromyography there is 1+ denervation present in the first dorsal interosseous muscle and extensor digitorum brevis muscles.

Putting this all together, a diagnosis of chemotherapy-induced peripheral neuropathy due to vincristine is made. The facial nerve involvement is thought to be related to the vincristine therapy. The patient's hematologist

wants to treat the facial nerve palsy with steroids and acyclovir. You refer the hematologist to the American Academy of Neurology's practice parameter on Bell's palsy: "A benefit from steroids, acyclovir, or facial nerve decompression has not been definitively established. However, available evidence suggests that steroids are probably effective and acyclovir (combined with prednisone) is possibly effective in improving facial functional outcomes" (see Grogan and Gronseth, 2001 page 830). Even though you are not enthused about treating the patient's Bell's palsy, his hematologist begins treatment. When you see the patient 8 weeks later, both his Bell's palsy and peripheral neuropathy seem to be improving.

KEY POINTS TO REMEMBER

- Patients with HIV may experience a number of neuromuscular complications, though HAART has decreased their frequency. Occurrence of peripheral neuropathy late in the course of HIV is usually multifactorial.
- Peripheral neuropathy in patients with malignancy may be due to direct spread or compression, chemotherapy-induced peripheral neuropathy, or paraneoplastic peripheral neuropathy.
- Vincristine disrupts the architecture of the microtubules, resulting in impaired axoplasmic transport. The peripheral neuropathy with vincristine is usually predominantly sensory. Recovery usually takes place after vincristine therapy has ended.
- Taxanes and platins may exhibit "coasting" after therapy has ended. Recovery after platin use may be incomplete.
- Treatment of Bell's palsy with prednisone and possibly acyclovir may be the best evidence-based therapy. Bell's palsy can be associated with vincristine treatment in lymphoma patients.

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9 Idiopathic Brachial Neuritis

A 61-year-old male presented to the emergency department after waking with severe, deep, aching pain in the left cervical region extending down into the shoulder. He had no recent history of trauma, surgical procedure, vaccination, or illness. On his initial evaluation he was unable to cooperate with a full motor examination because of severe pain. His chest X-ray and cardiac evaluations were normal including an electrocardiogram and cardiac enzymes. He was not on any medications. His past medical history, social history, and review of systems including bowel and bladder function were otherwise normal. Movement of the shoulder exacerbated his pain. Over the next week, the pain began to subside; and on follow-up exam 5 days later, shoulder abduction was weak. He was treated initially with anti-inflammatories but required opiates to achieve adequate pain control. Ten days after the onset of pain, he noticed paresthesias extending from his left deltoid down to his forearm and a dull, aching pain which escalated to a sharp sensation with almost any movement.

On general examination there was no swelling of the left arm and peripheral pulses were easily palpated. Motor, reflex, and sensory examinations of the uninvolved limbs were normal. Inspection revealed subtle asymmetries with some loss of muscle bulk in the left suprascapular fossa and the left deltoid. Scapular winging was noted on the left as well. Palpation of the trapezius/suprascapular muscles produced dull pain. Cervical compression tests were negative. Muscle testing revealed weakness of the biceps (4/5), triceps (3/5), supraspinatus (3/5), serratus anterior (2/5), and deltoid (3/5). Distal left upper extremity muscles had normal power. On sensory exam, there was decreased pinprick over the lateral shoulder. His primary care physician calls you for advice on how to proceed.

What do you do now?

This case requires an organized approach to localization. A careful history and physical examination are necessary. The clinical picture described above might bring to mind shoulder pathology secondary to a muscular, ligamentous, or joint process. One such possibility is an impingement syndrome. This would explain his difficulty with abduction and pain/weakness with isolation of the supraspinatus, but muscle atrophy, paresthesias, and sensory changes make a neurogenic etiology much more likely. While cervical spine pathology can be difficult to rule out simply on the basis of physical exam, the pattern of weakness did not point to a single nerve root, as we might expect if this was related to a nerve root impingement.

The weight of the evidence from the history and physical suggests a disorder affecting multiple nerve roots or the brachial plexus. Lack of distal weakness argues against peripheral nerve pathology. Its acute temporal profile suggests a traumatic, vascular, or inflammatory process and argues against infiltrative or compressive etiologies. There is no history of trauma, and the vascular portion of the examination is normal. The clinical presentation is most suggestive of brachial neuritis (brachial plexus neuropathy, acute brachial radiculitis, Parsonage-Turner syndrome, neuralgic amyotrophy, or paralytic brachial neuritis).

At this point, targeted testing is necessary to confirm localization and rule out alternative diagnoses. Initial lab work-up may include a complete blood count, creatine kinase, and hemoglobin A_{1C}. If there is clinical suspicion of human immunodeficiency virus or Lyme disease, these should be tested for as well since their presentation can mimic brachial neuritis. With acute brachial neuritis we would expect these to be normal. A lumbar puncture is not necessary when the clinical picture is suggestive of brachial neuritis. Electromyography typically reveals active denervation in several muscles, and this would correlate with atrophy and weakness. Median and ulnar nerve conduction studies are often normal; however, in many patients with brachial neuritis a reduction in sensory amplitudes may be seen. Motor nerve conduction studies are usually normal unless the paresis is severe. In these cases motor nerve action potentials will be reduced.

A chest radiograph is often obtained to look for evidence of a mass lesion such as an apical lung tumor, but more importantly, it may reveal an elevated hemidiaphragm, suggesting phrenic nerve involvement. Magnetic resonance imaging (MRI) of the cervical spine and plexus is typically

obtained to look for root compression or inflammation. Newer MRI techniques dedicated to peripheral nerve pathology appear to be more sensitive than prior techniques at imaging inflammatory conditions of peripheral nerves. Typically, T2 hyperintensities are seen within the plexus. Lesions have been imaged that may extend more proximally than suggested by clinical and electrophysiological data alone. This might explain involvement of the nerves that exit the plexus proximally such as the long thoracic, the phrenic, or even the dorsal primary rami.

In brachial neuritis, men are affected at more than twice the rate of women. Most are between 20 and 65 years of age. As with our patient, the onset of pain is typically sudden and severe, waking patients at night in more than 50% of cases. The pain is often described as "deep," "stabbing," "throbbing," or "aching." Arm movements typically exacerbate the pain, and coughing and sneezing typically have little effect. The pain tends to subside within several hours to 3 weeks but can last much longer in some. Often, as the pain subsides, weakness is noted. It is frequently not clear how acutely the weakness develops as patients avoid moving the arm due to pain; however, in many cases there is clearly sudden onset of paresis. The weakness can be very dramatic, even to the point of complete paralysis of some muscles. The most frequent presentation involves mainly the upper plexus, and in this form recovery is typically faster. Diffuse involvement is less common, and isolated lower plexus lesions are fairly rare. In fact, in cases where the lower plexus is involved primarily, the probability of a structural lesion is increased. The deltoid, supra- and infraspinatus, serratus, biceps, and triceps are the most commonly affected muscles. In some patients even the phrenic nerve can be involved, producing an elevated hemidiaphragm and shortness of breath. Complete paralysis of involved muscles is common, differentiating this disorder from compressive radiculopathies. Antecedent illness, vaccination, injury, unusual physical activity, or surgeries may be seen within a month of the onset of this condition; but many patients, like our case, cannot recall any such provocative event.

Pain control often requires a long-acting anti-inflammatory, often for several weeks. In addition, co-analgesics such as gabapentin, carbamazepine, or amitriptyline are useful for shooting, neuralgic pain seen later in the course. Physical therapy to maintain strength and mobility is important as many patients will avoid moving the extremity, which can lead to a frozen

shoulder. A sling may be required for support of the shoulder complex, though complete immobility is not advised. Although there are no randomized controlled trials supporting the use of steroids, many believe that they hasten the resolution of pain, especially if used early in the course. We typically use methylprednisolone (Solu-Medrol) 1000 mg per day for 3 days.

The prognosis for full recovery is generally good. Return of strength is often seen by 6–12 weeks, though some cases can take 2–3 years. As might be expected, longer recovery times are often required in lower plexus lesions or in older patients. Some patients have taken several years to regain strength and few never do. One-third of patients may continue to suffer from chronic pain, and the majority have persistent functional deficits after an average follow-up of more than 6 years. In idiopathic brachial neuritis, most cases are monophasic but up to 25% may relapse at some point in their life. This is in contrast to the hereditary form, where repeat attacks can be seen in 75%.

KEY POINTS TO REMEMBER

- **MRI may demonstrate evidence of inflammation in the brachial plexus or peripheral nerves.**
- **Antecedent illness, vaccination, injury, unusual physical activity, or surgeries may occur within a month of onset of brachial neuritis.**
- **Effective pain control and mobilization can reduce the chance of developing a frozen shoulder.**
- **Most cases are monophasic and prognosis is good, though one-third of patients may develop chronic pain.**

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10 Hereditary Neuropathy

A 55-year-old dentist friend of yours accosts you at a social event. He is concerned because he developed right foot weakness after a long airline flight from Hong Kong. He also has some back pain. You notice that the patient has a foot drop on the right when he walks. The following day you see him in consultation. The patient relates that he has always had problems with turning his ankles and difficulty in buying comfortable shoes. The patient also relates a history of numbness of his feet and that at times his hands will go numb. Approximately 10 years ago the patient had a diagnosis of lymphoma and underwent radiation and chemotherapy. Afterward he remembers he had severe numbness of his hands and feet and weakness that took a very long time to improve. On examination the patient has high arches (Fig 10–1) and curled toes. There is distal atrophy of the musculature of the hands and feet. Reflexes are absent in the lower and upper extremities. There is a right foot drop. Sensory examination demonstrates a stocking glove sensory loss of vibration greater than touch and pain sensation.

What do you do now?

The patient has numbness of his feet and hands with a right foot drop. The foot drop occurred after a long airline flight, which could suggest a compression injury to the peroneal nerve or a lumbosacral radiculopathy at the L5 level (Table 10–1). This can be distinguished usually by the presence or absence of radicular symptoms, L5 dermatomal versus peroneal sensory symptoms and signs, and the findings in an L5 radiculopathy of weakness of both the posterior tibialis and peroneus longus muscles, while in a peroneal neuropathy there would not be weakness of the posterior tibialis muscle. In addition, nerve conduction studies (NCS) and electromyography (EMG) would be very helpful in distinguishing a peroneal neuropathy from a lumbosacral radiculopathy. The patient's history of turning his ankles, difficulty in buying comfortable shoes, and numbness of his feet and hands suggests a long-term peripheral neuropathy. It is interesting to note that the patient relates severe numbness and weakness after chemotherapy for lymphoma. One of the medications which is used in standard lymphoma protocols is vincristine. Vincristine causes a sensorimotor peripheral neuropathy. Usually, the symptoms improve after vincristine is stopped; the presence of continued and severe symptoms may suggest an underlying peripheral neuropathy. Taking all of this together with the patient's high arches and curled toes suggests a hereditary peripheral neuropathy.



FIGURE 10-1 Pes cavus.

TABLE 10–1 Features of L5 Radiculopathy Versus Peroneal Neuropathy

	L5 Radiculopathy	Peroneal Neuropathy
Pain	Radicular	Can be at fibular head
Sensory Loss	L5 dermatome	Between great and second toes
Reflexes	AJ depressed	Normal
Mechanical Signs	Straight leg raise	Tinnel's sign at fib head
NCS	F waves prolonged	Abnormal peroneal motor NCS and F waves
EMG Abnormalities	AT PT EHL EDB paraspinals	AT EDB EHL PL

AJ, ankle jerk; NCS, nerve conduction study; AT, anterior tibialis; PT, posterior tibialis; EHL, exterior hallicus longus; EDB, exterior digitorium brevis, peroneus longus; PL.

The patient's history and examination suggest a peripheral neuropathy with a superimposed peroneal neuropathy. When a patient has a peripheral neuropathy, nerves are more susceptible to compression (Table 10–2). This can occur at usual sites of compression: the wrist for the median nerve, elbow for the ulnar nerve, fibular head for the peroneal nerve, spiral groove for the radial nerve, and inguinal area for the lateral femoral cutaneous nerve. At this point it would be very helpful to obtain a complete family history. It is important to ask the correct questions. Asking if anyone in the family has a peripheral neuropathy is not the correct question. It is important to ask specific questions (see Table 10–3): Does anyone in the family have high arches? Does anyone have curled toes? Does anyone have difficulty with buying shoes? Has anyone had casting of the feet as a child? The author remembers as a resident asking a patient with a peripheral neuropathy specific

TABLE 10–2 Common Sites of Compression

Median nerve	Wrist
Ulnar nerve	Elbow, wrist
Radial nerve	Spiral groove, forearm
Lateral femoral cutaneous nerve	Inguinal area
Peroneal nerve	Fibular head
Tibial nerve	Knee (baker's cyst), ankle
Sciatic nerve	Piriformis muscle

TABLE 10-3 Family History Questionnaire

High arches
Curled toes
Soak feet
Twist ankles easily
Use of cane/crutches
Foot surgery
Casting of feet as a child
Corrective shoes
Cramps
Skinny legs
Numbness feet/hands
Difficulty buying shoes
Burning of feet
Painful feet

questions relating to his family history and peripheral neuropathy. The patient denied any family history. As the patient was leaving, his brother was waiting for him. The brother was walking with the aid of two canes. I asked the patient, "I thought you said there was no one in your family with foot problems!" The patient replied, "My bother has bad arthritis." When I examined the brother, he had a severe peripheral neuropathy with high arches and curled toes. The construction of a pedigree chart is helpful, as well as actual examination of relatives. By careful questioning of the patient we were able to ascertain that his father had soaked his feet and had had to use a cane later in life because of weakness in his legs.

In our patient's case it would be helpful to perform EMG and NCS for a number of reasons. By performing the NCS we can ascertain if a peripheral neuropathy is present and, if so, what type. If the conduction velocities are slowed, that would suggest a demyelinative process. If amplitudes of the compound muscle and sensory nerve action potentials are reduced, it is most likely an axonal process. Active denervation on EMG examination would also suggest axonal pathology.

The system for classifying hereditary neuropathies was first developed by Dyck and Lambert. This was based on mode of inheritance and whether by NCS the peripheral neuropathy was demyelinative or axonal. As a result, by performing EMG and NCS we will be able to classify our patient's

peripheral neuropathy. In addition, we will be able to ascertain if the patient has a lumbosacral radiculopathy or a peroneal neuropathy. In a peroneal neuropathy the peroneal nerve conduction will be more affected and active denervation will be confined to the peroneal innervated muscles; the paraspinal muscles will be unremarkable.

The NCS demonstrate a peripheral neuropathy, demyelinative in character with a superimposed right peroneal neuropathy (Table 10–4). Examination by EMG revealed active denervation in the right anterior tibialis, extensor hallicus longus, and extensor digitorum brevis muscles with neuropathic motor units and reduced motor recruitment. This appears to be Charcot-Marie-Tooth (CMT)1A with a superimposed peroneal neuropathy (likely due to compression during the long airline flight). As our knowledge of the genetics of this disorder advances, more precise classification of the hereditary neuropathies is possible.

TABLE 10–4 Nerve Conduction Study of Our Patient

Motor Nerve Conduction

Nerve and Site	Latency	Amplitude	Conduction Velocity
Peroneal.L			
Ankle	6.6 ms	1.0 mV	
Fibula (head)	17.1 ms	0.5 mV	15 m/s
Tibial.R			
Ankle	8.8 ms	4.7 mV	
Popliteal fossa	20.1 ms	4.7 mV	33 m/s

F-Wave Studies

Nerve	F-Latency
Peroneal.L	69.0?
Tibial.R	63.0

Sensory Nerve Conduction

Nerve and Site	Peak Latency	Amplitude	Conduction Velocity
Sural.L			
Lower leg	5.0 ms	7 μV	33 m/s

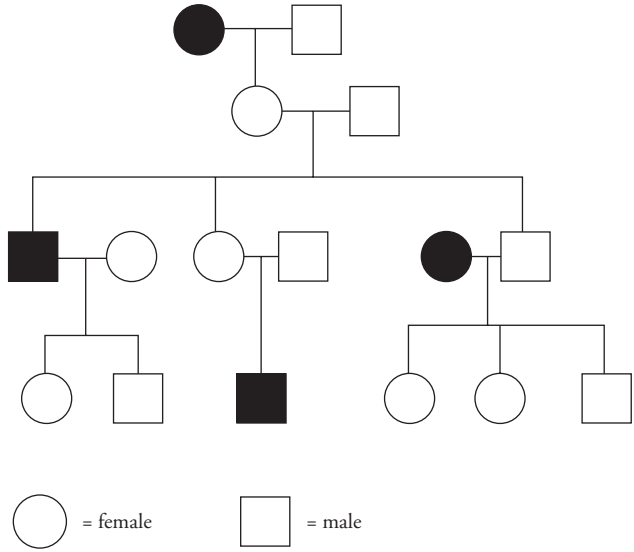


FIGURE 10-2 A pedigree chart of autosomal dominant hereditary neuropathy.

CMT1 A, B, and C are characterized by autosomal dominant inheritance (Fig. 10–2). Onset is usually in the first decade of life, but presentations may be later. There is distal muscle weakness and atrophy. The distal muscle stretch reflexes are absent, and all reflexes may be absent. Sensory loss tends not to be a specific modality. There is palpable nerve enlargement in 50% of cases. The easiest nerves to palpate are the superficial radial and postauricular nerves. There may be a tremor of the upper extremities and hammer toes are common (Fig. 10–1). The NCS reveal uniform slowing, usually by 25% or more of normal. This is a conduction velocity of <40 meters/second in the uppers and <30 meters/second in the lowers. Nerve pathology demonstrates onion bulb formation, loss of myelinated fibers, and thinly myelinated and demyelinated fibers. Gene defects are listed in Table 10–5. The mainstay of treatment is referral to physical therapy and occupational therapy. Patients can benefit from ankle/foot orthoses and adaptive devices for the upper extremity.

CMT2 A, B, and D are also characterized by autosomal dominant inheritance, and onset can be in the first or second decade but may be later. There is distal muscle weakness and atrophy. There is loss of distal muscle stretch

TABLE 10–5 Classification with Gene Abnormality of Demyelinating Autosomal Dominant Charcot-Marie-Tooth (CMT)

Disease	Gene	Location
CMT1A	PMP-22	17 p11
CMT1B	P zero	1q22
CMT 1C	LITAF	16p13
CMT 1D	ERG2	10q21
CMT X[a]	Connexin-32	Xq13
HNPP	PMP-22	17p11

[a]Sex-linked autosomal dominant.

Source: After the Web site of the Neuromuscular Disease Center (Washington University, St. Louis, MO), http://www.neuro.wustl.edu/neuromuscular, by Dr. Alan Pestronk.

reflexes, but a generalized areflexia is less common. Sensory loss is not modality-specific. There are no palpable nerves. Tremor is not present. Pes cavus and hammer toes are present but not always. The NCS show axonal features: reduced or absent sensory nerve action potentials. Motor NCS demonstrate relatively normal conduction velocity. Sural nerve biopsies show myelinated fiber loss and axonal atrophy. Genetic testing is also commercially available for some of these disorders.

There are further classifications of CMT as well as classifications of hereditary sensory neuropathies, with and without autonomic features, and hereditary motor neuropathies (HMN). It is important to remember that HMN may appear to be a slow form of amyotrophic lateral sclerosis; however, there are no upper motor signs, and HMN is usually symmetrical and of a much longer duration.

An additional neuropathy which is worth remembering is hereditary neuropathy with liability to pressure palsies (HNPP). Onset is in the second or third decade but may be later. It usually presents as multiple compression neuropathies. These may occur after surgery, childbirth, or simply sitting for a long period of time (peroneal neuropathy). The patient may have a generalized sensorimotor neuropathy. Patients may present with a painless brachial plexopathy. Usually, muscle stretch reflexes are present. Sensory loss is present in the distribution of the mononeuropathy(ies). Pes cavus may be present. The NCS document the compression neuropathies. There may also be a generalized peripheral neuropathy. On nerve biopsy there is a focal thickening of myelin in a sausage-like formation is seen; these are

called "tomaculi." Usually, there is some improvement in the clinical picture when prevention of nerve compressions is accomplished.

Whether to perform genetic testing of patients is a common question. In our experience, testing patients with CMT1 has a much higher yield then when CMT2 is suspected. We usually do not test unless there are atypical features, such as severe and rapid progression, or specifically requested by family members. We do not routinely screen all peripheral neuropathy patients for CMT. Nerve biopsy is usually not needed in the diagnosis of hereditary peripheral neuropathies.

Our patient was adamant in confirming his diagnosis by genetic testing. He had CMT1A with a point mutation of the PMP22 gene. His foot drop improved with physical therapy and precautions to avoid compression. Issues of proper foot care were also addressed. His family was referred for genetic counseling since his 16-year-old son noted frequent ankle sprains while playing basketball.

KEY POINTS TO REMEMBER

- Hereditary neuropathies may be undiagnosed until the patient has a compression neuropathy, orthopedic foot problems, or a persistent severe peripheral neuropathy after chemotherapy.
- High arches and curled toes are a common accompaniment of hereditary neuropathies.
- It is very important to obtain an extensive and detailed family history when suspecting a hereditary neuropathy.
- Important aspects for the classification of hereditary neuropathies are based on demyelinative versus axonal features on NCS and the mode of inheritance.
- New genetic information is assisting in the classification of these neuropathies, and commercial testing is available.
- The HNPP form presents as multiple compression neuropathies.

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11 Critical Illness Neuropathy

A 63-year-old male, status post–motorcycle collision was admitted to the intensive care unit (ICU) 20 days prior to this consultation. He was not wearing a helmet and was alert and oriented at the scene, where he was moving all four extremities. Initial injuries included multiple fractures, a pulmonary contusion, pleural effusions, a right subdural hematoma with minimal mass effect, and a splenic rupture. He was taken to the operating room emergently for a splenectomy. Later, computed tomography of the chest revealed bilateral hemothoraces. His hospital course was complicated by sepsis secondary to bilateral lower lobe pneumonia. He eventually required a gastrostomy tube placement and tracheostomy. On hospital day 20, after tapering sedating medications, it was noted that he was not moving his extremities though other parameters were improving. You are consulted for severe flaccid weakness of all four extremities.

Review of laboratory data reveals an elevated white count at 24,000, (trending downwards) persistent anemia; thrombocytosis; hypoalbuminemia; as well as

negative urine, blood, and sputum cultures. Cerebrospinal fluid (CSF) and electrolytes are normal. Creatine kinase (CK), though elevated earlier in the hospital course, is now normal. The remainder of the history (obtained from family) is unremarkable. Review of a recent magnetic resonance image of his brain and cervical spine reveals only a temporal lobe contusion and the previously visualized subdural hematoma. Specifically, the cervical cord and brainstem appear intact. His electroencephalogram (EEG) reveals mild frontal slowing but no epileptiform activity. Review of the chart does not disclose any rapid fluctuations of sodium. He still requires mild sedation. On examination his eyes are open but he exhibits minimal interaction with his surrounding environment. He does not follow any commands. Blink to threat is intact. His pupils are equal and reactive, though sluggish. Corneal reflexes are present. On motor examination, his extremities are flaccid and do not move spontaneously or with stimulation. He is areflexic, and his toes do not respond to plantar stimulation.

What do you do now?

The evaluation of severe weakness in the ICU requires an organized approach. Many patients in the ICU require medications that may cause neuromuscular weakness, so this needs to be checked carefully. The history is often impossible to obtain, and the value of the neurological examination is often limited due to inability of the patient to cooperate, or the use of sedating medications as in this case.

This patient's prior medical history, obtained from his wife, did not disclose either a reason for his accident or an independent reason for his continued weakness. Examples of this might include a previously known neuromuscular disease (e.g., myasthenia gravis), a myopathy, or a neuropathic process.

His examination, though limited, does not seem to suggest a central etiology, although the lack of upper motor neuron signs in critically ill patients may be unreliable. For example, both peripheral motor and sensory pathways need to be intact to produce upgoing toes, hyperactive reflexes, or spasticity. In addition, while cord or brainstem trauma might be suspected due to the nature of his injury, he did not have prominent spinal shock at the scene and imaging does not explain his flaccid weakness.

Nerve conduction velocity (NCV) and electromyography (EMG) can be useful in further localization. In cases like this, low-amplitude compound muscle action potentials (CMAPs), nerve action potentials with near normal conduction velocities, and evidence of mild active denervation might be expected. This pattern is consistent with generalized axonopathy and is often seen in the ICU. Slowed NCV or conduction block would not be consistent with critical illness polyneuropathy (CIP). Testing of the neuromuscular junction is done with repetitive stimulation. Train-of-four stimulation is used to assess the level of neuromuscular blockade, an important consideration in many patients in the ICU.

Critically ill patients frequently have severe electrolyte abnormalities, and rapid correction of sodium disturbances can cause central pontine myelinolysis. This condition produces the locked-in state in which the patient, though awake and alert, can move only his or her eyes. For this reason, it is imperative that there is some attempt to communicate with these patients through the use of eye movements. In this case, there was no history of overly rapid correction and imaging did not reveal any white matter abnormalities.

Antecedent illness, surgery, and trauma can also herald an episode of Guillain-Barré syndrome, a condition that can cause a rapidly ascending weakness that frequently requires intubation. Normal CSF in this case helps to rule this out. Presence of albuminocytological disassociation in the CSF would have supported a diagnosis of GBS. In addition, his EMG/NCV studies suggest an axonal etiology, which is rare (about 5%) in Guillain-Barré syndrome, making this less likely.

Muscle biopsy is useful in cases where the diagnosis is not clear and helps to distinguish neuropathy from myopathy, but is not routinely used in this situation. In some cases, it can identify a specific etiology, such as dermatomyositis, polymyositis, or a mitochondrial myopathy. Nerve biopsy is usually not helpful in these patients unless vasculitis is suspected. Vasculitis typically presents as a mononeuritis multiplex, but with diffuse involvement it can mimic a symmetrical axonal polyneuropathy.

Given his EMG findings and clinical picture, the most likely etiology is CIP or critical illness neuromyopathy. Neuromuscular disorders caused by critical illness are now recognized as the most important cause of newly acquired weakness in the ICU. "Critical illness" in this context refers to the syndrome of sepsis and multiple organ failure. "Sepsis" refers to the presence of the systemic inflammatory response syndrome (SIRS) caused by a known infection. While it is not clear what the prevalence of CIP is in SIRS alone, in sepsis some report its prevalence may be as high as 50%–70%. The occurrence of CIP, however, is very difficult to estimate. While the neurological examination is likely much less sensitive than electrophysiological studies, many of the additional cases picked up by EMG/NCV testing may be of limited clinical relevance. Finally, the timing of the evaluation is relevant since the condition often improves.

Patients with CIP develop distal weakness with depressed reflexes and frequently fail to wean from the ventilator. Cranial nerve abnormalities in CIP are rare and should suggest an alternative diagnosis. The condition has been associated with increased ICU stay, elevated serum glucose levels, and decreased serum albumin levels. The occurrence of CIP also correlates with the duration of ICU stay and severity of sepsis.

Severe weakness, elevated CK, and a myopathic pattern on EMG in critically ill patients, on the other hand, suggest critical illness myopathy. These patients often cannot adequately activate the muscle and demonstrate

the low amplitudes and early recruitment patterns typical of a myopathic process. Direct muscle stimulation can be useful in these cases. With this test, the muscle is stimulated directly, distal to the motor point, with recording of the motor unit potential (MUP) from the same muscle. This is compared to the MUP on that muscle when the nerve is stimulated. In a neuropathic process, stimulation of the nerve will produce a small MUP, while direct stimulation will produce a robust MUP. In a myopathic process, both responses will be small. While the technique seems simple, it is actually technically demanding and requires practice to obtain reliable results.

While sepsis is the most important risk factor for the development of critical illness myopathy, high-dose steroids, nondepolarizing neuromuscular blocking agents, and sedating agents such as propofol all confer additional risk. In addition, at least 33% of ICU patients treated for status asthmaticus develop critical illness myopathy. While many clinicians tend to split critical illness neuropathy and myopathy, this distinction may be artificial. In reality, most critically ill patients who develop severe weakness have some component of both when both electrodiagnostic studies and pathology are considered.

There is no specific treatment for critical illness neuropathy or myopathy. It revolves around medical management of the underlying disorder including prevention and management of sepsis, SIRS, and organ damage. Corticosteroids and neuromuscular blocking agents should be avoided if possible. Aggressive physical therapy at the time of diagnosis is helpful. This should start with stretching and passive range-of-motion exercises to avoid joint contractures and maintain mobility. Therapy is advanced as tolerated, and many patients require inpatient rehabilitation. Skin care will minimize breakdown, and respiratory therapy is used to limit the risk of additional pulmonary infection.

Long-term studies of prognosis in CIP and critical illness myopathy are lacking. Of patients who survive, those with mild polyneuropathy may recover within weeks and those with moderate to severe polyneuropathy within months. Most will probably have some persistent weakness. In patients with CIP and critical illness myopathy, higher levels of axonal loss, presence of necrosis on muscle biopsy, and higher CPK tend to have a worse outcome.

KEY POINTS TO REMEMBER

- Review of medications is an important place to start in sorting out neuromuscular weakness, especially in critically ill patients.
- Family members and witnesses can often provide valuable historical information in these patients. The extra effort to seek them out is often rewarded.
- It is important to consider a locked-in state in the differential of critically ill patients with weakness.
- EMG and NCV testing can be helpful in further localizing the lesion in these patients.
- The distinction between critical illness neuropathy and myopathy may be artificial and of limited clinical utility.
- In patients with CIP and critical illness myopathy, higher levels of axonal loss, necrosis on muscle biopsy, and higher CK levels are associated with a poorer prognosis.

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12 Chronic Inflammatory Demyelinating Polyneuropathy

A 55-year-old female presents with a 4-month history of slowly progressive weakness. She is having difficulty turning in bed and opening bottles. She also feels unsteady on her feet. She admits to tingling in her hands and feet. Past medical history is significant for type 2 diabetes (recent HBA_{1c} 7.8) and possible multiple sclerosis (MS). The diagnosis of MS was entertained 3 years ago when she was admitted for bifacial weakness. Magnetic resonance imaging (MRI) at the time showed several nonspecific subcortical signal changes. Lumbar puncture (LP) revealed a protein of 60 but otherwise was normal, including oligoclonal bands, immunoglobulin G index, and cytology. She made a full recovery about 1 month later. Family history is significant for "neuropathy" in her father that first manifested in his forties. Neurological exam is significant for 4/5 strength in all extremities. Sensory exam shows impaired vibratory and joint position sense in the toes and impaired vibratory sense in the fingers. There is mildly altered light touch and temperature sensation in the hands and feet. Reflexes are trace throughout. Cerebellar testing is normal. Gait is

mildly ataxic with a normal base, there is significant postural instability, and Romberg is positive. She does not have high arches or hammer toes. The primary care physician obtained an MRI of the brain and cervical spine that shows no new lesions. Routine labs, creatine kinase (CK), thyroid-stimulating hormone, and vitamin B_{12} are normal. Electromyography/nerve conduction studies (EMG/NCS) are consistent with a chronic generalized polyneuropathy that has demyelinating and axonal features. There is also active denervation in several distal muscles.

What do you do now?

This is a complex case with many variables. She does have evidence of a generalized polyneuropathy on EMG/NCS, which is commonly seen in patients with diabetes. Although demyelinating features may occasionally be seen in diabetes, other more common causes of a demyelinating peripheral neuropathy need to be considered. She does have a family history of neuropathy, but demyelinating hereditary peripheral neuropathy typically manifests at an earlier age. She also does not have any findings on foot inspection to suggest a hereditary neuropathy. Her proximal weakness, diffuse hyporeflexia, and sensory deficits are commonly seen in chronic inflammatory demyelinating polyneuropathy (CIDP). A useful concept to keep in mind is that the clinical pattern and laboratory features of CIDP are similar to those of Guillain-Barré syndrome (GBS, see Chapter 6), but the time course of progression over months to years (minimum 8 weeks) is very characteristic of CIDP. In contrast to GBS, CIDP is usually not clearly preceded by infection. Also, in CIDP distal sensory exam finding are frequently present, though vibration and joint position are more affected than the other sensory modalities. A superimposed myopathy could explain the patient's proximal weakness and hyporeflexia (although usually reflexes are normal in myopathy). However, there is no evidence of myopathy on EMG/NCS, and the CK is normal. Motor neuron disease (MND) would also be in the differential; however, the patient's impressive sensory exam findings and demyelinating features on her NCS are not consistent with MND. Of note, there is a rare pure motor variant of CIDP that often has bulbar findings which can mimic MND.

What about the history of possible MS and the brain MRI findings? Since the MRI from 3 years ago is stable and her past LP was negative for oligoclonal bands, it is highly unlikely that she has MS. Although nonspecific white matter changes often have no known etiology (and she does have a history of diabetes, which can cause small vessel MRI changes), is there any other explanation? Is there any way to tie the MRI findings into this clinical picture, and should she have any more tests?

Facial weakness, which occurred in our patient 3 years ago, is seen in 15% of CIDP patients (other cranial nerve findings, such as oculomotor nerve palsies, are much less frequent). The time course of CIDP can fit with the patient's admission 3 years ago as one-third of patients have a relapsing course with partial or complete recovery. The other two-thirds have a

progressive course over months to years. Of note, the typical age at onset is 50–70 years, and patients in this age range often have a progressive course. Younger patients typically have a relapsing course. Also, CIDP is one possible explanation for the patient's abnormal brain imaging. Brain demyelination has occasionally been reported in patients with CIDP.

The thought process for differential diagnosis and investigations (i.e., blood work, LP, EMG/NCS) must focus on the strong possibility of CIDP. This evaluation is very similar to one for possible GBS (see Chapter 6). In CIDP EMG/NCS are comparable to studies in GBS patients who are a few weeks into their illness except that in CIDP there will be chronic neuropathic changes such as large-amplitude, long-duration, polyphasic potentials. The NCS can be very helpful in differentiating CIDP (especially the sensory variant) from diabetic neuropathy because of the demyelinating features of CIDP. However, as mentioned previously, demyelinating features are seen occasionally in diabetes patients. Evidence of conduction block would have pointed further to CIDP. It is also important to note that there are diseases other than diabetes that can be associated with CIDP (Table 12–1).

This patient must have an LP, but since the patient also has diabetes, the results are less helpful as both conditions can lead to elevated protein. Elevated protein is seen in about 90% of patients with CIDP, although it may not show up or be very high in the first few months of the disease. The patient's elevated cerebrospinal fluid (CSF) protein 3 years ago could be secondary to diabetes or CIDP; however, if her repeat LP shows a protein

TABLE 12–1 Systemic Disorders Which May Be Associated with Chronic Inflammatory Demyelinating Polyneuropathy

Monoclonal gammopathy of undetermined significance
Plasma cell dyscrasias
HIV
Chronic active hepatitis
Inflammatory bowel disease
Connective tissue disease
Nephrotic syndrome
Diabetes mellitus
Central nervous system demyelination

of 100 or greater, it is predictive of CIDP. Both conditions have minimal to no cells in the CSF.

Remember to recognize that the neurological exam in diabetic peripheral neuropathy typically reveals distal, predominantly sensory abnormalities As mentioned previously, CIDP typically has both proximal and distal weakness, global rather than isolated distal reflex loss, and sensory findings. Also, impairment of mainly vibration and joint position sense is typical for CIDP because it affects the large myelinated fibers (unusual for diabetes). If the picture is consistent with a predominantly sensory CIDP (5% of cases), it is important to obtain anti-myelin-associated glycoprotein (MAG) and antisulfatide antibodies. In contrast to CIDP, these immunoglobulin M antibody–producing neuropathies have a monoclonal protein that is usually detected with serum protein electrophoresis (SPEP). However, if the SPEP is positive for a monoclonal protein, multiple myeloma must be ruled by a hematologist before these patients can be managed for CIDP.

This patient does not require further imaging, but MRI is often obtained as part of a radiculopathy evaluation. It is important to recognize that enhancement of the lumbar roots is seen in about 60% of CIDP patients. The brachial and/or lumbar sacral plexus can show similar findings. A nerve biopsy is usually not needed to diagnose CIDP. However, it may be considered to rule out other conditions (e.g., vasculitis, sarcoidosis) and/or to support the diagnosis of CIDP in difficult cases. Typically, the sural nerve is chosen, but the superficial radial or superficial peroneal may be considered if the sural nerve is not affected or shows no nerve conduction abnormalities. Note that the biopsy findings of CIDP are nonspecific but there may be evidence of demyelination and remyelination consistent with CIDP. Biopsy may also be normal and can be difficult to interpret in chronic cases due to axonal loss.

After this patient's work-up, if the clinical picture continues to suggest CIDP, immunomodulatory treatment may be very effective. Also, if the patient responds well to treatment, it further supports the diagnosis of CIDP rather than diabetic neuropathy. Medical treatment options and approach for CIDP are very similar to those for myasthenia gravis (see Chapter 25). Periodic infusions of intravenous immunoglobulin are often very effective. However, in contrast to myasthenia gravis, periodic intravenous methylprednisolone (Solu-Medrol) can be an effective, inexpensive

and relatively safe alternative for CIDP treatment (with less risk of long-term complications compared to oral prednisone regimens). It is also important to remember that CIDP patients with elevated immunoglobulin M antibody are typically less responsive to immunomodulatory treatment.

KEY POINTS TO REMEMBER

- Proximal and distal weakness, diffuse hypo-/areflexia, and distal sensory findings are classic for CIDP.
- One-third of patients with CIDP have a relapsing course with partial or complete recovery, whereas the other two-thirds have a progressive course over months to years.
- Diabetes and CIDP are usually associated with high CSF protein, but protein of 100 or greater is predictive of CIDP.
- If there is a monoclonal protein in suspected cases of CIDP, multiple myeloma must be ruled out.
- EMG/NCS are essential for evaluation of possible CIDP, but nerve biopsy may be needed for difficult cases to rule out other conditions such as vasculitis, sarcoidosis, and amyloidosis.

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13 Nutritional Neuropathies

You are asked to urgently evaluate a patient referred by a bariatric surgeon. The patient is a 40-year-old hairdresser who had a body mass index >50 kg/m^2 prior to her bariatric surgery. She had gastric bypass surgery 6 months ago and has lost approximately 30 kg. When you see the patient, she is complaining of balance problems and painful numbness of her legs and hands. The patient admits that she has not regularly attended meetings with the clinic dietitian. She relates that because of financial problems she has not been taking the recommended vitamin and mineral supplementation. In addition, the patient has had regular episodes of vomiting. Despite all of this, the patient is very pleased with her weight loss and feels the vomiting is helping to keep her weight off. Upon further questioning, it sounds as if the patient has features of a "dumping syndrome." On neurological examination the patient has brisk reflexes in the upper extremities and at the knees. Her ankle jerks are absent and toes are extensor. The patient has a positive Romberg sign. On sensory testing

there is decreased vibration sensation to a level above her knees and to the wrists. There are joint position errors at the toes.

What do you do now?

The patient has rapidly lost weight after a gastric bypass procedure. In addition, she has problems of vomiting, dumping syndrome, and not taking vitamin and mineral supplementation. Her clinical picture suggests a peripheral neuropathy. The brisk reflexes, extensor toes, and joint position errors suggest a myelopathy. Vitamin B_{12} deficiency is the most common nutritional deficiency after bariatric surgery. The clinical picture of peripheral neuropathy and a myelopathy is commonly associated with B_{12} deficiency. The pathological changes in the spinal cord are demyelination of the lateral and dorsal columns (Fig. 13–1). Vitamin B_{12} deficiency may be caused by poor absorption due to abnormal interaction of intrinsic factor and B_{12}, inadequate intake, or impaired hydrolysis of B_{12} from dietary protein. As a result, B_{12} supplementation is routine after bariatric surgery. A B_{12} level may not be an adequate assessment for B_{12} deficiency. If the B_{12} level is less than 100, it is usually indicative of B_{12} deficiency. Levels between 100 and 200 pg/ml and sometimes above 300 pg/ml may be associated with B_{12} deficiency. As a result, homocysteine levels and methylmalonic acid levels are very useful. These are metabolites that accumulate when B_{12}-dependent reactions are blocked.

Vitamin B1 or thiamine deficiency may also manifest as a Wernicke's syndrome, an encephalopathy, or peripheral neuropathy. Other deficiency states which may occur after bariatric surgery include folate, vitamin D, iron, copper, and potassium. Copper absorption occurs in the small intestine. Excretion of copper into the gastrointestinal tract is the major pathway

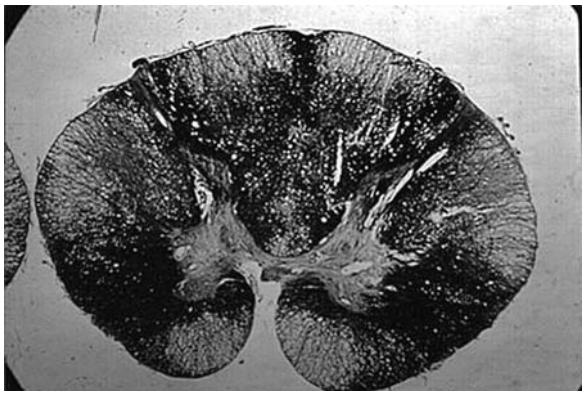


FIGURE 13-1 Illustration of spinal cord in B_{12} deficiency.

that regulates copper homeostasis and prevents deficiency or toxicity. The clinical picture of copper deficiency is very similar to that of B_{12} deficiency. It is a myelopathy and a peripheral neuropathy. Usually, copper is replaced orally, but sometimes intravenous administration is necessary.

As a result, the patient needs to have an adequate assessment of the nutritional status. Our patient was deficient in B_{12}, 100 pg/ml (normal 200–900 pg/ml) and B_1, 30 ng/ml (normal 80–150 ng/ml).

Even though neurological complications of bariatric surgery are well known, unlike in our patient the specific cause of the clinical picture may not be identified. Of patients undergoing surgery for obesity, 5%–16% may have neurological complications. Reviews of the complications of bariatric surgery list peripheral neuropathy as the most common. When peripheral neuropathy occurs, the most common cause identified is thiamine deficiency. Other prospective studies suggest that myelopathy related to B_{12} or copper deficiency is the most common neurological complication. Factors that increase the risk of developing neurological complications include the rate of and absolute weight loss, prolonged gastrointestinal symptoms, failure to attend a nutritional clinic after surgery, less vitamin and mineral supplementation, reduced serum albumin and transferrin levels, postoperative surgical complications requiring hospitalization, and having had a jejunoileal bypass performed (Table 13–1). In a series of bariatric surgery patients with neurological complications, all had protracted vomiting.

The prevention of neurological complications following bariatric surgery is dependent on the close follow-up of these patients. Patients need to attend regular sessions with a dietitian, and adequate nutritional supplementation must be given. Routine surveillance should be done at intervals

TABLE 13-1 Risk Factors for Peripheral Neuropathy After Bariatric Surgery

Fast rate of weight loss and large amount of weight loss
Prolonged gastrointestinal symptoms
Failure to attend a nutritional clinic
Lack of or inadequate vitamin and mineral supplementation
Reduced serum albumin and transferrin levels
Postoperative complications requiring hospitalization
Jejunoileal bypass performed

TABLE 13-2 Recommended Regimen after Bariatric Surgery

Multivitamins with recommended daily allowances[a]
B_{12} 50–200 μg
Supplemental ironCalcium supplement, 1 g of elemental calcium
Copper supplementation?

[a]Folic acid, B_{12}, vitamin D, and iron should be included.

of 3–6 months. Laboratory examinations should include complete blood count, serum iron, iron binding capacity, B_{12}, and alkaline phosphatase. It is unclear whether screening for copper deficiency should be routinely performed. In addition, approximately 1 year after bypass patients will complain of "aches and pains." This is thought to be due to bypass bone disease, which is most likely due to bone demineralization. This syndrome occurs due to impaired calcium absorption and concurrent vitamin D deficiency. Routine vitamin and mineral supplementation should be given (Table 13–2). A multivitamin with recommended daily allowances should be given. It is important to note that even the recommended daily allowances of B_{12} may be inadequate; therefore, additional B_{12}, 50–200 μg, is indicated. Also, supplemental iron is recommended. As a result, the following is recommended: a multivitamin–mineral combination containing B_{12}, folic acid, vitamin D, and iron with an additional iron tablet preferably with vitamin C, additional B_{12} as above, and a calcium supplement equivalent to 1 g of elemental calcium. Continued use of these supplements has been advocated.

A similar picture may also occur in patients with anorexia nervosa and eating disorders. Electrolyte imbalances as a result of induced vomiting or laxative overuse may ensue. We have evaluated patients with severe weakness due to hypokalemia as a result of diuretic and laxative abuse in this situation. Other gastrointestinal conditions can lead to a picture of vitamin and mineral deficiency such as inflammatory bowel disease.

It would be worthwhile at this point to discuss other vitamin deficiency states and their presentation. There are inherited forms of vitamin E deficiency, but more commonly vitamin E deficiency can occur insidiously in the context of gastrointestinal illnesses. These can include hepatobiliary disease, chronic pancreatitis, Crohn's disease, tropical sprue, and celiac disease, as well as patients on total parenteral nutrition. The common denominator of most of these disorders is the interference of the absorption of lipids; in

addition, malnutrition or total parenteral nutrition can be associated with vitamin E deficiency. The clinical features of vitamin E deficiency can include both central (CNS) and peripheral nervous system (PNS) symptoms and signs. The CNS signs can include night blindness, extensor toe signs, tremor, ophthalmoplegia, pigmented retinopathy, dysarthric speech, and tremor. The PNS signs include large fiber loss, resulting in vibratory and joint position sense loss, and absent reflexes; muscle strength may also be affected. The pathology of vitamin E deficiency includes the posterior columns and spinocerebellar tracts, the basal ganglia, and the cerebellum as well as third and fourth cranial nerve nuclei. Pathological changes in the sural nerve are relatively mild. Treatment is with vitamin E replacement.

Thiamine deficiency usually occurs in the context of malnutrition, chronic alcoholism, gastric surgery (bariatric surgery), ulcerative colitis, and hyperemesis gravidarum in pregnancy. Ingested thiamine is absorbed in the small intestine. Absorption may be inhibited by a number of factors including alcohol ingestion, malnutrition, aging, folate deficiency, and concurrent ingestion of antithiamine factors. These factors are present in some raw fish and plants. Thiamine is involved in carbohydrate metabolism and in the formation of myelin. The neuromuscular features of thiamine deficiency include muscle cramping, distal paresthesias affecting the feet with burning pain, distal sensory loss, depressed reflexes, and ankle edema. Autonomic features may be present as well, such as abnormal thermoregulation and gastrointestinal and genitourinary dysfunction. The best laboratory test is erythrocyte transketolase activity before and after the addition of thiamine pyrophosphate. Thiamine levels are more widely available, but they can be unreliable. Nerve conduction studies demonstrate an axonal peripheral neuropathy affecting both sensory and motor nerves, predominantly in the lower extremities. Sural nerve pathology demonstrates large myelinated axonal degeneration. The treatment of thiamine deficiency is thiamine intravenously or intramuscularly, 100 mg daily for 7 days, then 50 mg orally until the response plateaus.

The existence of a unique peripheral neuropathy which is caused directly by the neurotoxic effects of alcohol is controversial. It is unclear whether the peripheral neuropathy seen in chronic alcoholics is a direct toxic effect of alcohol or related to a vitamin and mineral deficiency state. It is said that in some alcoholics with peripheral neuropathy nutritional status is normal.

It has been our experience that the majority of patients with excessive and chronic alcohol usage who have peripheral neuropathy are malnourished. The body mass index is usually normal or decreased, and diet histories show that the majority of the caloric intake is from either alcohol or carbohydrates. Certainly, alcohol consumption can exacerbate a preexisting peripheral neuropathy such as diabetic peripheral neuropathy. The examination in alcoholic peripheral neuropathy is very similar to that in peripheral neuropathy associated with thiamine deficiency. The soles of the feet are very sensitive, and often when testing for the Babinski response the patient has a very painful reaction. The feet often appear red and swollen. Treatment is vitamin and mineral replacement, especially thiamine and B_{12}, and alcohol abstinence. Disulfiram, which is now less commonly used in the treatment of alcoholism, can cause a peripheral neuropathy.

Our patient was treated for her vitamin deficiencies and had some improvement. Also, gastroenterology helped with her vomiting and dumping syndrome. It is important to realize that the neurological deficits associated with B_{12} deficiency may not be completely reversed with treatment.

KEY POINTS TO REMEMBER

- **Vitamin B_{12} and B1 (thiamine) deficiencies may be associated with peripheral neuropathy after bariatric surgery.**
- **Copper deficiency has a similar presentation as B_{12} deficiency; zinc can interfere with copper absorption.**
- **A definitive cause for the bariatric surgery patient's peripheral neuropathy cannot always be found.**
- **Both B_{12} and E deficiency result in CNS and PNS pathology.**
- **It is still unclear whether alcohol causes a peripheral neuropathy by direct toxic effects in an adequately nourished individual.**

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14 Pyridoxine Toxicity

This patient is a 32-year-old female who presented with severe ataxia, worsening over 8 months. She initially noticed that she was unsteady walking at night on uneven ground. This progressed to the point that she required a cane to get around. She has had progressive difficulty with typing as well as manipulating objects with her fingers and can no longer work. Her past medical history was significant only for severe premenstrual syndrome, and she has been very frustrated by swelling of her feet related to this. She denies any medications or supplements with the exception of pyridoxine, which she obtained from an online source. She was using this to treat her edema. Her initial doses were 500 mg/day, but in the past 4 months she has escalated this to 3 g/day. Her new primary care physician suggested that she discontinue pyridoxine about 1 month ago and referred her to neurology for further work-up. At her initial neurology visit, her symptoms were unchanged.

On examination, her reflexes are absent in the lower extremities and trace in the upper extremities. She has remarkable loss of joint position sense; light touch,

pinprick, and temperature sensation in the upper and lower extremities; as well as mildly decreased sensation to light touch, pinprick, and temperature in a perioral distribution. She has mild difficulty with finger-to-nose testing with her eyes open, which becomes worse with her eyes closed. Her gait is severely ataxic with a broad base and requires the use of a cane. She has a positive Romberg test. She is wondering whether this was all caused by pyridoxine supplementation and is fearful it will be permanent.

What do you do now?

The presence of severe progressive global sensory impairment in the absence of motor impairment and lack of any evidence on history and examination to suggest a central lesion strongly suggests a sensory neuropathy or even neuronopathy as the cause. With all neuropathies, careful attention to medications known to cause neuropathy is essential (Table 14–1).

After the history and examination, additional targeted studies are used to better characterize the problem. Nerve conduction studies (NCS) with electromyography (EMG) are typically used to both provide objective evidence of neuropathy and to further help with localization. This patient should be strongly suspected of having a pyridoxine neuropathy or neuronopathy, given her history. In these cases NCS typically reveal moderately slow to absent distal sensory nerve conductions with low amplitudes and preservation of motor nerve conduction velocities. Needle EMG is typically normal. Even in cases where the diagnosis seems certain, there should be

TABLE 14-1 Selected Medications Associated with Neuropathy

Colchicine
Dapsone
Disulfiram
Gangliosides
Gold salts
HMG-CoA reductase inhibitors
Hydralazine
Isoniazid
Metronidazole
Misonidazole
Nitrofurantoin
Nondepolarizing neuromuscular blockers
Nucleoside analogues
Penicillamine
Phenytoin
Pyridoxine
Sulfasalazine
Suramin sodium
Tacrolimus
Paclitaxel
Thalidomide
Vidarabine
Vincristine

Source: Peltier AC, Russell JW. Advances in understanding drug-induced neuropathies. Drug Saf 2006;29(1):23-30.

at least some basic work-up done to rule out other common, treatable causes of neuropathy. Laboratory work-up typically includes thyroid-stimulating hormone; complete blood count and differential; antinuclear antibody, electrolyte, vitamin B_{12}, folate, and vitamin E levels; a Lyme titer; rapid plasma reagin; and a glycosylated hemoglobin level. If appropriate risk factors are present, human immunodeficiency virus should be tested for as well. Cerebrospinal fluid should also be obtained. While this would typically be normal in a pyridoxine-induced neuropathy, chronic immune-mediated neuropathies remain on the differential and are potentially treatable with intravenous immunoglobulin, plasmapheresis, or other immune modulating therapies. Other entities to be considered in similar presentations include Sjögren syndrome, and paraneoplastic sensory neuropathies.

Pyridoxine has been recommended for premenstrual syndrome, hyperemesis gravidarum, carpal tunnel syndrome, autism, schizophrenia, and hyperkinesis, though there is no evidence that any of these are caused by deficiency states. Many patients assume that since it is a water-soluble vitamin, it is safe, leading to dose escalation. Pyridoxine-induced neuropathy typically produces a syndrome very similar to the case described with early and progressive sensory ataxia, initially in a stocking glove distribution and later even affecting the face in a perioral distribution. All sensory modalities and fiber types are affected, though there may also be a predilection for larger fibers. Pathology reveals axonal degeneration, though biopsy is not necessary. Muscle stretch reflexes are typically absent and central signs are lacking, though L'hermitte's sign has been described in some cases. Typical daily doses that cause neuropathy range from 2–6 g, but chronic lower doses in the range of 200 mg/day have also produced striking neuropathies. Nerve biopsy should not be necessary, though histopathological examination of nerves after megadoses of pyridoxine in dogs has revealed selective degeneration of the sensory neurons of the dorsal root. Studies with smaller doses have revealed that fiber degeneration was more severe distally, with relative sparing of the cell bodies. Direct toxicity to nerve cells has been demonstrated in cell culture, with low doses causing inhibition of axon sprouting and large doses producing cell death. This and the relative permeability of the blood–nerve barrier at the level of the dorsal root ganglion compared to elsewhere may explain why this syndrome causes a neuronopathy.

Obviously, treatment involves discontinuing pyridoxine supplementation. Patients often have some improvement over time. When our patient stopped pyridoxine supplementation, she did not see improvement; and by the time she arrived in our office, she was very frustrated. This is not unexpected; in one prospective series, "coasting" was demonstrated. That is, symptoms of toxicity continued to progress for 2–3 weeks after discontinuation of pyridoxine supplementation. This and the very slow improvement described in the early series on this disorder suggest that many patients will demonstrate improvement but it may take a very long time. Patients with more severe involvement will have only limited recovery or no recovery at all.

Lessons learned from pyridoxine and other toxicity syndromes underscore the importance of an accurate dietary history, including any food or vitamin supplements, extreme diets, and history of bariatric surgery. One example is licorice toxicity. It is more widely used outside the United States as an alternative treatment for several ailments; it has mineralocorticoid and glucocorticoid properties and can cause hypertension, edema, weakness, muscle spasm, and metabolic acidosis. Another is l-tryptophan, which can cause an eosinophilic myalgia syndrome with neuritis. The internet provides patients with ready access to information, often of dubious quality, as well as the opportunity to buy exotic, untested substances in large doses. It is not surprising that obtaining this often overlooked portion of the history can be the key step in diagnosing these conditions.

KEY POINTS TO REMEMBER

- Pyridoxine toxicity has been associated with severe sensory neuropathy or neuronopathy affecting all fiber types.
- Recovery from pyridoxine neuropathy can be delayed significantly after discontinuing supplementation. Some patients may not recover at all.
- While most cases have been reported with high doses (2–6 g), some reports of striking neuropathy have been described on doses as low as 200 mg/day.
- The food supplement industry and Internet resources make unusual dietary practices and alternative treatment commonplace. Obtaining an accurate dietary history may be the critical step in diagnosing these conditions.

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15 Vasculitic Neuropathy

A local neurologist calls for advice regarding a 55-year-old female who presents with a pattern of mononeuritis multiplex neuropathy. Six months prior she developed an acute painful right foot drop with sensory loss confirmed as peroneal neuropathy by electromyography/nerve conduction studies (EMG/NCS), and 2 months prior she developed left hand weakness and sensory loss confirmed as ulnar neuropathy. She has no history of rheumatological conditions and takes only hydrochlorothiazide for hypertension. Family and social history are noncontributory. She has no systemic complaints on review of symptoms. Labs are unremarkable including B_{12}, thyroid-stimulating hormone, serum protein electrophoresis, antinuclear antibodies (ANA), rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), C-reactive protein, C and P antineutrophil cytoplasmic autoantibodies (ANCA), HbA_{1c}, Lyme serologies, and angiotensin-converting enzyme (ACE) level.

What do you do now?

At first glance, the possibility of vasculitis may seem low as vasculitic neuropathy is most often secondary to a systemic vasculitis such as Wegener granulomatosis, polyarteritis nodosa, Churg-Strauss syndrome, or systemic lupus erythematosus. However, this patient could have an isolated peripheral nervous system vasculitis (nonsystemic vasculitic neuropathy). Her clinical presentation is consistent with classic vasculitic neuropathy as ischemic injury to the nerve leads to abrupt-onset, painful, focal, or multifocal sensorimotor neuropathy. Her neuropathy classification as a mononeuritis multiplex pattern is correct as two or more nerves are involved. This is the most specific pattern for vasculitic neuropathy. As in this case, the distal portion of longer nerves tends to be most affected. Foot drop from peroneal involvement is the most common initial presentation. It is important to note the less common presentations as there may be a more symmetric pattern, although sequential nerve involvement is often discovered with a careful history. Also, the course of vasculitic neuropathy can be more insidious and at times even painless.

This patient's lack of systemic symptoms must not deter from further investigation for vasculitis as systemic symptoms are typically absent in nonsystemic vasculitic neuropathy. It was appropriate for the neurologist to obtain a vasculitis serological screen in this case. However, vasculitis serological markers are frequently normal in nonsystemic vasculitic neuropathy (as was the case for this patient). A vasculitis screen for neuropathy cases with lower index of suspicion includes ANA, ESR, RF, and C and P ANCA. As the index of suspicion is much higher for a vasculitis in this patient, other laboratory studies should be obtained. These include extractable nuclear antigens, anti-double-stranded DNA (especially if ANA-positive but even if it is not), hepatitis B and C serologies, human immunodeficiency virus (HIV) antibodies, and complement levels (see Table 15–1). Cryoglobulins may be considered if the patient is positive for hepatitis C or RF. It is useful to know that the polyclonal immunoglobulins in mixed cryoglobulinemia always demonstrate reactivity to RF. Hepatitis B (associated with polyarteritis nodosa), hepatitis C (positive in 80% of cases of cryoglobulinemia), and HIV can directly or indirectly lead to vasculitic neuropathy. It is also important to exclude these conditions because immunosuppressive vasculitis treatment can lead to worsening viremia.

TABLE 15-1 Serologies to Consider for Possible Vasculitic Neuropathy

ANA
Anti-double-stranded DNA
Antibodies to ENA (e.g., anti-Ro/La)
ANCA (C and P)
Rheumatoid factorComplement levels (C3 and C4)
Cryoglobulins
ESR and CRP
Hepatitis C and B serologies
Lyme serologies
HIV antibodies
ACE level
Paraneoplastic antibodies (e.g., anti-Hu and anti-CRMP5)

ANA, antinuclear antibodies; ENA, extractable nuclear antigens; ANCA, antineutrophil cytoplasmic autoantibody; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; HIV, human immunodeficiency virus; ACE, angiotensin-converting enzyme.

There is no clear indication for lumbar puncture to diagnose vasculitic neuropathy. The spinal fluid may have elevated protein and/or cells or can even be normal. The EMG/NCS in nerves affected by vasculitis typically show an axonal pattern, often with evidence of denervation. Radicular or plexus involvement can also occasionally occur.

Nerve with or without muscle biopsy will be required to make the diagnosis of vasculitic neuropathy. Nerve biopsy is typically from a sensory nerve that is clinically involved. The sural is the most common site and should be chosen if this patient's NCS show an abnormal sural response. The superficial peroneal and superficial radial nerves are less common alternatives. There is evidence that a combined nerve and muscle biopsy has higher sensitivity versus a nerve biopsy alone for diagnostic confirmation of vasculitis. Along with the typical risks of biopsy (e.g., infection, bleeding), the patient must be informed that anesthesia of the skin supplied by the biopsied nerve is expected and occasionally patients develop chronic pain after nerve biopsy. The biopsy may also show pathological findings of sarcoidosis or lymphoma, which can occasionally present with a mononeuritis multiplex pattern. However, this patient's clinical presentation and lab results were not suggestive of these diagnoses. Although this patient does not have diabetes, keep in mind that it can occasionally lead to a painful

vasculitic mononeuritis multiplex pattern and is often associated with weight loss (also commonly seen in vasculitis). As a paraneoplastic process can result in vasculitis, a malignancy evaluation should be done if vasculitic neuropathy is confirmed (see Chapter 19).

It is important to manage systemic vasculitis with a rheumatologist. Nonsystemic vasculitis has a much better prognosis; immunosuppressive treatment is less aggressive, but it is best to have a rheumatologist's assessment and follow-up of the patient. The neurologist's role is usually focused on the assessment of treatment response. There is no conclusive evidence on how to treat nonsystemic vasculitis. Mild cases may be treated with steroids alone, but there should be a low threshold to add cyclophosphamide. A typical starting dose for prednisone is 1 mg/kg daily or intravenous methylprednisolone (Solu-Medrol) 1 g for 3 days before switching to prednisone. Once stable on cyclophosphamide for a few months, the rheumatologist will typically discontinue it and then start a less toxic immunotherapy such as methotrexate. Then, in a couple of months, a slow steroid taper is initiated (usually over about 6 months). If still in remission, the methotrexate is then often stopped. It is important to be aware that new nerve infarctions can occur for up to several weeks after commencement of therapy. Treatment may not need to be intensified if this situation occurs.

KEY POINTS TO REMEMBER

- **The most specific pattern for vasculitic neuropathy is mononeuritis multiplex; however, some patients may present with a symmetric polyneuropathy.**
- **Vasculitis serological markers are frequently normal in nonsystemic vasculitic neuropathy.**
- **Consider a combined nerve and muscle biopsy to increase diagnostic yield, but at least a nerve biopsy must be done before considering potentially toxic immunosuppressive treatments.**

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16 Piriformis Syndrome

This patient is a 66-year-old female who presents with pain extending from her right buttock down her leg. It started with a slip and fall injury several months ago in which she landed on her buttocks; since then she has had intermittent pain along with numbness and tingling. The pain extends down the posterior aspect of her right thigh, the lateral aspect of her right calf, and even into the foot at times. Over the past 4–5 weeks, the pain has been increasing in severity, and she now has right lateral foot numbness as well. She often feels some minor improvement when crossing her right leg over her left while sitting. The pain is worse when sitting, especially for long periods of time. She denies any weakness in her legs, back pain, or bowel or bladder changes. Coughing, sneezing, and straining do not exacerbate her symptoms. Her medications include aspirin, enalapril, and atenolol. Her past medical history, family history, and social history were otherwise noncontributory. The straight leg raise test is reported as very painful and clearly reproduces her symptoms.

Prior to our evaluation, she had radiographs of the pelvis and knee as well as an ultrasound to look for a deep vein thrombosis, but these were negative. An outside magnetic resonance image (MRI) of the lumbosacral region was also done but revealed only mild degenerative changes with no sign of nerve root compression. She is referred to you because of possible radiculopathy in spite of her negative MRI scan.

What do you do now?

The work-up should begin with a careful observation and examination of the patient. At presentation, she was generally uncomfortable and unable to sit, pacing the room for most of the visit. She had difficulty with parts of the motor examination on the right, mainly due to pain, but generally power seemed normal. On sensory exam, she had reduced sensation to pinprick on the right lateral foot, but both vibratory and joint position sensation at the great toe were normal. Deep palpation over the sciatic notch reproduced her symptoms; while this finding might suggest piriformis involvement, it is very nonspecific and often seen with radiculopathy. The straight leg raise test produced a pain finding in the region of the sciatic notch on the right at 45 degrees with some radiation into her posterior thigh. At 40 degrees, with foot dorsiflexion (which stretches the sciatic nerve but not the hamstrings), this finding was reproduced, suggesting sciatic irritation. In the seated position, resisted active external rotation of the right hip from a position of full passive internal rotation exacerbated the pain.

This history and examination suggest sciatica as the source of her symptoms. Sciatica is an undifferentiated problem with many potential etiologies. The most common cause is nerve root compression, commonly as a result of a herniated nucleus pulposus in the lumbar region. Additional sources of sciatica include spinal stenosis, or a pelvic outlet entrapment such as piriformis syndrome. Facet syndrome can also produce leg pain. Spinal stenosis typically causes patients to walk with a stooped posture and prefer sitting, in contrast to pelvic outlet entrapment syndromes, in which sitting becomes extremely painful.

The negative MRI of the lumbosacral spine along with the characteristic historical and examination findings listed in this case should suggest an extraspinal source of compression. Any irritation of the sciatic nerve can produce a similar pattern with radiation into the posterior thigh, usually passing the knee. Extraspinal compression of the sciatic nerve is possible in close proximity to the sciatic notch. Sources can include inflamed or contracted hip rotators (including the piriformis muscle), aneurysms or arterial malformations, tumors, endometriosis, adhesions after total hip replacement, and malunited fractures. With this list, it should be clear that additional imaging is necessary at this point.

While computed tomographic scans (CT) are insensitive for identifying sources of sciatic compression, MRI can be helpful. As with all MRI scans,

planning of the scan requires a specific clinical indication to optimize the selection of appropriate sequences. While it is still important to search for evidence of mass lesions that could compress the sciatic nerve, there are also findings that can help confirm sciatic compression rather than simply rule out competing alternatives. Patients with piriformis syndrome will often have an enlarged or swollen piriformis muscle on MRI. In addition, magnetic resonance neurography (MRN) may markedly increase our sensitivity for establishing the site of the lesion. MRN suppresses the signal from tissue adjacent to nerves, allowing increased water content at the site of pathology to be better appreciated. In one study, MRN was able to demonstrate increased signal in the sciatic nerve at the level of the sciatic foramen in 12 of 14 patients. These techniques represent a considerable advancement in our ability to identify nerve pathology (Fig. 16–1).

Although the possible etiologies listed above need to be at least considered and to some extent investigated, this case sounds most suggestive of entrapment of the sciatic nerve under the piriformis muscle. The concept of a "piriformis syndrome" has fallen into and out of favor over the years. The argument is that the close approximation of the sciatic nerve to the piriformis muscle produces a vulnerability to this syndrome. Anatomically, the piriformis is a deep external rotator of the hip which passes from the anterior sacrum through the sciatic notch to insert on the upper border of the greater trochanter. The sciatic nerve runs directly under the piriformis muscle in most cases. The syndrome is typically brought on after blunt trauma or a fall on the buttocks. Pain usually extends down the posterior aspect of the thigh and into the leg. Atrophy of gluteal muscles has been described in long-standing cases. Although any maneuver, posture, or position that stretches the sciatic nerve can exacerbate the pain, the most common sign is inability to sit on the affected side. Another physical finding with some specificity is pain in flexion, adduction, and internal rotation (FADIR) of the hip. Patients may also complain of dyspareunia and pain with bowel movements. Sometimes pain can be relieved by traction and external rotation of the lower extremity.

Cadaver studies suggest that anatomical variation might explain this syndrome. The sciatic nerve pierces the piriformis in 22% of cases, presumably increasing the likelihood of compression. In one case, MR findings diagnosed anomalous portions of the piriformis muscle that compressed the S2 nerve

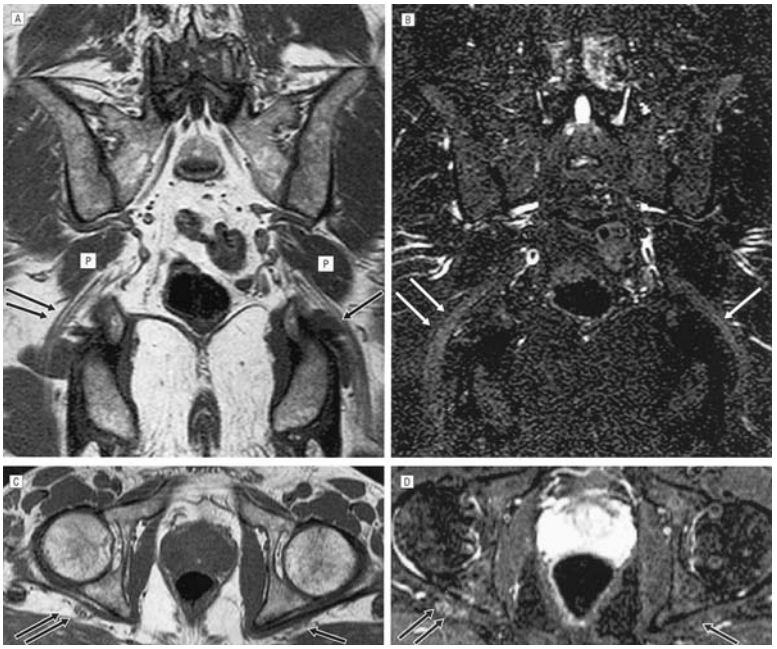


FIGURE 16-1 Coronal and axial T1-weighted (*A, C*) and short tau inversion recovery (STIR) (*B, D*) sequences through the lumbosacral plexus and sciatic nerves bilaterally. *A, C*, The anatomical T1-weighted sequences demonstrate the course of the sciatic nerves (*double* and *single arrows*) exiting the sciatic notch beneath the piriformis muscles (p). *B, D*, The STIR sequences demonstrate the right sciatic nerve (*double arrows*) to be larger and higher in signal compared with the left sciatic nerve (*single arrows*) as it exits the sciatic notch. Source: Lewis AM, Layzer R, et al. Magnetic resonance neurography in extraspinal sciatica. Arch Neurol 2006;63(10):1469–1472. Copyright © 2006, American Medical Association.

just as it left the S2 foramen. Surgical release led to immediate and lasting relief. There are strong arguments, however, that the effect of anatomical variation is small. In cases where these anatomical anomalies are found, they are bilateral in 90%, yet the syndrome is almost always unilateral. In addition, the posterior tibial nerve is the most commonly affected, while the common peroneal nerve is much more often found to divide the piriformis. Finally, the incidence of anatomical variability in the general population is the same as for patients with piriformis syndrome who undergo surgery.

Electromyography (EMG) can also be helpful in further localizing the lesion, especially in cases of piriformis syndrome. Evidence of paraspinal

muscle denervation suggests a root lesion and would not be expected in most cases of extraspinal compression. Since the inferior gluteal nerve innervating the gluteus maximus may also be compressed in piriformis syndrome, this muscle may reveal signs of denervation as well. The H-reflex can be particularly helpful since both the afferent and efferent limbs are compressed with the same lesion, leading to a very prolonged response.

Historically, piriformis syndrome has been a diagnosis of exclusion. With advances in technology, including improved MR and neurophysiological techniques, we can localize the lesion much more accurately than was previously possible. This should lead to a positive diagnosis of piriformis syndrome with increasing frequency.

Treatment of piriformis syndrome is typically conservative, with nonsteroidal anti-inflammatory drugs, analgesics, and occasionally muscle relaxants. Ultrasound and physical therapy with a focus on stretching programs have been effective. Spray and stretch techniques with a vapocoolant such as ethyl chloride, pioneered by Simons and Travell, have been used to reduce the myofascial component of pain. More aggressive therapy can include injection of anesthetic and possibly steroids into the piriformis which can confirm the diagnosis. This is followed by botulinum toxin injection into the piriformis. Finally, surgical release of the piriformis can be useful in refractory cases.

KEY POINTS TO REMEMBER

- **Newer MRI techniques may greatly assist in the diagnosis of extraspinal sciatica.**
- **The FADIR position (flexion, adduction, and internal rotation of the hip) typically reproduces pain in patients with piriformis syndrome.**
- **EMG/nerve conduction studies can help to further localize the lesion in extraspinal sciatica.**
- **Abnormalities of the H-reflex are helpful in diagnosis.**

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SECTION II

Myopathy

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17 Myotonic Dystrophy

This patient is a 52-year-old female who presents with multiple pain complaints, weakness, blurred vision, palpitations, and memory loss. She reports that the pain and weakness have been slowly progressive for years and describes aching throughout most of her body, mainly on the left side with radiation into her right hip. She has a history of blurred vision, and bilateral cataracts were discovered 4 years prior to this evaluation. In addition, her long history of palpitations led to a diagnosis of supraventricular tachycardia. She also has symptoms of gastroparesis and was followed for several years by gastroenterology. Her surgical history includes a cholecystectomy, appendectomy, and hysterectomy. She has back and thigh pain on the right more than the left and trouble getting out of chairs. She complains of long-standing and progressive choking with swallowing for no apparent reason and occasional hiccoughs.

On examination she was a good historian in spite of her complaints of memory impairment. Her neurological examination revealed mild bilateral ptosis with mildly reduced facial expressions. On motor examination she

had difficulty abducting her arms to shoulder level and reduced ability to release her grasp when shaking hands. She had difficulty rising from a chair but no clear muscle wasting. The remainder of the neurological examination was normal. Her primary care physician consults you to help in sorting out her weakness from her other varied complaints.

What do you do now?

Patients with symptoms involving multiple systems can be very confusing to sort out, and sometimes it takes years before the clinican can make a clear diagnosis. Further history in this patient revealed that she had family members with myotonic dystrophy (also called dystrophia myotonica, DM1), and clinically she exhibited percussion myotonia, which in conjunction with multisystem involvement was very suggestive of DM.

Clinical myotonia is manifest by delayed relaxation of muscle after voluntary contraction or percussion. Patients with myotonia often experience muscle stiffness, but symptoms improve after repeated use. This can be tested by asking them to quickly release their grip or having them squeeze their eyes shut and then open them rapidly. Percussion of distal upper extremity muscles such as the thenar muscles may cause involuntary contraction, a sign consistent with myotonia. Electromyography (EMG) is typically used to confirm these findings and will reveal spontaneous, painless discharges that wax and wane with respect to both amplitude and frequency. These "myotonic discharges" have a characteristic sound on EMG that is easily recognizable and is often described as a "dive bomber". Additional studies that can help confirm electrical myotonia include repetitive stimulation, exercise testing, and the cooling test. Repetitive stimulation at 5–10 Hz produces a decrement in myotonia, a useful but nonspecific finding. In the so-called short exercise test, a compound muscle action potential (CMAP) is recorded prior to and following a brief (10–30 seconds) period of exercise. In patients with DM type 1 (DM1), this will cause a decrease in the CMAP. In DM2, there is no change. Cold triggers weakness in patients with paramyotonia congenita. It can be demonstrated by measuring CMAPs prior to and after cooling of the limb. The decrement can be >75% in these patients.

Conditions with both clinical and electrical myotonia include myotonia congenita, DM1, and DM2. The most common is DM1, which is caused by expansion of an unstable trinucleotide (CTG). It demonstrates remarkable anticipation. This means the disease has an earlier onset and is more severe in subsequent generations due to longer CTG repeats. DM1 is arbitrarily divided into four groups: congenital, childhood, adult, and late-onset/asymptomatic. Adult onset is the most common and is likely in our case. These patients often have distal limb, facial, and neck extensor weakness. Weakness contributes to the characteristic facies seen in this disorder

producing lack of expression (Figure 17.1). Patients often have a weak and open or "tented" mouth. Atrophy of the masseter and temporalis produce a very narrow appearing face, referred to as "hatchet facies. Later in the course, they have visible wasting of the sternocleidomastoid muscles. Patients can exhibit frontal balding, cardiac conduction abnormalities, respiratory failure (especially with anesthesia), posterior subcapsular cataracts, irritable bowel syndrome, and testicular atrophy with reduced fertility in affected males. Cognitive impairment is common, though it does not tend to progress as much as weakness over time. These symptoms are often manifest by a dysexecutive syndrome with lack of initiative, inactivity, and an apathetic attitude. This may cause patients to miss visits and underestimate symptoms. Excessive daytime sleepiness, commonly secondary to obstructive sleep apnea, is common; and continuous positive airway pressure and modafinil may be useful in these cases. Pain can also be very prominent in DM1 and DM2 but does not parallel myotonia. It is frequently more



FIGURE 17-1 This patient has an early case of myotonic dystrophy. She exhibits some of the typical facial features including relative lack of facial expression. Photo courtesy of Stephen Mason.

evident in the lower extremities, where an associated peripheral neuropathy may be the cause. Overall, progression is slow, with patients often severely disabled by the sixth decade. Pneumonia secondary to aspiration is common and can precipitate respiratory failure.

In 1994, another form of DM was discovered that was similar but lacked a congenital form. It preferentially involved proximal rather than distal muscles and lacked the CTG repeat. In 2001 it was found to be caused by a CCTG expansion in the ZNF9 gene. This form is now known as myotonic dystrophy type 2, or DM2. Anticipation in this form is not nearly as striking as in DM1.

The diagnosis DM1 and DM2 is made by genetic testing in patients with characteristic EMG findings noted above. Muscle biopsy is not typically necessary, though type 1 fiber atrophy and "tram tracking" of nuclei are specific for DM1. Often, DM2 reveals type 2 fiber atrophy with pyknotic nuclear clumps. Other laboratory findings include hypogammaglobulinemia, evidence of male hypogonadism, and an elevated creatine kinase.

After confirmation of the diagnosis with genetic testing, patients with DM1 and DM2 will need to be followed by cardiology for development of cardiac conduction defects. Some will require a pacemaker. All will need surveillance for cataracts with periodic slit lamp examinations. Severe ptosis may require upper blepharoplasty. Laboratory surveillance should include glycosylated hemoglobin and thyroid-stimulating hormone as there is an association with diabetes and hypothyroidism. Metformin is often used as these patients tend to be hyperinsulinemic with insulin resistance. Symptomatic treatment for myotonia typically starts with mexiletine 75 mg bid to tid with weekly increases by 50 mg up to 200 mg tid or clinical effect. The main side effect is nausea; however, there is also a rare proarrhythmic possibility, so most will include cardiology in this decision. Phenytoin, carbamazepine, procainamide, and quinidine are less effective and may also be proarrhythmic. Gabapentin is relatively safe but typically a less effective option than mexiletine. There is no known treatment for the weakness, the more debilitating factor in most patients with this disease. Genetic counseling should be offered to the patient and family members, and all patients with DM should receive a medic alert bracelet and be educated about the possibility of respiratory failure with anesthesia as well as dysphagia and the potential for aspiration.

KEY POINTS TO REMEMBER

- The findings of both clinical and electrical myotonia should suggest myotonia congenita, DM1, or DM2.
- Myotonic dystrophy demonstrates anticipation, where the disease has an earlier onset and more severe course with subsequent generations due to increasing trinucleotide repeats.
- Myotonic dystrophy is associated with multisystem problems and requires comanagement with a cardiologist as well as an ophthalmologist.
- Executive dysfunction can lead to missed appointments and an apathetic attitude, causing patients to underestimate symptoms. Providers should take extra care that these patients do not "slip through the cracks" in our health-care system.
- There is an association with diabetes and hypothyroidism, so glycosylated hemoglobin and thyroid-stimulating hormone should also be monitored.

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18 Metabolic Myopathy

A 20-year-old male presents to the emergency department with a 1-day history of lower extremity weakness. He noticed it when he woke up and had a little difficulty getting out of bed. He also complains of pain in his legs and arms for the last 2 days. He is concerned that his urine is very dark. He has had two similar episodes of weakness, when he was 12 and 16 (after playing hockey); but the symptoms were less severe and his urine was not this dark. He made a full recovery within a day or two. He did not seek medical attention at those times. Past medical history is otherwise negative. He does not take any medications and denies alcohol, tobacco, or drug use. Family history is negative for neurological disease, although he is an only child. Review of systems is remarkable for a gastrointestinal illness for the past few days, and he has had very poor oral intake during this period. Neurological exam reveals 4/5 weakness proximally in the arms and legs but is otherwise unremarkable. Labs are significant for a

creatine kinase (CK) of 5000; aspartate transaminase (AST) and alanine transaminase (ALT) of 110 and 100, respectively; and urinalysis with 1+ ketones.

What do you do now?

The patient's history, exam, and high CK are consistent with an acute myopathic process. A troponin should also be ordered and will be negative in an isolated myopathy. His history is also consistent with myoglobinuria; however, his urinalysis was negative except for ketones. In myoglobinuria, a urinalysis is positive for blood but negative for red blood cells; however, the test is not always sensitive (myoglobin clears 1–6 hours post–muscle injury). A serum myoglobin can also be ordered, but myoglobin is cleared from the serum quickly as well.

An acute myopathy with myoglobinuria may be caused by many conditions (see Table 18–1); however, his history of previous attacks is highly suggestive of a metabolic myopathy. The fact that the patient has no history of fixed weakness from previous attacks is most consistent with impaired lipid metabolism. If he had a history of fixed proximal weakness between attacks, this would suggest a disorder of carbohydrate metabolism (glycolytic defect), although absence of fixed weakness can occur. Adult patients with carbohydrate or fatty acid disorders typically have a history since childhood of exercise-induced myalgias, cramps, and fatigue. Episodes of myoglobinuria tend to present later, usually in the second decade. The metabolic myopathy that most commonly leads to myoglobinuria is the adult form of carnitine palmityltransferase II (CPT II). This is an autosomal recessive disorder of impaired fatty acid transport across the inner mitochondrial membrane. It clinically manifests after sustained exercise, fasting, or a febrile illness (there is also a lethal neonatal form). Although this patient has no

TABLE 18–1 Causes of Myopathy with Myoglobinuria

Metabolic or mitochondrial myopathies (very rarely inflammatory myopathies)
Muscle compression (i.e., blunt trauma, crush injury, coma)
Illicit drug use (e.g., cocaine, amphetamines)
Alcohol
Medications (e.g., zidovudine, statins, propofol)
Strenuous exertion (e.g., extreme exercise, seizures)
Neuroleptic malignant syndrome
Malignant hyperthermia
Infection (e.g., influenza, HIV, legionella)
Severe electrolyte imbalance (hypokalemia, hypophosphatemia)
Endocrinopathies (rare)

history of recent exercise, he does have a gastrointestinal illness with very poor oral intake. It is important to keep in mind that patients with glycolytic defects often are symptomatic after brief bursts of physical activity; however, low-intensity exercise (e.g., a paced jog) can also precipitate an attack. Patients with disorders of glycolysis often describe that after brief rest their cramps and weakness will resolve; activity can then be resumed at the previous level ("second wind phenomenon").

This patient's CK is markedly elevated, which is typical for an acute metabolic myopathy (the CK may be normal between attacks). An electromyogram/nerve conduction study is not required for diagnosis of a metabolic myopathy but is often done to evaluate for other atypical neuromuscular presentations. As there is suspicion for CPT II, carnitine levels should be ordered. Obtain a total serum carnitine, which will usually be low while the acylcarnitine fraction is increased. This pattern is also consistent with secondary causes of carnitine deficiency, such as valproic acid or zidovudine use, chronic dialysis, and disorders of beta oxidation (i.e., very long, long, medium, and short chain acylcoenzyme A dehydrogenase deficiencies). This patient is not taking any of these medications, and disorders of beta oxidation are not relevant here as most patient present in infancy or childhood with Reys-like episodes. Of note, if both the acylcarnitine and carnitine levels are low, this is consistent with a primary carnitine myopathy, which is usually a disorder of fatty acid metabolism. It typically presents with progressive proximal weakness, while myoglobinuria is rare. However, this patient does not fit this type of presentation either. There is also a systemic variant of primary carnitine myopathy that manifests by age 10, but weakness is overshadowed by multisystem involvement.

The next step for this patient will be serological genetic testing. There are several CPT II mutations, and only some can be diagnosed in this manner. If genetic testing is negative, muscle (or skin) biopsy will be required for diagnostic confirmation (results showing reduced enzyme activity). This enzyme is not routinely measured and must be specifically requested. Although likely not pertinent to this patient, there is no genetic test available for myopathic carnitine deficiency; but muscle biopsy shows lipid accumulation and low carnitine levels (<2%–4% of normal in primary form and <25%–50% for secondary causes).

For patients where there is concern for a glycolytic problem, muscle biopsy is usually diagnostic. In the case of myophosphorylase deficiency, there will be low or absent myophosphorylase activity; however, if this is highly suspected, the biopsy should be delayed for at least 1 month when there is a history of overt myoglobinuria. The reason is that there may be a false-positive presence of myophosphorylase as fetal isozyme can be present in the first month after myoglobinuria. Deficiencies of phosphofructokinase, phosphorylase kinase, phosphoglycerate kinase, phosphoglycerate mutase, lactate dehydrogenase, and myoadenylate deaminase (MADA) can resemble myophosphorylase deficiency; and muscle biopsy will rule out these conditions. A MADA deficiency is the most common enzyme deficiency found on muscle biopsy. However, there are asymptomatic patients with this deficiency; thus, a positive result must be interpreted with caution. The forearm ischemic exercise test may also be helpful in the diagnosis of glycolytic disorders.

When it comes to any unexplained myopathy, especially if there is concern for a metabolic myopathy, there should be consideration of a mitochondrial disease. Many mitochondrial disorders present with multiple neurological problems, such as deafness, seizures, encephalopathy, ptosis, or ophthalmoplegia. In these cases blood tests for mitochondrial mutations are needed, which can pick up many of the most common mitochondrial myopathies. Examples are myoclonic epilepsy with ragged red fibers (MERRF); mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS); and progressive external ophthalmoplegia. Brain magnetic resonance imaging as well as lumbar puncture and serum looking for elevated lactate and/or pyruvate also become important (but beyond the scope of this discussion).

There are, however, a few mitochondrial disorders that present with an isolated or mainly a myopathic picture (i.e., mitochondrial myopathia with recurrent myoglobinuria, succinate dehydrogenase deficiency, and primary coenzyme Q_{10} deficiency). These conditions can present as late as early adulthood. Usually, CK is elevated, and serum lactate may be elevated. Muscle biopsy is needed for diagnosis and, if done in an affected muscle, is very sensitive and specific. If this patient had one of these myopathies instead of CPT II, it should be discovered on biopsy. It is important not to

miss primary coenzyme Q_{10} deficiency as replacement leads to full resolution of weakness.

There is no treatment for CPT II deficiency, but patients should avoid fasting, avoid intense exercise lasting greater than 30 minutes, and be aware that exposure to cold or general anesthetic may precipitate an attack. Primary carnitine deficiency treatment is carnitine 2–6 g daily in adults, which will improve strength for many patients. Finally, the patient's treatment for myoglobinuria (reflecting rhabdomyolysis) needs to be addressed. He had no renal damage supported by laboratory testing, but he should be hydrated aggressively with normal saline to prevent renal damage (also serum alkalization may be considered in severe cases). Electrolytes must be monitored frequently. Details of myoglobinuria management can be found in the sources listed under "Further Reading."

KEY POINTS TO REMEMBER

- **Patients with carbohydrate or fatty acid disorders usually have a history since childhood of exercise-induced myalgias, cramps, and fatigue; however, myoglobinuria does not typically occur until the second or third decade.**
- **Since myoglobin clears within hours after muscle injury, urinalysis or serum may be negative for myoglobin.**
- **Patients with CPT II usually have low total serum carnitine and high acylcarnitine fraction; however low levels of both are consistent with primary carnitine myopathy.**
- **There are mitochondrial disorders that lead to isolated myopathy, which may not manifest until adulthood; and muscle biopsy is required for diagnosis.**

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19 Inflammatory Myopathy

A 55-year-old male has a 3-month history of progressive upper and lower extremity weakness. Lately, he has had trouble walking up stairs and lifting his arms to wash his hair. He says his shoulders and thighs often ache but he does not feel it is severe enough to take pain medications. He denies vision changes, difficulty swallowing, or numbness. Past medical history is remarkable for kidney stones. He takes an aspirin daily. Family history is negative for neurological disease. He does not smoke or drink, he works as a teacher, and he is married. Review of systems is remarkable for constipation, and he mentions a rash on and around his elbows for about 6 months that his primary care physician (PCP) diagnosed as psoriasis. General exam is remarkable for a mild scaly erythematous rash on both elbows and the posterior forearms. Neurological exam shows normal mental status and cranial nerves. Strength is 4/5 in proximal upper and lower extremities. Distal strength is normal except for grip strength 4+/5 bilaterally. Muscle bulk and tone are normal. Reflexes are 1+/4 in all extremities, and toes are downgoing.

Coordination, sensation, and gait testing are normal. Recent labs obtained from his PCP include a normal complete blood count, basic metabolic panel, urinalysis, thyroid-stimulating hormone, and parathyroid hormone; however, erythrocyte sedimentation rate (ESR) is 50, creatine kinase (CK) is 3000, and antinuclear antibodies (ANA) are positive at 1:80.

What do you do now?

This patient's symmetric weakness is predominantly proximal; the lack of sensory findings and elevated CK are clearly consistent with a myopathy. It is tempting to be impressed by the elevated CK and to focus solely on an evaluation of a myopathic process. However, it is important to remember that significant CK elevations are not specific for a myopathy. As is the case for this patient, modest elevations (i.e., up to five to ten times normal) can be seen in motor neuron disease (MND) or chronic inflammatory demyelinating polyneuropathy (CIDP). This patient has symmetric mainly proximal weakness and lack of bulbar and upper motor neuron signs, which are atypical for MND. His sensory exam is normal, and his reflexes are present, which would be very atypical for CIDP. Any patient with progressive weakness in the absence of sensory findings may have neuromuscular junction dysfunction, but he has no ocular or bulbar findings, which would be unusual for myasthenia gravis. Lambert-Eaton myasthenic syndrome (LEMS) may lack ocular/bulbar signs, but leg weakness is typically more impressive than arm weakness. Often, LEMS is accompanied by autonomic symptoms, but this patient has no significant autonomic complaints (except for constipation). His proximal arm pain suggests a myopathy and often points to an inflammatory myopathy.

The main inflammatory myopathies to consider are polymyositis, dermatomyositis, and inclusion body myositis (IBM). This patient's presentation does not raise concern for a hereditary myopathy due to his older age, although rarely limb-girdle muscular dystrophy, mitochondrial myopathies, and acid maltase deficiency can present later in life. Thyroid and parathyroid disease have been ruled out from the blood work. He takes no concerning medications (e.g., a statin) and denies use any of illicit drugs (e.g., cocaine) that could lead to an inflammatory myopathy. Human immunodeficiency virus infection can occasionally present as an inflammatory myopathy, and it is reasonable to test for it.

A common question that arises is how do you know which inflammatory myopathy a patient like this has? This patient's age and gender fit well with IBM as it is seen in patients over 50 and most patients are males. However, dermatomyositis can occur at any age and polymyositis occurs in patients over 20. The distribution of his weakness is inconsistent with IBM, which affects predominantly wrist/finger flexors and knee extensors (often asymmetric). Foot drop is also common in IBM. A unique feature is that patients

may have mild (asymptomatic) distal sensory findings on exam secondary to a sensory neuropathy. Dermatomyositis and polymyositis affect mainly proximal muscles symmetrically, as seen in this patient. Patients with IBM also tend to present after years of slow progressive weakness, while dermatomyositis and polymyositis typically present over weeks (within days or even up to several months can occur). As the name suggests, most physicians know that dermatomyositis is almost always preceded or accompanied by a rash; however, this patient's rash may be labeled as "psoriasis" and disregarded. The "textbook" dermatomyositis rashes are described as eyelid "heliotrope," chest "V," shoulders "shawl" distribution, and over the knuckles (Gottron papules). However, dermatomyositis patients may develop a rash on their extensor surfaces (or even scalp) that can look like psoriasis. Serum CK is almost always elevated (often up to 50 times higher than normal) in dermatomyositis and polymyositis, whereas it is normal to mildly elevated in IBM. Higher CKs do not correlate with increased weakness.

An electromyogram/nerve conduction study (EMG/NCS) must be performed on this patient to help confirm a myopathic process. Typically, EMG shows myopathic features in all three conditions (however there are occasional cases of normal EMG). Abnormal spontaneous activity (e.g., fibrillations, complex repetitive discharges) are often seen in inflammatory myopathies, in contrast to other myopathies. Later in the course motor units may also show neuropathic patterns (more common in IBM), reflecting chronic muscle disease; and IBM may lead to a sensory peripheral neuropathy demonstrated with NCS. This patient's EMG/NCS will likely be consistent with a myopathy, but even if the study is unimpressive, his presentation suggests dermatomyositis, which raises another diagnostic dilemma. Dermatomyositis is the only inflammatory myopathy strongly associated with malignancy. It would be prudent to obtain computed tomography of the chest, abdomen, and pelvis; but in the context of the patient's constipation, he will also need a colonoscopy to evaluate for colon cancer. A female patient would also need a mammogram.

While the malignancy work-up is in progress, biopsy confirmation should be pursued. A skin biopsy may be sufficient for the classic dermatomyositis presentation with classic skin findings. However, his rash is certainly suggestive, but not classic, for the condition. Muscle biopsy will usually confirm the diagnosis for these idiopathic inflammatory myopathies,

and each condition has characteristic findings. However, keep in mind that in some cases the muscle biopsy may be inconclusive. In these cases, magnetic resonance imaging (MRI) of the proximal legs and/or arms could be considered (see Fig. 19-1). An MRI can show muscle signal abnormalities in inflammatory myopathies and aid in choosing a muscle for biopsy. However, many muscle experts rely only on the neurological exam and EMG to select a biopsy site. Quadriceps is typically used, but a biopsy site that has recently been evaluated with EMG should not be used. If biopsy results are negative or nonspecific, the response to treatment can be a helpful diagnostic tool. Dermatomyositis and polymyositis typically respond very well to steroids and other immunomodulators (e.g., intravenous immunoglobulin G), while IBM responds very poorly or not at all.

To tie up the loose ends on this patient, remember that dermatomyositis (and polymyositis) can be associated with interstitial lung disease and cardiac abnormalities. Make sure to obtain an electrocardiogram and echocardiogram and keep in mind that these inflammatory myopathies almost never cause troponin elevations. A pulmonologist will need to follow the patient. Also, what about the patient's elevated ANA? As part of the work-up, other vasculitis serological markers should be obtained (e.g., anti-double-stranded DNA, extractable nuclear antigen). If these are elevated,

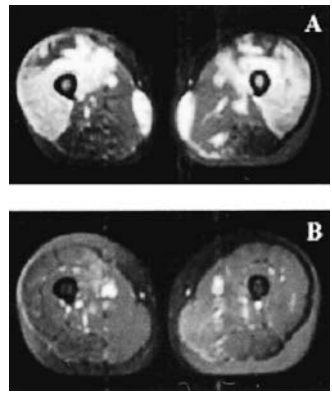


FIGURE 19-1 An example of MRI of the proximal legs taken (A) before and (B) after immunosuppressive treatment in a patient with dermatomyositis. Note that areas of inflammatory edema are of high signal on T2 weighted images. Source: Tomasova Studynkova, J., F. Charvat, et al. (2007). "The role of MRI in the assessment of polymyositis and dermatomyositis." *Rheumatology* (Oxford) 46(7): 1174–9.

TABLE 19–1 Idiopathic Inflammatory Myopathies

	Demographics	Typical Exam Findings	Typical CK level	Diagnostic Confirmation
IBM	Most are male, age >50	Asymmetric weakness and atrophy of finger/wrist flexors and knee extensors, proximal weakness less impressive, mild distal sensory loss (neuropathy)	Mild elevation or normal	Muscle biopsy, no response to immunosuppressive treatment
Polymyositis	Age >20	Proximal symmetric weakness	Marked elevation	Muscle biopsy, response to immunosuppressive treatment
Dermatomyositis	Any age	Proximal symmetric weakness,rash	Marked elevation	Skin and/or muscle biopsy, response to immunosuppressive treatment, evaluation for underlying malignancy

IBM, inclusion body myositis; CK, creatine kinase.

this raises the possibility of an overlapping connective tissue disorder. All three inflammatory myopathies may be associated with connective tissue diseases such as systemic lupus or scleroderma. In contrast to IBM, ESR and ANA are more likely to be elevated in dermatomyositis and polymyositis. The anti-Jo antibodies can be seen in dermatomyositis and may be a marker of worse prognosis. Because of clinical overlap, there is good reason to have a rheumatologist assist with diagnosis and management of inflammatory myopathies (see Table 19–1).

KEY POINTS TO REMEMBER

- Usually, EMG shows myopathic features in polymyositis, dermatomyositis, and IBM; however, a normal EMG does not rule out these conditions.
- Patients with dermatomyositis always require an aggressive search for an underlying malignancy.
- Muscle biopsy is required for diagnosis of the idiopathic inflammatory myopathies, though a positive skin biopsy may be sufficient for classic dermatomyositis with a classic rash.

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20 Periodic Paralysis

This patient is a 19-year-old male who presents to the emergency department after waking with stiffness and weakness in all four extremities severe enough that he could not get up. He reports that for about 2 years prior to this visit he would frequently awaken with severe stiffness in the morning, which would resolve after a couple of hours. He denies any antecedent illness or fever. Since his arrival to the emergency department, he has noticed some improvement, especially in the upper extremities. He denies smoking, alcohol use, or any illicit drug use and is not on any medications. His physical examination in the emergency department is unremarkable with the exception of moderate weakness. Initial laboratory findings reveal a critically low potassium level of 2.3. His thyroid-stimulating hormone, complete blood count, liver function tests, creatine kinase, urine electrolytes, and urine toxicology screen were otherwise negative. His electrocardiogram (EKG) is normal. You are passing through the emergency room when you get "curbsided" about this case of episodic weakness.

Further exam reveals generally reduced tone and normal bulk. There is no percussion myotonia. At the time of this examination, he had already noticed significant improvement but is still symmetrically weak in the lower extremities. His reflexes are normal, and his toes are downgoing. The remainder of his neurological exam is normal. The emergency department physician asks whether this is a neuromuscular problem and whether it requires a medicine consult.

What do you do now?

While he is being treated for hypokalemia, you should consider the anatomic distribution and temporal profile of his weakness. Possible causes include renal, adrenal, or thyroid dysfunction; renal tubular acidosis; diuretic or laxative abuse; and finally, a channelopathy.

In this case there are no signs such as upgoing toes, increased tone, or hyperactive reflexes that would suggest a central etiology. The weakness is not confined to a single limb, peripheral nerve pattern, or root level; and the temporal profile is acute. While the acute onset of weakness often suggests a vascular etiology, the anatomic distribution does not fit a vascular event. Indeed, it appears the patient may have had prior episodes, although they were not as severe. This presentation, associated with critically low potassium, improvement after replacement, and an otherwise normal laboratory work-up, should make you consider hypokalemic periodic paralyses.

The primary periodic paralyses (PPP) are a heterogenous group of autosomal dominant channelopathies affecting sodium, calcium, and potassium channels, typically with high penetrance. Lack of a family history could suggest new mutations or lack of penetrance in recent generations, although more often it reflects the inaccuracy of the patient's recall. Historically, PPP have been divided into the hyperkalemic and hypokalemic forms. Some syndromes have normal potassium, and the term "normokalemic periodic paralysis" has been used by some (see Table 20–1).

Distal renal tubular acidosis is clinically characterized by episodic weakness with reduced reflexes, hypokalemia, hypercalciuria, hypocitraturia, and hyperchloremic metabolic acidosis. Patients may have osteomalacia and related bone pain. They have proximal, more than distal, weakness. It is endemic in Thailand and rarely seen in Western countries. Patients can have anemia with spherocytosis and hemolytic anemia.

Thyrotoxic periodic paralysis in unlikely in our case due to normal thyroid studies but is important for the clinician to remember. It is more common in patients of Asian descent, where myalgias and signs of thyrotoxicosis are distinct and precede paralysis. In non-Asians, paralysis may precede other signs. The incidence is about 2% of thyrotoxicosis from any cause, with onset between 20 and 50 years of age. (For a more complete discussion, see Lin, 2005.)

Andersen—Tawil syndrome is a rare hereditary disorder clinically characterized by the triad of dyskalemic periodic paralysis (potassium can be high,

TABLE 20-1 **Primary Periodic Paralysis**

	Potassium Levels During Attack	Duration of Attacks	Treatment
Hyperkalemic periodic paralysis	Increased	<4 hours	Thiazide diuretics, acetazolamide
Paramyotonia congenita	Increased	2–24 hours	Mexiletine
Congenital myasthenic syndrome	Normal	Hours to days	AChE inhibitors
Hypokalemic periodic paralysis	Decreased	Hours to days	Acetazolamide, K^+, K^+-sparing diuretics
AndersenTawil syndrome	Normal, elevated or decreased	1–36 hours	Acetazolamide
Thyrotoxic periodic paralysis	Decreased	Hours to days	Beta-blockers, antithyroid treatments, K^+, K^+-sparing diuretics
Distal renal tubular acidosis	Decreased	Hours	K^+

low or normal), cardiac arrhythmias, and multiple dysmorphic features. Diagnosis is by genetic testing, though in 30%–40% of cases no mutations are found. Given the low prevalence in the population, normal EKG, and the lack of dysmorphic changes on examination, this diagnosis would seem unlikely in our patient.

Hypokalemic periodic paralysis is the most common PPP and is the likely diagnosis in our case. It is clinically characterized by acute, episodic, flaccid weakness associated with a drop in potassium lasting several hours to days. It commonly occurs in the morning after waking, as in our case, but can be triggered by exercise, cold, emotional stress, a carbohydrate-rich meal, alcohol, or infection. Clinical criteria for the diagnosis of hyper- and hypokalemic periodic paralysis were proposed by an expert committee at

the 87th European Neuromuscular Center International Workshop in 2000. (Meola G, et al.)

Diagnostic Criteria for Primary Hypokalemic Periodic Paralysis

1. Two or more attacks of muscle weakness with documented serum K <3.5 mEq/l
2. One attack of muscle weakness in the proband and one attack of weakness in one relative with documented serum K <3.5 mEq/l
3. Three of six clinical or laboratory features outlined below:
    a. Onset in the first or second decade
    b. Attack duration (muscle weakness involving one or more limbs) >2 hours
    c. Positive triggers (high-carbohydrate meal, rest after exercise, stress)
    d. Improvement with K intake
    e. Positive family history or genetically confirmed skeletal calcium or sodium channel mutation
    f. Positive McManis short exercise test
4. Exclusion of other causes of hypokalemia (renal, adrenal, thyroid dysfunction; renal tubular acidosis; diuretic and laxative abuse)

Diagnostic Criteria for Primary Hyperkalemic Periodic Paralysis

1. Two or more attacks of muscle weakness with documented serum K >4.5 mEq/l
2. One attack of muscle weakness in the proband and one attack of weakness in one relative with documented serum K >4.5 mEq/l in at least one attack
3. Three of six clinical or laboratory features outlined below:
    a. Onset before third decade
    b. Attack duration (muscle weakness involving one or more limbs) <2 hours
    c. Positive triggers (exercise, stress)
    d. Myotonia
    e. Positive family history or genetically confirmed skeletal sodium channel mutation
    f. Positive McManis short exercise test

4. Exclusion of other causes of hyperkalemia (renal, adrenal, thyroid dysfunction; K-sparing diuretic use)

Laboratory findings in hypokalemic periodic paralysis include low potassium during attacks as well as elevated creatine kinase (CK) levels. Baseline levels of potassium and CK should be checked between attacks for comparison. Amplitudes of compound muscle action potentials are decreased during attacks, increased interictally and immediately after exercise, but progressively reduced during rest. Some patients can develop a limb girdle pattern of permanent weakness, in which case a myopathic pattern will be seen on EMG. Myotonic discharges are usually not seen in hypokalemic periodic paralysis but are commonly seen in hyperkalemic forms. Muscle biopsy is typically not required, but in difficult cases with negative genetic testing it may reveal central vacuoles, increased fiber-size variation, fiber splitting, angulated muscle fibers, and internalization of nuclei or tubular aggregates.

Hypokalemic periodic paralysis is genetically heterogenous. Two of three missense mutations in the calcium channel gene account for 70% of cases, and 10%–20% of cases will have a point mutation in the sodium channel gene. In the past, provocative tests have been used to establish the diagnosis. They carry the risk of provoking a severe attack and require the presence of an experienced physician and possibly an anesthesiologist. Monitoring of cardiac function, serum potassium, and glucose levels is mandatory. Now these tests are restricted to cases in which genetic testing fails to make a diagnosis.

Electromyography (EMG) can also help in sorting out the diagnosis, especially when genetic testing is not readily available. Since exercise can trigger, aggravate, or relieve symptoms in muscle channelopathies, it can be combined with electrophysiological studies and used as a functional test. The combination of EMG with short and long exercise tests can be used to identify five patterns that correlate well with specific channel mutations. In the short exercise test, compound muscle action potentials are recorded over the abductor digiti minimi (ADM) with surface electrodes at rest and then after a brief period (10 seconds) of exercise. In the long exercise test, the muscle is exercised for 10 minutes. Both tests are very specific in distinguishing periodic paralysis from normal controls and patients with other myopathic disorders. (For more details about those procedures, see Fournier et al., 2004.)

Treatment of hypokalemic periodic paralysis consists of lifestyle and diet changes, including small and frequent meals to avoid carbohydrate loads, mild exercise, and avoidance of strenuous workouts. Many patients will need potassium supplementation. During acute attacks, oral potassium (20–30 mEq every 15–30 minutes until potassium is normalized) is usually sufficient. Acetazolamide has been considered the treatment of choice for years to decrease the severity and duration of attacks, though evidence is limited. Other carbonic anhydrase inhibitors may be useful as well. Gastrointestinal disturbances, drowsiness, paresthesias, and electrolyte imbalance are the most common long-term side effects of these medications.

KEY POINTS TO REMEMBER

- **While the periodic paralyses are autosomal dominant with high penetrance, family history is often negative for several reasons, including lack of recall or new mutations.**
- **Both the hyperkalemic and hypokalemic forms can be treated with acetazolamide.**
- **It is important to look for secondary causes that might be treatable, such as thyrotoxic periodic paralysis or distal renal tubular acidosis.**
- **Attacks of weakness in the hypokalemic forms may be precipitated by exercise, cold, emotional stress, a carbohydrate-rich meal, alcohol, or infection.**
- **It is important to obtain baseline levels of potassium and CK between attacks for comparison.**

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21 Statin Myopathy

A 68-year-old female is seen by her family doctor for a 3-week history of pain in her shoulders, arms, and thighs. She also admits to some difficulty getting up out of chairs and tires easily when she walks up stairs. Past medical history is significant for hypertension, hyperlipidemia, and a transient ischemic attack (TIA) about 1 year ago. She was admitted for a 10-minute aphasic episode. At that time she was started on simvastatin 30 mg daily (low-density lipoprotein was 130). Her other mediations are aspirin and verapamil. There is no family history of muscle disease, and she does not smoke or drink. Neurological exam is significant for 4+/5 hip flexor strength bilaterally but otherwise normal. Routine labs (complete blood count, basic metabolic panel, thyroid-stimulating hormone, urinalysis) were normal except for a creatine kinase (CK) of 1000 and mild elevation of aspartate transaminase (AST) and alanine transaminase (ALT). Her doctor suspects a statin myopathy and has the patient stop the simvastatin.

Three weeks later she sees her doctor again and says that her symptoms have resolved. Her neurological exam and CK level are now normal. The doctor calls for advice on management.

What do you do now?

The diagnosis here is clearly a statin myopathy. The risk overall is very low, but because of the frequent and increasing high use of statins, this situation is commonly encountered. As in this case, statins can lead to a painful proximal myopathy. The myopathy may also be painless. Myalgias may be the sole manifestation, and exercise intolerance is a commonly reported symptom. In severe cases of statin myopathy, myoglobinuria can occur, but typically these patients have other risk factors. Statin myopathy typically develops within weeks to months of starting therapy (mean about 6 months); however, it is important to note that it can occur at any time during statin use. The etiology is unknown and may be secondary (in part) to mitochondrial dysfunction or an underlying inflammatory process.

Often, CK is grossly elevated in statin myopathy but may be normal. Remember that this patient's elevated AST/ALT can reflect muscle or liver damage; therefore, one should check for γ-glutamyltransferase, which is specific for liver injury. Routine serum CK monitoring is not recommended; however, it is best to obtain a baseline CK level (along with liver function tests) prior to starting a statin. If electromyography is performed, it typically shows a myopathic pattern (may include myotonic discharges), although it can be normal.

It is important to determine if this patient had any risk factors for statin myopathy. She was on a low dose of simvastatin, which is associated with lower risk. She does not have any comorbid conditions that increase risk such as hypothyroidism, renal failure, liver disease, or known muscle disease. The patient's medications must be examined carefully as several can increase the risk of statin myopathy. Any medication that inhibits the cytochrome P-450 system enzyme CYP3A4 involved in statin metabolism can be a factor. This patient takes verapamil, which is on the list. Other medications include macrolide antibiotics, human immunodeficiency virus protease inhibitors, amiodarone, niacin, gemfibrozil, itraconazole, and cyclosporine (see Table 21–1 for a more complete list).

The primary care physician made the correct management decision to stop the simvastatin as it must be discontinued in any patient with evidence of myopathy or myalgias while taking the medication. The myopathy often improves/resolves within a few weeks, and >90% of patients recover within 6 months. This patient improved rapidly, which solidified the diagnosis. However, in cases that do not improve clinically or by CK level over about

TABLE 21-1 Common Medications that are Inhibitors of CYP3A4

Clarithromycin and other macrolide antibiotics
Indinavir and other HIV protease inhibitors
Itraconazole and other antifungal "conazoles"
Metronidazole
Amiodarone
Amlodipine, verapamil, and other calcium channel blockers
Digoxin
Fibrates
Niacin
Cyclosporine
Tacrolimus
Ethynylestradiol
Sertraline, fluoxetine, fluvoxamine (older SSRIs)
Alprazolam

SSRI, selective serotonin reuptake inhibitor.

a month or two, a muscle biopsy should be done. If a biopsy shows nonspecific inflammation, steroid treatment should be strongly considered. Note that there are cases of apparent statin myopathy which transformed into a chronic inflammatory myopathy after cessation of the statin. The mechanism is unclear, but one possibility is that a statin may precipitate an underlying polymyositis.

This patient was placed on a statin because of a recent TIA (and known hyperlipidemia). There are important benefits for statins in patients such as this. What should be done for this patient? The reintroduction of a statin in a patient with previous myopathy or myalgias is a risk/benefit issue determined on a case-by-case basis. This patient's clear need for a statin warrants another trial. Since pravastatin and possibly fluvastatin are less toxic, strong consideration of a careful trial of pravastatin is needed when her CK normalizes (she is already clinically back to baseline, which is also important). The verapamil should be replaced with a non-CYP3A inhibitor (e.g., metoprolol, lisinopril). At first, CK should be checked weekly, and the patient must be told to report any weakness or pain as soon as possible. Weakness is a clear indication to stop the statin and avoid further statin trials. If the patient has only myalgias and/or elevated CK, supplementation with coenzyme Q_{10} (150 mg daily) just prior to statin reinitiation can be considered. It should then be continued during statin treatment. This approach could

also be utilized prior to this patient starting pravastatin. There is no good evidence that coenzyme Q_{10} prevents or treats statin myopathy, but some small trials suggest a positive effect on myalgias.

KEY POINTS TO REMEMBER

- Statin myopathy can occur at any time during use.
- The CK level is often very high in statin myopathy but may be normal.
- Medications that inhibit statin metabolism, via the cytochrome P-450 system, can increase risk of myopathy.
- A statin must be discontinued in any patient with evidence of myopathy or myalgias.
- A muscle biopsy must be obtained if statin myopathy does not improve within a few months.
- Pravastatin is the least toxic statin and can be considered if a patient has a history of myopathy with another statin.
- Coenzyme Q_{10} has not been shown to prevent or treat statin myopathy, but it may have some benefit in treating isolated myalgias.

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22 Limb-Girdle Muscular Dystrophy

An 18-year-old male is referred for a 3-year history of slowly progressive weakness. His main problem is getting up out of chairs. Family history is negative for neurological disease. He does not smoke, drink, or use drugs. He is planning to start college soon. Review of systems is negative. Neurological exam is positive for 4/5 hip flexion and extension as well as 4+/5 knee extension and flexion bilaterally. Shoulder abduction is 4+/5, but otherwise upper extremity strength is normal. Reflexes are normal. Sensation and coordination are intact. He has some difficulty getting out of a chair without using his arms, but he has a normal gait. His calves display mild hypertrophy. Routine labs are remarkable for a creatine kinase (CK) of 950. Electromyography/nerve conduction studies (EMG/NCS) ordered by his family physician are consistent with a myopathy (myopathic motor units but no spontaneous activity), and no other neuropathic changes are seen. An electrocardiogram (EKG) and echocardiogram are normal. Serological genetic testing is negative for dystrophin abnormalities.

What do you do now?

The EMG/NCS confirmed a myopathy, but an etiology has not been discovered as of yet. The slowly progressive weakness in this teenager is concerning for a muscular dystrophy. An inflammatory myopathy (usually dermatomyositis in younger patients) is highly unlikely because of the more indolent nature of his presentation. He also has no rashes and does not have any systemic symptoms of a rheumatological condition that are associated with a polymyositis overlap syndrome. He denies toxin exposure, does not use alcohol or drugs, and does not take medications, which narrows the differential diagnosis further. The patient's lack of episodic weakness or myoglobinuria is not consistent with most metabolic or mitochondrial myopathies. An important exception is acid maltase deficiency; however, most adult cases do not present until the third or fourth decade, and juvenile cases almost always present in the first decade. Most congenital myopathies would have presented by now, and in these myopathies weakness remains rather stable. This patient's symmetrical proximal pattern of weakness narrows the differential diagnosis of suspected muscular dystrophy to Becker muscular dystrophy (BMD) or limb-girdle muscular dystrophy (LGMD). He is too old for Duchenne muscular dystrophy (DMD) as these patients usually become wheelchair-bound by age 13. Although he does not have a family history of myopathy, many cases of muscular dystrophy are caused by sporadic mutations.

The LGMDs can be autosomal dominant (LGMD 1A–1E) or autosomal recessive (LGMD 2A–2J); the latter tend to have an earlier onset and more rapid course. This patient's onset of weakness was at a typical age for BMD (X-linked recessive) as many start to develop symptoms between the ages of 5 and 15. However, some patients may present in their twenties all the way up to their fifties. The pattern of weakness is the same for LGMD and BMD, with initial weakness of proximal lower extremities, followed by proximal upper extremity weakness several years later. Facial and distal strength are preserved until the end stage. The exception to this pattern of weakness is the scapuloperoneal forms that may be seen in LGMD 1B, 2A, and 2C–2F. Another exam finding for this patient is calf pseudohypertrophy, which is commonly associated with DMD; however, BMD and most of the autosomal recessive LGMD patients typically have calf pseudohypertrophy (and often complain of calf pain).

This patient's high CK level is consistent with a myopathy but is not helpful in differentiating between these two muscular dystrophies. The CK

levels are typically greater than five to ten times normal in BMD (greater than ten times or more in DMD), but levels decrease with disease progression. In LGMD, CK levels have large variability (autosomal recessive forms are associated with higher CK levels). Keep in mind that even though this patient has no known history of muscle disease, female carriers of BMD/DMD can have mildly increased CK values and mild calf hypertrophy. This patient's primary care physician made the correct initial step by ordering serological genetic testing for BMD. The test looks for a dystrophin mutation (the dystrophin quantity is <5% in DMD and >5% in BMD). As this patient had the typical clinical presentation for BMD, further testing would not be needed if he had a confirmed family history of the disease via genetic testing or muscle biopsy. The fact that his blood test was negative does not rule out BMD as the sensitivity is about 75%. The test will also be negative if the patient actually has a form of LGMD such as LGMD 2I, 2A, or one of the sarcoglycanopathies 2C–2F (see Table 22–1). Therefore, since the genetic testing is negative for DMD/BMD in this patient, the following serological tests should be obtained: LGMD 2I (FKRP gene mutation), LGMD 2A (calpain-3), and LGMD 2C–2F (sarcoglycans). If these are negative, then a muscle biopsy must be done. The biopsy must be analyzed for absent or impaired antidystrophin antibody binding seen in BMD and special antibodies including those against sarcoglycans for LGMD. Other

TABLE 22-1 Limb-Girdle Muscular Dystrophy (LGMD) Genetic Tests

Autosomal Dominant
LGMD1A: Myotilin (research laboratory only)
LGMD1B: Lamin A/C
LGMD1C: Caveolin-3[a]
Autosomal Recessive
LGMD2A: Calpain-3
LGMD2B: Dysferlin
LGMD2C–F: Sarcoglycan A, B, C, D
LGMD2G: Telethonin (research laboratory only)
LGMD2H: TRIM32 (research laboratory only)
LGMD2I: FKRP
LGMD2J: Titin (research laboratory only)

[a]No testing available for LGMD1D and E.

nonspecific muscular dystrophy findings are fiber-size variability and replacement of muscle by fat and connective tissue.

An EMG is not needed for diagnosis of muscular dystrophy, but it can rule out anterior horn cell disease by confirming a myopathic EMG pattern (as was the case for this patient). It is also helpful in cases of suspected muscular dystrophy without a family history (as was also the case for this patient), if CK levels are low, or in evaluation of possible female carriers for DMD/BMD who are symptomatic.

It is no surprise that this patient does not appear to have cognitive abnormalities as cognitive problems are much less severe in BMD and usually even a lower risk in LGMD (in contrast to DMD). However, all muscular dystrophy patients (especially those with early-onset BMD and LGMD) are susceptible to cardiac and respiratory disease. Cardiology and pulmonology consults are required. Regular pulmonary function tests, EKGs, and echocardiograms are needed (female carriers must also be monitored for dilated cardiomyopathy starting in their twenties).

Treatment of BMD and LGMDs includes maintaining function and preventing contractures. A muscular dystrophy clinic with a multidisciplinary approach is helpful for coordination of care. There is no role for steroids in BMD or LGMD (in contrast to DMD). With respect to prognosis, the clinical course of these muscular dystrophies is similar for affected family members. Although many adult-onset LGMD and BMD patients do relatively well, early-onset cases may develop cor pulmonale or cardiac failure and can be severely compromised or can die by mid-adulthood.

Determination of the specific type of muscular dystrophy can be very difficult. In our patient it is important to gain as much information as possible to best assist in appropriate genetic testing and counseling. A consult from a clinical geneticist is often very helpful.

KEY POINTS TO REMEMBER

- **Serological genetic testing does not rule out BMD or LGMD; therefore, if clinical suspicion is high, a muscle biopsy must be done.**
- **Management of LGMD requires cardiology and pulmonology input as all patients with muscular dystrophy are at risk for cardiac and pulmonary disease.**
- **In contrast to DMD, there is no role for steroids in BMD or LGMD.**

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23 Cramps

A 30-year-old tennis instructor complains of severe cramps when playing tennis in warm weather. He has always had cramps, but now the cramps are worse, involving his proximal legs and rarely his arms. The patient remembers that his father may have complained of cramps throughout his life; he died of a myocardial infarction at age 65. The patient stresses that he tries to keep well-hydrated, drinking water throughout the day. The patient is not on any medications and has no significant past medical history. His neurological examination is unremarkable. Specifically, his muscle bulk and strength are normal. On examination no myotonia, fasciculations, or cramping could be observed. You have the patient run up two flights of stairs to see if you can provoke any cramps; they do not occur. His laboratory examination including creatinine kinase (CK), thyroid studies, and chemistry profile is normal.

What do you do now?

Cramps are very common, occurring in 95% of students enrolled in an exercise class and 40%–60% of elderly outpatients. Cramps can be a very vexing problem for both physicians and patients. The cause of cramps usually cannot be clearly ascertained, and this can exacerbate the patient's frustration. In evaluating the patient with cramps it is important to first clearly define if the patient's symptoms are cramps (Table 23–1). Cramps have an abrupt onset and short duration, the muscle is strongly contracted, and the cramp is palpable and relieved by stretching or massage. Hyperexcitable nerve terminal arborization is felt to be the cause. Cramping occurs most often after voluntary contraction in a shortened muscle. Usually, cramps occur in a single muscle; most commonly it is the gastrocnemius muscle. If cramps occur diffusely, a neuromuscular cause should be considered. Cramps may occur at night or at rest. Electromyography (EMG) performed during a cramp demonstrates very rapid, >50 hertz, irregular discharges of motor unit potentials. Activation of an antagonistic muscle slows the frequency of the cramping muscle. An EMG is most helpful to ascertain if there is a neuromuscular cause for the cramping.

The etiology of cramps includes many varied conditions (Table 23–2). Systemic disorders associated with cramps include dehydration and metabolic abnormalities such as hyponatremia, hypomagnesemia, hypocalcemia, hypokalemia, and hypoglycemia. Endocrine disturbances such as hyperthyroidism or hypothyroidism and adrenal insufficiency may be the cause of cramps. During pregnancy cramps occur more frequently during the

TABLE 23-1 Characteristics of Cramps

Abrupt onset, short duration
Muscle is strongly contracted
Cramp is palpable, relieved by stretching or massage
Cramping occurs after voluntary contraction in a shortened muscle
If cramps occur diffusely, a neuromuscular cause should be considered
Cramps occur at night or at rest
Electromyography during a cramp demonstrates very rapid, >50 Hz irregular discharges of motor unit potentials
Activation of an antagonistic muscle slows the frequency of the cramping muscle

TABLE 23-2 Conditions Associated with Cramps

Systemic disorders: dehydration, metabolic abnormalities, hyponatremia, hypokalemia, hypomagnesemia, hypocalcemia, and hypoglycemia
Endocrine disturbances: hyperthyroidism or hypothyroidism, adrenal insufficiency, pregnancy later months
Drugs and toxins: clofibrate, anticholinesterase medications, diuretics, lithium, terbutaline, beta-adrenergic agonists
Motor nerve disorders: amyotrophic lateral sclerosis, hereditary and acquired motor neuropathies, root pathology
Spontaneous activity syndromes: Issac's syndrome, stiff-person syndrome, cramp- fasciculation syndrome
Myopathies: Becker muscular dystrophy, McArdle's disease, mitochondrial disorders, disorders associated with fatty acid metabolism, myoadenylate deaminase (AMPD1) deficiency

later months. There are a number of drugs and toxins which may be associated with cramps. The most common include clofibrate, anticholinesterase medications, diuretics, lithium, terbutaline, and ß-adrenergic agonists.

With our patient's normal neurological examination and laboratory testing, a neuromuscular cause for his cramps is unlikely. Nerve conduction studies (NCS) and EMG studies would be very helpful in excluding neuromuscular disease as a possible cause. Motor nerve disorders which are associated with cramps include amyotrophic lateral sclerosis (ALS), hereditary and acquired motor neuropathies, and root pathology. In these conditions, the neurological examination would demonstrate the characteristic lower motor neuron findings of weakness, atrophy, and fasciculations. In ALS there would be upper motor neuron findings as well: increased tone, brisk reflexes, and pathological reflexes. The NCS may show decreased amplitude of the motor nerve compound muscle action potentials. On EMG examination active denervation, fasciculations, neuropathic motor units, and reduced motor recruitment patterns are seen. Any disorder that results in denervation may cause cramps, such as a polyneuropathy.

There are a number of spontaneous activity syndromes associated with cramps. Again, other symptoms are prominent in addition to cramps. These conditions include Isaac's syndrome, stiff-person syndrome, and cramp-fasciculation syndrome.

In Isaac's syndrome there is a diffuse stiffness at rest, and 70% of patients have weakness. Hyperhidrois is also common. There is visible myokymia and neuromyotonia. An EMG examination demonstrates neuromyotonia, myokymia, and fasciculations. Potassium channel antibodies present in 28%–100% of patients depending on the type of antibody testing used. Treatment is with mexiletine, carbamazepine, or phenytoin.

Stiff-person syndrome usually occurs in females. There is severe axial muscle contraction. The individual walks like a "tin soldier." This condition can be worsened by emotional triggers. Autonomic involvement, especially hyperhidrosis and gastrointestinal problems, can be a feature. The presence of antiglutamic dehydrogenase antibodies is helpful in confirming the diagnosis, as is EMG, which demonstrates continual motor unit discharges in widespread muscles, especially the axial muscles. Treatment is difficult, employing both immune modulating therapy—for example, steroids, plasma exchange, and human immunoglobulin—as well as antispasticity medications such as baclofen or diazepam. In our experience the use of intrathecal baclofen is usually not tolerated due to side effects.

Cramp-fasciculation syndrome usually occurs in young to middle-aged adults. These cramps are painful, involuntary, abrupt, and usually in the gastrocnemius and quadriceps muscles. These cramps are palpable. This is associated with muscle pain and stiffness. Strength is normal. There may be potassium channel antibodies in some patients. Repetitive stimulation may produce cramp discharges. An EMG examination demonstrates fasciculations.

Myopathic disorders may also be associated with cramps. These muscle disorders usually have an elevated CK level, weakness, and EMG abnormalities. These include Becker's muscular dystrophy and McArdle's disease. Becker's muscular dystrophy is the result of a dystrophin mutation. There is extremity weakness, which is more prominent proximally, along with pseudohypertrophy, especially of the calves. There may be contractures of the ankles. A cardiomyopathy may be present. This is a slowly progressive disorder. Testing for dystrophin can be performed to confirm diagnosis. McArdle's disease is a glycogen storage disease, which is caused by a deficiency of myophosphorylase. It is the most common of the various types of glycogen storage diseases but is still rare (1/100,000). It usually presents

in childhood but sometimes not until the third or fourth decade of life. Symptoms include exercise intolerance with myalgia, early fatigue, painful cramps, weakness of exercising muscles, and myoglobinuria. This is appreciated by the patient complaining of "cola-colored urine." Patients may exhibit a "second wind" phenomenon. This describes the patient's ability, after resting, to resume normal activities due to alternative routes of energy metabolism. As patients age, there may be increasing weakness and substantial muscle loss. For diagnosis a muscle biopsy will document the absence of myophosphorylase; periodic acid-Schiff stain can show abnormally stored glycogen. The ischemic forearm exercise test findings consistent with McArdle's disease would be an absence of lactate elevation and an exaggerated rise of ammonia levels. The EMG examination demonstrates electrically silent cramps. Genetic testing on muscle may be performed.

There are other myopathic disorders which are more commonly associated with myalgias, although cramps are sometimes mentioned. These include the mitochondrial disorders, disorders associated with fatty acid metabolism, and myoadenylate deaminase (AMPD1) deficiency.

Finally, polymyalgia rheumatica is worth remembering as an important and relatively common disorder (12–65/100,000 patients above 50 years of age). This disorder is associated with myalgias and stiffness. It is very responsive to treatment and can be associated with giant cell arteritis. Usually, the onset is rapid, with proximal pain especially of the shoulders or lower back and hips. On examination there is no clear weakness, although on muscle testing there may not be normal strength due to the patient's discomfort and pain. Laboratory testing demonstrates an elevated erythrocyte sedimentation rate (ESR) and C-reactive protein. Levels of CK are normal. The EMG examination is normal except for perhaps decreased voluntary recruitment due to discomfort. Treatment with low doses of prednisone results in a dramatic improvement of the patient's symptoms. It is especially important in the elderly to remember to use therapy to prevent osteoporosis associated with the use of prednisone. Following the ESR to monitor therapy and a slow taper of prednisone are recommended.

We stressed to our patient to use a sports drink that has electrolyte supplementation. Three weeks later the patient called to say his symptoms had improved (Table 23–3).

TABLE 23-3 Some Medications and Supplements Used to Treat Cramps

Quinine sulfate
Carbamazepine
Phenytoin
Verapamil
Amitriptyline
Vitamin E
Riboflavin
Calcium

KEY POINTS TO REMEMBER

- A number of disorders as well as medications may cause cramps. It is important to differentiate cramps from muscle pain.
- An EMG performed during a cramp demonstrates very rapid, >50 hertz, irregular discharges of motor unit potentials.
- Any denervating condition can be associated with cramps, such as ALS.
- There are a number of spontaneous activity syndromes associated with cramps; there are other symptoms which are prominent. These are Isaac's syndrome, stiff-person syndrome, and cramp-fasciculation syndrome.
- McArdle's disease is a glycogen storage disease. An EMG examination demonstrates electrically silent cramps.
- Polymyalgia rheumatica presents with muscle pain and stiffness. It is associated with giant cell arteritis. The ESR is very elevated. There is a remarkable improvement in symptoms with low-dose prednisone.

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SECTION III

Neuromuscular Junction and Autonomic Neuropathy

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24 Myasthenia Gravis

The patient is a 72-year-old female with a lower left facial droop and bilateral ptosis. Her daughter noticed her facial droop, which prompted a visit to the emergency department. She recalled that 3–4 days prior to her first visit she had difficulty with eating, and noticed pocketing of food in her left cheek. She also noticed drooping of her eyelids when reading. She complained of severe fatigue and has noticed she cannot do housework for longer than 10 minutes before needing rest.

Her initial examination revealed a hypophonic voice with a nasal quality, ptosis, left lower facial weakness, and mild global weakness. Her initial laboratory work-up was negative and included a complete blood count, electrolytes, prothrombin time, partial thromboplastin time, hepatic function tests, thyroid-stimulating hormone, and urinalysis. Her electrocardiogram and computed tomography of the head were normal. You are called by the emergency room physician for help in further work-up of her weakness.

What do you do now?

A review of the history and a complete neurological examination are necessary to narrow the differential. Her voice was hypophonic with a nasal quality, suggesting palatal weakness. The prominent lower left facial droop with sparing of the frontalis suggests supranuclear weakness. Stroke commonly produces this pattern, though the temporal course is more acute and bilateral ptosis would be unlikely. In spite of these inconsistencies, cranial nerve findings with facial weakness warrant magnetic resonance imaging. Motor neuron disease can also produce weakness, with bulbar and neck extensor weakness, often in older patients. It presents more insidiously and is relentlessly progressive, with widespread denervation, remarkable distal atrophy, and upper motor neuron signs making it an unlikely diagnosis in this patient.

Diseases that affect the muscle or the neuromuscular junction (NMJ) should still be in our differential. While it is more common for diseases of the NMJ to present as weakness without a clear pattern, they can also mimic either a central or a peripheral process. There are primarily two disorders that affect the NMJ, myasthenia gravis and Lambert-Eaton myasthenic syndrome (LEMS). In myasthenia, antibodies are directed against postsynaptic nicotinic receptors at the NMJ. In contrast, LEMS impairs the release of acetylcholine through an antibody mediated attack on presynaptic voltage gated calcium channels. These antibodies can be demonstrated in the laboratory which confirms the diagnosis. LEMS causes proximal muscle weakness, depressed muscle stretch reflexes, and autonomic symptoms like dry mouth. Reflexes may improve slightly after exercise. Malignancy is found in 50%–70% of patients with LEMS, and distal weakness can be the presenting symptom, as opposed to myasthenia where bulbar weakness, often in the form of ptosis or diplopia, is seen initially.

Given the association of LEMS with malignancy and our patient's weight loss, computed tomography (CT) of the chest should be obtained. This has the added benefit of identifying the thymoma or thymic hyperplasia seen in 20% and 70% patients with myasthenia, respectively. If clinical suspicion was higher, a CT of the abdomen and pelvis or a positron emission tomographic scan might be helpful to look for evidence of malignancy.

The hallmark of myasthenia is fatigability, which would appear to be easily documented at the bedside. In practice this can actually be difficult. This patient's history reveals that she becomes tired easily when doing

housework, reading, or watching TV. These findings are common in patients with myasthenia, and they typically feel better after a night's rest, with worsening of symptoms later in the day. Fatigability is often tested with sustained upgaze, a task that commonly produces ptosis or diplopia within 30–60 seconds in these patients. Repeated muscle testing can also bring out weakness. Another useful finding is neck flexor weakness. Many neuropathic and myopathic disorders will cause neck extensor weakness and even the "dropped head sign." However, with the exception of myasthenia, there are relatively few conditions that will affect predominantly the neck flexors.

Myasthenia can present at any age but has a bimodal peak in the third and sixth decades. Ocular weakness is the presenting symptom in most patients and may be the only symptom in 10%. More often, it progresses in a rostrocaudal direction, in contrast to LEMS which progresses from distal to proximal muscles. Weakness of the diaphragm can produce shortness of breath, and 15%–20% of patients will require some form of ventilation. Orthopnea with rapid resolution upon sitting is another common pattern seen in neuromuscular weakness.

Other conditions that can mimic myasthenia include botulism, toxic/metabolic neuropathies, and brainstem diseases. Botulism will cause dry mouth, double or blurred vision, bulbar weakness, vomiting, and diarrhea or paralytic ileus with severe constipation. It leads to body paralysis, affects the diaphragm, and can cause respiratory failure. Pupillary involvement is common in botulism, and unusual in myasthenia. Repetitive stimulation on nerve conduction studies will produce an incremental response in botulism.

Several medications can cause weakness and either mimic myasthenia or exacerbate it. Some of these include penicillamine, curare, aminoglycosides, procainamide, and quinine. Weakness typically improves after the offending drug is stopped. Hyperthyroidism is an important treatable cause of nonspecific weakness and should be excluded with appropriate laboratory testing. Progressive external ophthalmoplegia (PEO) is a mitochondrial disorder that can mimic ocular myasthenia, but these patients do not have variability of ptosis and do not complain of double vision. Oculopharyngeal muscular dystrophy (OPMD) can also mimic myasthenia in older patients, especially when speech or swallowing problems are present in addition to ocular weakness. These patients have progressive ptosis and dysphagia followed by extraocular weakness and may not complain of double vision.

The lack of motor fluctuations and relatively progressive nature of both PEO and OPMD should help differentiate them from myasthenia.

Classically, the "Tensilon test" is used to make the diagnosis of myasthenia. This test is 80%–90% sensitive for myasthenia. This should only be done when there is an objective finding to follow, such as ptosis, markedly dysconjugate gaze, or dysarthria. A cardiac monitor is necessary, and atropine should be available since edrophonium can cause bradycardia. Baseline testing should be repeated before administration of edrophonium. A small test dose (2 mg) is then administered intravenously. If tolerated, the remaining 8 mg is given. The effects usually last less than 10 minutes.*

With the advent of improved laboratory testing to assist with the diagnosis of myasthenia, the Tensilon test may not be required. Antibody tests will be positive in 30%–50% of patients with ocular myasthenia and 80%–90% of patients with generalized myasthenia. Acetylcholine receptor antibody testing is available against binding, modulating, and blocking antibodies. Most would start with binding, but if this is negative, the other two

TABLE 24-1 Myasthenia

	Myasthenia Gravis	Lambert-Eaton Myasthenic Syndrome
Common pattern of weakness	Ocular or bulbar weakness initially with craniocaudal progression	Limb weakness initially with progression to bulbar muscles later
Exercise	Worsens weakness	Improves weakness
Associated tumors	Thymic tumors	Small cell lung carcinoma
Muscle stretch reflexes	Normal or increased	Decreased but improves with exercise
Autonomic involvement	Absent	Present
Autoantibody in serum	Acetylcholine receptor antibodies and possibly MuSK.	Antibodies against calcium channels
Repetitive stimulation	Decremental response	Incremental response

* Since late February 2008, has been out of production. Once supplies are gone, the Tensilon test will no longer be an option.

should be obtained. Muscle-specific receptor tyrosine kinase is a newer test used in seronegative patients and is positive in another 30%–40% of patients with generalized myasthenia. It is rarely detectable in ocular myasthenia.

Electrodiagnostic studies can also assist in diagnosing myasthenia. Nerve conduction, repetitive stimulation, exercise testing, and single fiber electromyography (EMG) can be done. Typically, routine nerve conductions are normal, and abnormalities should make us question the diagnosis. When using repetitive stimulation, we look for a decremental response of 10% or more. The sensitivity of the test improves when testing proximal nerves or following exercise. Single fiber EMG is extremely sensitive for myasthenia, but it is not specific; also, abnormalities are seen in several myopathic and neuropathic disorders. It is typically done only when there is a high index of suspicion and other tests are negative (Table 24–1).

KEY POINTS TO REMEMBER

- **Variable weakness with fatigability is highly suggestive of NMJ localization.**
- **Myasthenia can present with falsely localizing findings.**
- **Neck extensor weakness is commonly seen in myasthenia gravis, but neck flexor weakness is more specific.**
- **Most patients with myasthenia can now be diagnosed with laboratory tests alone.**
- **In patients with a neuromuscular localization, it is important to consider LEMS, which is often associated with malignancy.**

Further Reading

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25 Treatment of Myasthenic Crisis

This patient is an 80-year-old female with a history of myasthenia gravis, previously well controlled with pyridostigmine alone, who presents to the emergency department with worsening weakness. She is short of breath and this most pronounced supine. She is diagnosed with a lower lobe pneumonia. Swallowing triggers a weak cough. Her motor examination reveals generalized weakness. You are consulted for the question of intubation and additional treatment recommendations.

What do you do now?

Weakness due to worsening myasthenia can easily predispose patients to aspiration and subsequent pneumonia. Regarding the question of intubation, there are several clinical criteria that can be used to help determine the need for ventilation. Increasing weakness, dysphagia, dysphonia, and dyspnea are all considered general warning signs. Rapid and shallow breathing, tachycardia, weak cough, staccato speech, accessory muscle use, paradoxical breathing, orthopnea, increased weakness of the neck, and cough after swallowing are all concerning. One bedside test that can be followed easily is the single breath count. Normal individuals can frequently get to 50 on a single breath. A single breath count of less than 15 suggests severe impairment of the patient's vital capacity.

Objectively, we can follow vital capacity as well as maximum inspiratory and expiratory pressures. An easy rule of thumb is the 20–30–40 rule. That is, vital capacity less than 20 ml/kg, a maximum inspiratory force greater than –30 cm water, or a maximum expiratory force of less than 40 cm water are rough objective predictors of the need for intubation. Most of the data on predictors of the need for mechanical ventilation in neuromuscular disease come from studies on Guillain-Barré syndrome. Myasthenia gravis fluctuates more and therefore is less predictable. Our threshold for intubation should therefore be slightly lower with myasthenia gravis. Noninvasive methods such as bilevel positive airway pressure (BiPAP) can be helpful in the ambulatory setting to reduce the work of breathing, and some use this to try and avoid intubation in acute episodes. Again, because of the fluctuating course of weakness in myasthenia gravis, it should be used with caution in acute cases, especially if upper airway weakness is present.

Occasionally, patients with worsening weakness take excessive pyridostigmine, leading to cholinergic crisis, a condition of excessive acetylcholine at the neuromuscular junction. Symptoms include worsening weakness, hypersalivation, abdominal pain, and diarrhea. This can be difficult to distinguish from myasthenic crisis, a rapid worsening of myasthenia gravis that leads to intubation. While treatment with a test dose of edrophonium can distinguish the two, in practice these patients are in acute distress and it may be better to start by treating the more severe myasthenic crisis. If symptoms worsen when receiving pyridostigmine (Mestinon), cholinergic crisis should be suspected.

Short-term treatment options used in more severe cases include plasma exchange and intravenous immunoglobulin (IVIG). With plasma exchange the goal is to remove offending antibodies, while IVIG supplies pooled antibodies. While there is no statistical difference in the effectiveness of the two approaches, IVIG is generally better tolerated and easier to administer. It is therefore recommended in myasthenic crisis or in patients with severe weakness.

In the long term, this patient, like most patients with myasthenia gravis, will require immunosuppressant therapy. This has historically included corticosteroids, and many patients continue to use them or have been on them in the past. It may be best to try and avoid this where possible but, when employed, it is important to start with a low dose, such as 15–20 mg/day, and titrate up to clinical response or 60 mg/day, whichever is lower. This modest starting dose is necessary as the myasthenia gravis symptoms can worsen initially for reasons that are unclear. If the patient is already on a ventilator, high-dose therapy can be started without dose titration. Benefit is often seen after 6–8 weeks of therapy and, when improvement plateaus, a slow, alternate-day taper is started. A dose reduction of 10% every 6 weeks as tolerated is typical. While on steroids, patients will need to be followed closely for known complications. Many patients will require some dose of steroids indefinitely. In an effort to limit steroid dose, other immunosuppressants, such as azathioprine, cyclosporine, and cyclophosphamide, are commonly used. More recently, the better-tolerated mycophenolate mofetil has also been used with good results, and it is generally our preferred agent. It is usually started slowly at 500 mg/day, and slowly increased to 1000–1500 mg twice daily. Therapeutic effects in our experience begin within 1–2 months. Regular monitoring of blood counts and chemistry profile is essential. It is also important to have the patient inform you of any febrile illnesses while on therapy. With any immunosuppressant medication, a history of tuberculosis exposure should prompt skin testing and, if positive, maintenance plasmapheresis or IVIG should be considered.

Signs and Symptoms that can Suggest the Need for Intubation

1. Severe and increasing generalized weakness or worsening dropped head sign
2. Dysphagia, dysphonia, or dyspnea on exertion or at rest

3. Alterations in breathing pattern including orthopnea; rapid, shallow, or paradoxical breathing; and accessory muscle use
4. Tachycardia
5. Weak cough or increased frequency of cough after swallowing
6. Staccato speech
7. Single breath count of less than 15 or a progressively worsening single breath count
8. Vital capacity <15 ml/kg, <1 l (or a 50% drop in vital capacity)
9. Maximum inspiratory pressure >–30 cm water
10. Maximum expiratory pressure <40 cm water
11. Nocturnal desaturations

KEY POINTS TO REMEMBER

- **Clinical signs and the single breath count, in addition to more formal pulmonary function tests, can help guide the need for intubation in patients with potential myasthenic crisis.**
- **Excessive pyridostigmine can lead to cholinergic crisis, which can be difficult to distinguish from myasthenic crisis. When in doubt, initiate treatment for the latter, including intubation to protect the airway. If the patient worsens, suspect cholinergic crisis.**
- **Myasthenia gravis tends to fluctuate more than other neuromuscular diseases that typically require ventilation, so the threshold for intubation should be slightly lower with this diagnosis.**
- **In the short term, IVIG can be very helpful in improving symptoms of myasthenia gravis.**

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26 Diagnosis of Autonomic Neuropathy

You are called by the emergency room (ER) physician. The ER physician is evaluating a 44-year-old plumber who has subacute onset of syncope. He is having trouble standing upright due to low blood pressure. He is also complaining of difficulty initiating urination and constipation. The patient feels that his vision is blurry and grays out at times. He has felt that his symptoms have increased over the last week. Prior to these symptoms, the patient had a mild upper respiratory tract infection. You come in to evaluate the patient. His past history is unremarkable except for hypertension treated with a beta-blocker. The patient has smoked approximately one pack of cigarettes per day for the last 25 years. He drinks two beers per day. On general examination the patient appears ill. His blood pressure is 120/70 mm Hg supine, with a heart rate (HR) of 65 beats per minute (bpm); upon sitting up, the patient feels woozy, his blood pressure is 88/50 mm Hg, and his pulse is 67 bpm. The patient feels too weak to continue standing. The patient has dry lips and has no axillary sweating. Bowel sounds are hypoactive. The bladder

seems dilated on percussion. On general neurological examination the patient's mental status is intact. Cranial nerves demonstrate sluggish pupils at 5 mm. Reflexes are symmetrically present. The patient complains of some tingling of the feet, but sensory examination to all modalities is normal.

What do you do now?

The patient has symptoms of an autonomic neuropathy (AN). The blood pressure decrease is >30 mm Hg systolic and 15 mm Hg diastolic, which certainly qualifies as orthostatic hypotension (OH). The definition of OH is a decrease of 20 mm Hg systolic and 10 mm Hg diastolic within 3 minutes of standing. In addition, the patient's HR minimally increases upon sitting. If his OH were due to dehydration, his HR would markedly increase upon standing. The patient also exhibits other symptoms and signs of AN. His visual blurring may be due to his OH and presyncope or problems with pupillary dilation and constriction. Patients with OH often complain of fatigue. The lack of axillary sweating suggests a defect in sudomotor function. It is important to note that sudomotor function is sympathetically mediated, although the end organ neurotransmitter is acetylcholine. The pupils appear to be mid-position with no reaction to light. This suggests both parasympathetic and sympathetic defects. The patient also has symptoms and signs of gastrointestinal and urinary problems, which are predominantly due to parasympathetic dysfunction. Taken together this appears to be a relatively acute onset of an AN, involving both the parasympathetic and sympathetic divisions (Table 26–1). The clinical picture follows an upper respiratory tract infection, which suggests an autoimmune

TABLE 26-1 Causes of Peripheral Autonomic Neuropathy

Acute
Autoimmune autonomic ganglionopathy
Paraneoplastic autonomic neuropathy
Guillain-Barré syndrome
Acute porphyria
Botulism
Lambert-Eaton syndrome
Toxic neuropathies
Chronic
Diabetes
Amyloidosis
Inherited sensory and autonomic neuropathy
Toxic neuropathies
HIV infection
Pure autonomic failure
Connective tissue disorders

basis. This would point us to the diagnosis of autoimmune autonomic ganglionopathy (AAG). The differential diagnosis in this situation is not large but would include Guillain-Barré syndrome (GBS) with prominent autonomic features. The lack of a somatic peripheral neuropathy makes this diagnosis unlikely. In GBS there is usually prominent weakness with some sensory findings and absent reflexes. Cranial nerves, especially the facial nerve, can be commonly affected; and respiratory insufficiency is an important complication to anticipate. Cerebrospinal fluid protein is elevated in GBS and can also be elevated in AAG. Nerve conduction studies in GBS will demonstrate the usual findings of prolonged F waves, slowed motor nerve conduction, and conduction block. Abnormalities of sensory nerve conduction can also be present. It is important to remember that in GBS autonomic symptoms and signs may be prominent. The other condition in our differential would be paraneoplastic autonomic neuropathy (PAN). The most common malignancy associated with this condition is small cell cancer of the lung. Other malignancies include ovarian carcinoma, breast carcinoma, lymphoma, and thymoma. The time course is usually subacute and slowly progressive. Usually, PAN presents prior to the discovery of the malignancy. It can present with other paraneoplastic syndromes, such as Lambert-Eaton syndrome or limbic encephalitis, or it can be the only manifestation of a paraneoplastic syndrome. The most common antibody associated with PAN is anti-Hu, also known as type I antineuronal nuclear antibody. In a series of patients with anti-Hu antibodies, dysautonomia was present in 10%–30%. The presentation of PAN is identical to that of AAG. There is a variant of PAN where severe gastrointestinal dysfunction is present. This picture includes pseudo-obstruction, regurgitation, nausea, and inability to eat. Treatment of the underlying malignancy may be helpful. Treatment results with immune modulating therapies have not been compelling. It is important to note that the diagnosis of PAN can be difficult in the patient with malignancy due to the confounding factors of chemotherapy and systemic illness. If the time course is unclear, other conditions to consider in the differential diagnosis of PAN include amyloidosis and diabetic autonomic neuropathy (DAN). In these two conditions the clinical picture is much slower. Usually in DAN, OH is a late manifestation. The distal polyneuropathy would be more prominent than the autonomic component in diabetics. In amyloidosis there is usually an apparent distal polyneuropathy

as well, carpal tunnel syndrome may be present. Biopsy of the appropriate tissue demonstrating amyloid with Congo red stain is diagnostic. In familial forms of amyloidosis genetic testing may be performed.

In our patient the two most likely possibilities are AAG and PAN. The patient's history of smoking would be worrisome for a malignancy and possible PAN. The patient was admitted, and routine chest radiographs and computerized tomography of the chest were unremarkable. The patient's blood work was unremarkable, including complete blood count, chemistry profile, erythrocyte sedimentation rate, C-reactive protein, and serum protein electrophoresis. Spinal fluid protein was elevated at 68 mg/dl. It was assumed that this was most likely AAG but that an occult malignancy could still be present.

What are the features of AAG (Table 26–2)? As discussed, AAG usually has an acute or subacute presentation. Usually, OH and gastrointestinal dysfunction are common features, occurring in 70% of patients. There can also be sweating disturbances, sexual dysfunction, bladder and bowel dysfunction, and visual problems including dry eyes. In its presentation, AAG may be spotty, affecting parasympathetic function more or less than sympathetic and certain end organs more than others. A preceding viral infection, usually an upper respiratory tract infection, is reported. There is not a significant somatic polyneuropathy present, although some patients may complain of tingling. Nerve conduction studies are unremarkable.

Are there other diagnostic tests that can be performed? Autonomic testing can document the clinical abnormalities (Table 26–3). This testing can range from very simple to quite sophisticated. The testing battery usually includes HR response to deep breathing (Fig. 26–1), heart response to the Valsalva maneuver, orthostatic blood pressure measurements, and measurements of sweating. With more sophisticated equipment instantaneous

TABLE 26-2 Features of Autoimmune Autonomic Ganglionopathy

Acute or subacute onset
Monophasic course
Sympathetic and parasympathetic deficits
Pupillary and gastrointestinal findings common
No somatic peripheral neuropathy
Antibodies against neuronal acetylcholine receptor
Antecedent viral infection

TABLE 26-3 Autonomic Testing

Heart rate responses to deep breathing	cardiac parasympathetic
Valsalva maneuver	cardiac parasympathetic
Blood pressure measurements	sympathetic
Sweat tests	sympathetic sudomotor

blood pressure measurements can be performed. In addition, frequency analysis of HR can determine parasympathetic and sympathetic components. Further gastrointestinal, genitourinary, and pupillary testing can also be performed. The autonomic testing would not differentiate the cause of our patient's autonomic dysfunction; it would only document and measure the severity.

In up to 50% of patients with AAG there are autoantibodies directed against the ganglionic acetylcholine receptor. The level of these antibodies can correlate with the severity of the autonomic testing and clinical picture.

The course of AAG is monophasic illness. It is very unusual for there to be reoccurrences of the disease. Recovery is slow and may be incomplete. We are surprised that recovery in AAG may continue over a longer period than in GBS. There are recent reports of immune modulating therapy being beneficial in AAG. These therapies have included intravenous immunoglobulin

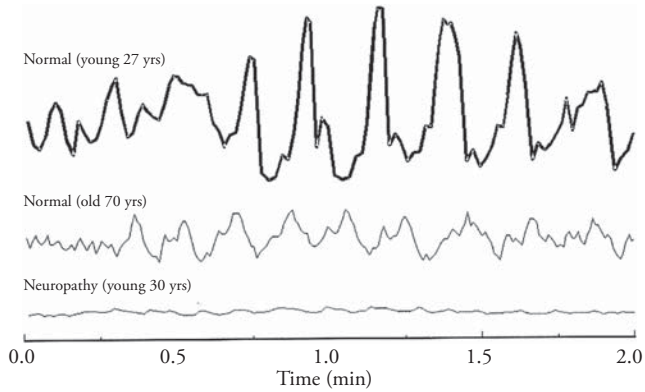


FIGURE 26-1 Heart rate responses to deep-breathing normal and a patient with diabetic autonomic neuropathy. Source: Novak V, Mendell, JR. Evaluation of the peripheral neuropathy patient using autonomic reflex tests. In: Mendell JR, Kissel JT, Cornblath DR (eds), Diagnosis and Management of Peripheral Nerve Disorders. New York: Oxford University Press, 2001.

(IVIG) therapy, plasma exchange, and immunosuppressive agents such as rituximab.

Our patient had a minimal response to IVIG therapy. His persistent OH was an ongoing problem despite treatment. The patient developed a persistent cough 6 months later. Repeat chest radiographs and computerized tomographic scans of the chest were unremarkable. Positron emission tomography demonstrated suspicious uptake in the right lung. Bronchoscopy confirmed a small cell carcinoma of the lung.

KEY POINTS TO REMEMBER

- **Orthostatic hypotension is defined as a >20 mm Hg systolic and 10 mm Hg diastolic drop in blood pressure within 3 minutes of standing.**
- **In dehydration OH demonstrates an increase in HR upon standing.**
- **We can differentiate AAG from GBS by the lack of peripheral nerve involvement and normal nerve conduction studies.**
- **In 50% of patients with AAG there are antibodies directed against the ganglionic acetylcholine receptor.**
- **Autonomic testing can document and assess the severity of the autonomic deficits but cannot define the disease.**
- **Amyloidosis, AAG, paraneoplastic autonomic neuropathy, diabetic autonomic neuropathy, and GBS are considered in the differential diagnosis of acute or subacute AN.**

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27 Management of Autonomic Neuropathy

An endocrinology colleague calls you concerning a patient of his. The patient is a 45-year-old gentleman with type 1 diabetes and poor control for the last 20 years. He has renal insufficiency, diabetic retinopathy treated with laser therapy, and two myocardial infarctions. The patient also has a severe sensorimotor neuropathy. The endocrinologist is worried because the patient appears very ill. The patient is very weak and has severe vomiting, abdominal distention, and urinary retention. The endocrinologist tells you the patient has passed out twice.

What do you do now?

The patient has long-standing, poorly controlled diabetes with a number of typical complications. His gastrointestinal and urinary complaints appear to be related to autonomic dysfunction. The symptom of passing out may be due to orthostatic hypotension (OH), which is probably also a manifestation of autonomic neuropathy (AN). It would be helpful to review some of the peripheral nervous system complications of diabetes.

Diabetes can be associated with cranial mononeuropathies, diabetic lumbosacral plexopathies (Bruns-Garland syndrome), mononeuropathy multiplex (usually on a compressive, rather than a vascular, basis), distal sensory neuropathy, and diabetic AN (DAN) (Table 27–1).

The most characteristic diabetic cranial mononeuropathy is the diabetic third nerve. It is important to remember that the pupil is spared in this condition. Another common cranial nerve which is affected is the seventh nerve, which results in the clinical picture of Bell's palsy. In Bell's palsy the forehead is weak due to frontalis muscle weakness. Taste on the anterior two-thirds of the tongue is affected. There may be tearing due to lacrimal gland dysfunction (being innervated by the seventh cranial nerve) and corneal irritation due to eye closure weakness. Hearing impairment may be present due to involvement of the motor branch to the stapedius muscle. Hearing complaints may include a buzzing noice or heightened sensitivity to loud noises.

Diabetic lumbosacral plexopathy is also called "Bruns-Garland syndrome." This is an acute presentation of hip pain associated with proximal

TABLE 27-1 Simplified Classification of the Common Diabetic Neuropathies

Symmetrical
Sensory or sensorimotor polyneuropathy
Autonomic neuropathy
Focal and Multifocal Neuropathies
Cranial neuropathy
Trunk and limb mononeuropathies
Asymmetrical lower limb motor neuropathy (Bruns-Garland syndrome)
Mixed Forms

Adapted from Bruce T, Dyck PJ. Classification of diabetic neuropathies. In: Dyck PJ, Thomas PK (eds), Diabetic Neuropathy. Philadelphia: WB Saunders, 1999.

leg weakness. The muscles most commonly involved are the iliopsoas, quadriceps, and thigh adductors. This syndrome usually occurs in the context of poor control of diabetes, a distal symmetrical polyneuropathy, and systemic symptoms of weight loss, malaise, and possibly fever. It is felt that this syndrome may be an autoimmune disorder. As a result, treatment with intravenous immunoglobulin and steroids has been suggested. It is important to carefully monitor and control blood glucose levels if steroids are used. This condition should always be considered in a diabetic with hip pain and proximal weakness since the clinical picture may be mistaken for a lumbosacral radiculopathy and surgery may be planned. A proximal distribution of weakness is unusual in lumbosacral radiculopathies, especially with a paucity of sensory findings. As with all neuropathies associated with diabetes, good control of glucose is essential.

The most common neuropathy in diabetes is distal sensory polyneuropathy (DSN). The frequency of DSN ranges from 10% to 65% of diabetic patients. It can occur in both type 1 and type 2 diabetics. There are a number of risk factors which may be related to DSN, including age, control of diabetes, hypertension, elevated lipids, peripheral vascular disease, and smoking. The condition may be painful or painless. Treatment is to optimally control the patient's diabetes. In addition, if it is a painful neuropathy, the usual treatments for pain should be considered. These include tricyclic antidepressants, gabapentin, pregabalin, duloxetine, and compounding creams. A multicenter trial of alpha lipoic acid demonstrated that it may be beneficial in improving the symptoms of DSN.

Finally, DAN occurs in approximately 35% of diabetic patients, although clinically significant DAN occurs in only 5% of patients (Table 27–2). It increases with age, duration of diabetes, and severity of hyperglycemia. It is felt that DAN is a significant risk factor for mortality. Older literature points to a 50% mortality rate at 5 years in diabetics with DAN. It is unclear why there is this increased rate of mortality. It may be due to denervation and the imbalance of sympathetic and parasympathetic innervation of the heart. The lack of parasympathetic innervation of the heart results in a fixed tachycardia and absence of the normal heart rate variability with deep breathing. It is important to note that OH is a very late finding in DAN as opposed to other causes of AN. In diabetics, OH occurs in large part as a result of efferent sympathetic vasomotor denervation, which causes reduced

TABLE 27-2 Features of Diabetic Autonomic Neuropathy

Gustatory sweating, hyperhidrosis of trunk, anhidrosis of feet, hands, and trunk
Erectile dysfunction, retrograde ejaculation
Diabetic bladder, retention can lead to overflow incontinence
Resting tachycardia
Gastroparesis, vomiting, regurgitation, reflux, constipation
Lack of hypoglycemic awareness
Painless cardiac ischemia

vasoconstriction of the splanchnic and peripheral vascular beds. The OH can be exacerbated by insulin administration and large meals.

Sweating disturbances, such as gustatory sweating, occur in DAN. This is a condition where the patient sweats while eating even though the food is not spicy. It usually occurs on the face and trunk. It is felt to be due to denervation supersensitivity, which can occur in the autonomic nervous system, or aberrant regeneration. Patients will have a lack of sweating usually in a "stocking-glove" (distal limb) distribution, which conforms to their DSN. This lack of sweating can be a factor in the development of foot ulcers since the normal skin integrity may be affected. There are studies of sweating on the feet of diabetics which link impaired sweating to the development of diabetic foot problems.

The most common manifestation of DAN is male erectile dysfunction (ED). This occurs in approximately 30%–75% of diabetic males. It may be the earliest symptom of DAN. Less commonly, ejaculatory problems due to sympathetic denervation such as retrograde ejaculation may occur. Also, ED may be the result of additional factors such as a sensory neuropathy or vascular disease.

Bladder symptoms are present in up to 50% of patients, and physiological evidence of bladder dysfunction may be as frequent as 87% of type 1 diabetics. The diabetic bladder has an increased threshold for micturition followed by decreased detrusor activity, leading to incomplete emptying. This can progress to overflow incontinence. In this situation recurrent urinary tract infections are common.

Gastrointestinal problems in diabetes can produce several specific clinical syndromes. Delayed gastric emptying (diabetic gastroparesis) is present in up to 50% of diabetics, although many patients are asymptomatic. The gastroparesis may manifest as nausea, postprandial vomiting, bloating,

belching, loss of appetite, and regurgitation. Gastroparesis often impairs the establishment of adequate glucose control because of the difficulty in titrating insulin to caloric absorption. Constipation is common in diabetics, being reported in 60% of patients. The constipation may be the result of loss of the gastrocolic reflex and loss of extrinsic and intrinsic autonomic innervation. Diabetic diarrhea is usually profuse and watery and occurs at night. The diarrhea can alternate with constipation and last for days. Fecal incontinence is often exacerbated by diarrhea.

The treatment of AN will be briefly discussed in relation to the problems discussed above (Table 27–3).

For OH, simple measures may be helpful, such as increasing fluid and salt intake. In addition, raising the head of the bed 10–20 degrees activates the renin–angiotensin–aldosterone system and decreases nocturnal diuresis. It is important for the patient to decrease recumbent time and to perform physical countermeasures, such as muscle tensing and squatting. It is essential to discontinue medications which may lower blood pressure. We find that patients do not tolerate fitted elastic stockings very well. The patient should eat small and frequent meals to avoid postprandial hypotension. Medications which can be used are fludrocortisone, midodrine, and pyridostigmine. (Pyridostigmine may work by inhibiting acetylcholinesterase, which increases sympathetic ganglionic neurotransmission since acetylcholine is

TABLE 27-3 Treatment of Diabetic Autonomic Neuropathy

Orthostatic hypotension: increase fluid salt intake, raising head of the bed, physical countermeasures, small and frequent meals, fluorohydrocortisone, midodrine, pyridostigmine
Sweating: anticholinergics (if tolerated)
Bowel: frequent and small meals, erythromycin, metoclopramide, H2 agonists, proton pump inhibitors, stool softeners, osmotic laxatives
Bladder: evaluation of medications, bladder training, medications not that helpful, catheterization
Erectile: check medications and alcohol usage, trial of sildenafil, urological consultation
Cardiac: careful evaluation of medications in relation to heart rhythm, painless cardiac ischemia

the neurotransmitter.) It is important to note that continued but less severe upright hypotension and supine hypertension can occur with treatment. The supine hypertension is felt to be less worrisome by some investigators, but careful treatment with clonidine may help to decrease the supine hypertension while not exacerbating the upright hypotension. Cardiac parasympathetic denervation may make the patient's heart rhythm more sensitive to anticholinergic and sympathetic medications.

Sweating disturbances may be very vexing to treat. Anticholinergics can be helpful in decreasing sweating, but cardiac effects should be carefully assessed. There are topical creams which can decrease sweating, such as glycopyrrolate in a 0.5% cream. Anhidrosis is very difficult to treat.

The initial treatment of ED should include a history of medications which the patient is taking as well as alcohol usage. If there is no obvious contributing factor, a trial of sildenafil can be suggested. If there is no improvement, referral to a urologist specializing in ED can be helpful.

The medications of a patient with "diabetic bladder" should be reviewed to determine if there are narcotics or anticholinergics which are affecting bladder function. The diabetic patient should be instructed to have scheduled voiding and to use techniques to try to fully empty the bladder. Evaluation by a urologist with cystometrics can assist. Bethanecol and phenoxybenzamine may be of limited use. Clean, intermittent self-catheterization is the primary therapy for impaired or absent detrusor muscle activity due to AN. The interval between catheterizations should be designed to maintain a residual volume of less than 100 cc and to avoid incontinence.

The gastrointestinal problem of gastroparesis can be treated with frequent, small meals and pharmacotherapy. The dopamine agonist metoclopramide continues to be the first-line therapy for gastroparesis. Given in doses of 5–20 mg orally, 30 minutes before meals and bedtime, metoclopramide accelerates gastric emptying and has a central antiemetic action. It also may release acetylcholine from intramural cholinergic neurons or directly stimulate the antral muscle. If one is treating patients with Parkinson's disease, extreme care must be exercised using metoclopramide as it can worsen parkinsonian symptoms.

Erythromycin may possess motilin (which increases gut motility) agonist properties. Gastric antisecretory agents such as the histamine-2 (H_2) antagonists and proton pump inhibitors may be used as supplementary agents to

treat the symptoms of gastroesophageal reflux. The majority of patients can be treated with these medical interventions, and jejunostomy tube placement rarely is necessary. Severe cases with intractable vomiting may benefit from nasogastric suctioning.

Bowel hypomotility in AN can also be substantially improved by a regimen that includes increased fiber with a concomitant increase in fluid, stool softeners, and an osmotic laxative. Contact cathartics should be used infrequently. Bowel hypomotility may be accompanied by intermittent bowel hypermotility. Trials of a gluten-free diet and restriction of lactose should be attempted. Cholestyramine, clonidine, somatostatin analogues, pancreatic enzyme supplements, and antibiotics such as metronidazole may benefit some patients.

Often, patients will require hospitalization. This promotes safety while establishing the best OH treatment. A regimen of fluids, glucose, and electrolyte monitoring is easier; and medication adjustments can be made with better confidence and more quickly. Gastrointestinal function can be monitored as well with titration of pharmacological treatment. Bladder function can be assessed and, if necessary, patients can learn self-catheterization. Unfortunately, despite all of the above measures, a significant fraction of patients will have progressive dysfunction and occasionally sudden death, presumably on the basis of cardiac arrhythmia.

KEY POINTS TO REMEMBER

- Diabetic AN occurs in 35% of diabetic patients but is clinically significant in only 5%.
- Diabetic AN is associated with increased mortality (50% mortality at 5 years).
- Orthostatic hypotension can be treated with pyridostigmine.
- Gastroparesis can lead to difficulties in glucose control; frequent small meals and metoclopramide can be helpful.
- Erectile dysfunction is the most common manifestation of DAN, occurring in 30%–70% of male diabetics; and pharmacological treatment of the diabetic bladder is difficult.

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