26 Polyneuropathy

Nerve conduction studies and electromyography (EMG) play key roles in the evaluation of patients with suspected polyneuropathy. Although polyneuropathy has hundreds of potential causes, they can be grouped into several large categories (Figure 26–1). The first step in the evaluation of a patient with polyneuropathy is to reduce the differential diagnosis to a smaller, more manageable number of possibilities. This usually can be accomplished by acquiring several critical pieces of information from the history, physical examination, and electrophysiologic studies.

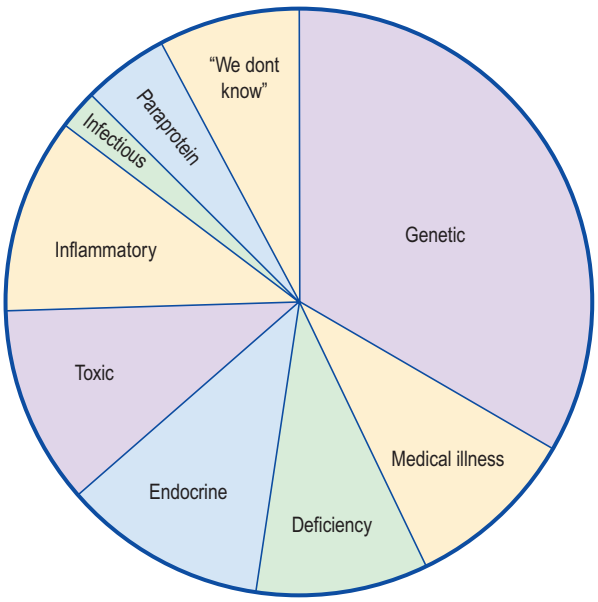


FIGURE 26–1 Overview of polyneuropathy. Although there are literally hundreds of causes of polyneuropathy, they can be grouped into several large categories. Note that even after a complete evaluation, there remain a sizable number (approximately 20%) of patients in whom the diagnosis remains uncertain. Disclaimer: the various categories are for illustrative purposes only, and their relative sizes in the chart should not be interpreted as authoritative, as there are insufficient prevalence data on the various categories of polyneuropathies. However, genetic neuropathies are very common, as are toxic, deficiency (such as vitamin deficiency), endocrine, and other medical conditions that may result in a polyneuropathy. In addition, paraproteins account for a small number (5–10%) of polyneuropathies, especially in patients with difficult to diagnose polyneuropathy.

Electrophysiologic studies can be used (1) to confirm the presence of a polyneuropathy, (2) to assess its severity and pattern, (3) to determine whether motor, sensory, or a combination of fibers are involved, and, most importantly, (4) to assess whether the underlying pathophysiology is axonal loss or demyelination. In cases in which a demyelinating polyneuropathy is found, further differentiation between an acquired and inherited condition can often be made. The information obtained from electrophysiologic testing, in conjunction with key pieces of clinical information, usually allows the differential diagnosis to be narrowed considerably so that further laboratory testing can be more appropriately applied and a final diagnosis reached.

CLINICAL

Polyneuropathy literally means dysfunction or disease of many or all peripheral nerves. Because peripheral nerves can react to disease in only a limited number of ways, polyneuropathies of many different causes may present with similar symptoms and signs. Indeed, most patients with polyneuropathy first present with a combination of sensory and motor symptoms and signs in the feet and lower legs, which later spread proximally in the legs and then into the hands and arms. Despite the many similarities, one can always limit the differential diagnosis of a polyneuropathy by determining the answers to seven key questions.

Key Question No. 1: What is the Temporal Course and Progression of the Polyneuropathy (Acute, Subacute, Chronic; Progressive, Stepwise, Relapsing/Remitting)?

The temporal course and progression can be obtained by the history alone and often confirmed by electrophysiologic studies. Most polyneuropathies are chronic, and their onset cannot be easily determined. Acute polyneuropathies are notably less common (Box 26–1). Among them, Guillain–Barré syndrome (and its most common variant, *acute inflammatory demyelinating polyneuropathy* [AIDP]) is the most distinctive, with an onset over a few days or a few weeks at most. Similarly, most polyneuropathies are slowly progressive (Figure 26–2). Polyneuropathies that progress

DOI: 10.1016/B978-1-4557-2672-1.00026-X

Box 26–1. Acute Polyneuropathies

Guillain–Barré syndrome
Porphyria
Diphtheria
Drugs (e.g., dapsone, nitrofurantoin, vincristine)
Toxins (e.g., arsenic, thallium, triorthocresylphosphate)
Tick paralysis
Vasculitis

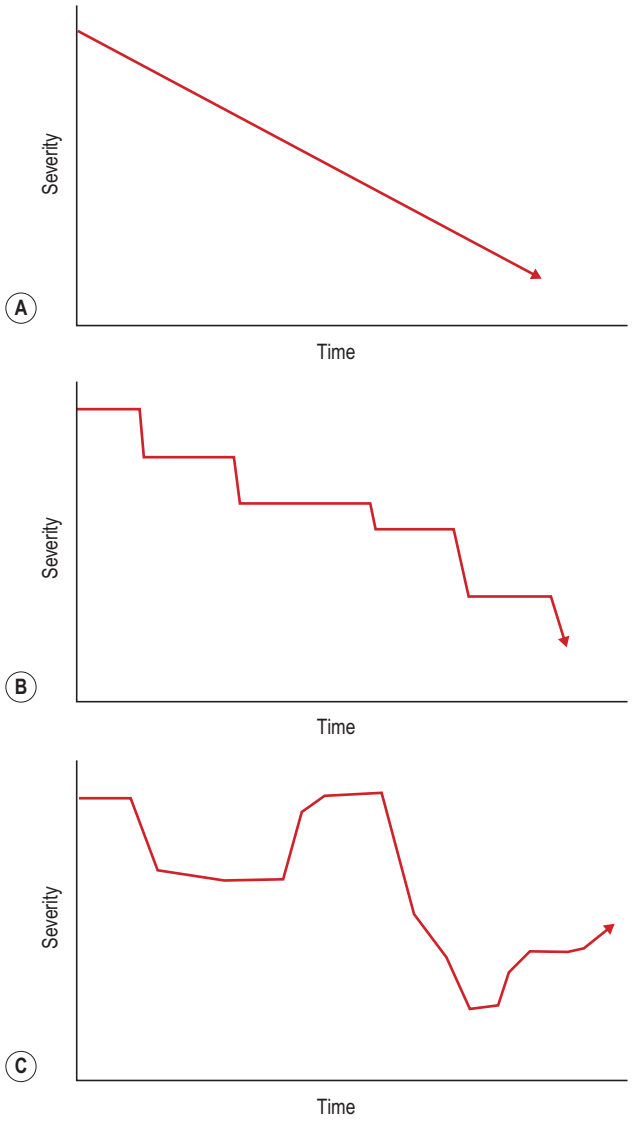


FIGURE 26–2 Temporal progression of polyneuropathy. The pattern of the temporal progression is one of the key historical points in determining the etiology of a polyneuropathy (n.b., worsening severity is denoted as going downward). **A:** Slowly progressive; **B:** Stepwise progressive; **C:** Relapsing / remitting.

in a stepwise fashion are infrequent and are often associated with a mononeuropathy multiplex pattern (discussed later). Likewise, the history of a relapsing/remitting course is distinctly unusual and suggests either an intermittent exposure/intoxication or a variant of chronic inflammatory demyelinating polyneuropathy (CIDP).

Key Question No. 2: Which Fiber Types are Involved (Motor, Large Sensory, Small Sensory, Autonomic)?

The next step is to determine which fiber types are involved. This information is obtained primarily from the history and confirmed by physical examination and electrophysiologic tests. Nerve fibers can be categorized either by the modality carried (motor, sensory, autonomic) or by fiber size. All motor fibers are large-diameter, myelinated fibers, whereas all autonomic fibers are small-diameter, mostly unmyelinated fibers. However, sensory fibers may be either large or small in diameter. Large sensory fibers mediate vibration, proprioception, and touch, whereas small sensory fibers convey pain and temperature sensations.

When nerve is diseased, it can react in a limited number of ways. Thus, many peripheral nerve disorders present with similar symptoms despite different etiologies. Symptoms and signs of nerve dysfunction result either from lack of function (*negative* symptoms and signs) or from abnormal function or overfunctioning (*positive* symptoms and signs). For example, anyone who has "fallen asleep" on his or her arm can remember the initial numbness or lack of feeling (negative symptoms), followed by intense pins-and-needles paresthesias (positive symptoms) as circulation is restored. Characteristic positive or negative sensory symptoms and signs caused by diseased nerves help one recognize which fiber types are involved (Table 26–1).

Determining which fiber types are involved has important diagnostic implications. Most polyneuropathies involve both sensory and motor fibers on electrophysiologic testing, even though, clinically, most distal axonal polyneuropathies exhibit sensory symptoms and findings long before the disease process becomes sufficiently severe to cause actual weakness. Patients with certain hereditary polyneuropathies (e.g., Charcot–Marie–Tooth polyneuropathy) and conditions such as lead poisoning, porphyria, and Guillain–Barré syndrome may exhibit predominantly motor symptoms and signs. On the sensory side, pure sensory neuropathies also are unusual and often suggest a primary process affecting the dorsal root ganglia. These *sensory neuronopathies* are quite rare and are characteristically seen acutely or subacutely as a paraneoplastic syndrome, postinfectious process, or associated with Sjögren's syndrome or pyridoxine (B_6) intoxication. Chronic sensory neuronopathies may be seen in the inherited sensory neuropathies and as a component of some inherited neurodegenerative conditions (e.g., Friedreich's ataxia).

Large and small fibers are affected in most polyneuropathies. Only a few polyneuropathies preferentially affect small fibers (Box 26–2). Manifestations include autonomic dysfunction and a distal sensory deficit, particularly for pinprick, often associated with painful, burning dysesthesias. It is essential to appreciate that routine nerve conduction studies assess only large myelinated fibers. A patient who has a pure small-fiber polyneuropathy, *with complete sparing of the large fibers*, may have completely normal electrophysiologic studies. Conversely, large-fiber

Table 26–1. Negative and Positive Symptoms and Signs of Peripheral Nerve Disease

	Negative	Positive
Motor	Weakness Fatigue Hyporeflexia or areflexia Hypotonia Orthopedic deformities (e.g., pes cavus, hammer toes)	Fasciculations Cramps Myokymia Restless legs "Tightness"
Sensory		
Large fiber	Decreased vibration sensation Decreased joint position sensation Hyporeflexia or areflexia Ataxia Hypotonia	"Tingling" "Pins and needles"
Small fiber	Decreased pain sensation Decreased temperature sensation	"Burning" "Jabbing" "Shooting"
Autonomic	Hypotension Arrhythmia Decreased sweating Impotence Urinary retention	Hypertension Arrhythmia Increased sweating

Box 26–2. Small-Fiber Peripheral Polyneuropathies

Diabetes
Amyloidosis (inherited and acquired)
Toxins (especially alcohol)
Drugs (especially ddI, ddC)
Hypertriglyceridemia
Hereditary sensory neuropathies
Tangier disease
Fabry disease
Acquired immunodeficiency syndrome
Idiopathic (especially in the elderly)

polyneuropathies always show abnormalities on electrophysiologic testing. Predominantly large-fiber polyneuropathies result in clinical sensory deficits (particularly for vibration and touch), weakness, and loss of tendon reflexes, with little or no autonomic and pain/temperature sensation loss.

Key Question No. 3: What is the Pattern of the Polyneuropathy (Distal Dying Back [Distal-To-Proximal Gradient], Short Nerves, Multiple Nerves; Symmetry, Asymmetry)?

The overall pattern of the polyneuropathy is determined largely based on the clinical examination and is supplemented and confirmed by electrophysiologic studies. In most polyneuropathies, there is a distal-to-proximal gradient of symptoms and signs. Distal symptoms and findings occur in most polyneuropathies, in part indicating the frequency with which axonal loss is the underlying pathologic process. Most axonal polyneuropathies exhibit a distal-to-proximal, dying back pattern, reflecting that the chance of damage to a nerve is length dependent (Figure 26–3). Thus, the longest nerves are affected first, resulting in a stocking-glove distribution of symptoms. Patients initially develop numbness or weakness of the toes and feet, which then slowly progresses up the leg. When the process reaches the upper calf, the fingertips become involved as well, because the distance from the lumbosacral spinal cord to the upper calf is the same as that from the cervical spinal cord to the fingertips. Only rarely will polyneuropathies preferentially affect the shorter, more proximal nerves before the distal ones (e.g., in porphyria, proximal diabetic neuropathy, and some cases of inflammatory demyelinating polyneuropathy).

After determining whether a distal-to-proximal gradient is present, one should next assess the polyneuropathy for symmetry. Nearly all polyneuropathies are symmetric. *The*

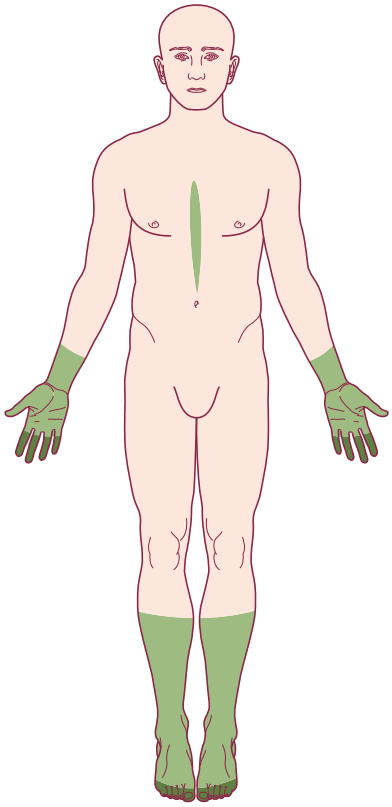


FIGURE 26–3 Stocking-glove pattern of polyneuropathy. Most polyneuropathies, especially axonal polyneuropathies, are length dependent, resulting in a stocking-glove distribution of symptoms and signs. Symptoms first present in the toes and then progress up the leg. When the polyneuropathy reaches the upper calves, the fingertips become involved as well. As the polyneuropathy worsens, symptoms may develop over the anterior chest and abdomen, representing distal degeneration of the thoracic intercostal nerves.
(Reprinted with permission from Schaumburg, H.H., Spencer, P.S., Thomas, P.K., 1983. Disorders of peripheral nerves. FA Davis, Philadelphia.)

presence of any significant asymmetry is a key finding; it usually excludes a large number of toxic, metabolic, and genetic conditions that cause only a symmetric pattern. Asymmetry implies the possibility of (1) a mononeuropathy multiplex pattern, (2) a superimposed radiculopathy or entrapment neuropathy, or (3) a variant of CIDP. Nerve conduction studies and EMG frequently are useful in sorting out these possibilities.

The pattern of a *mononeuropathy multiplex* is one of the most important patterns to recognize and differentiate from the length-dependent, dying-back, axonal polyneuropathy. The clinical presentation is distinctive: there is an asymmetric, stepwise progression of individual cranial and/or peripheral neuropathies (Figure 26–4). Over time, a confluent pattern may develop, which may be difficult to distinguish from a generalized polyneuropathy. In most cases, the individual neuropathies are of named nerves (i.e., median, ulnar, peroneal, etc.) as opposed to small nerve twigs. Mononeuropathy multiplex has a limited differential diagnosis (Box 26–3) and most often occurs in the setting of vasculitis and vasculitic neuropathy. As each subsequent nerve is infarcted, pain develops (often severe), followed hours or days later by weakness and numbness in the nerve's distribution. Although other organ systems are often involved, the initial clinical presentation of systemic vasculitis may involve only the peripheral nervous system. Indeed, there are now well-recognized cases in which vasculitis remains confined to the peripheral nervous system.

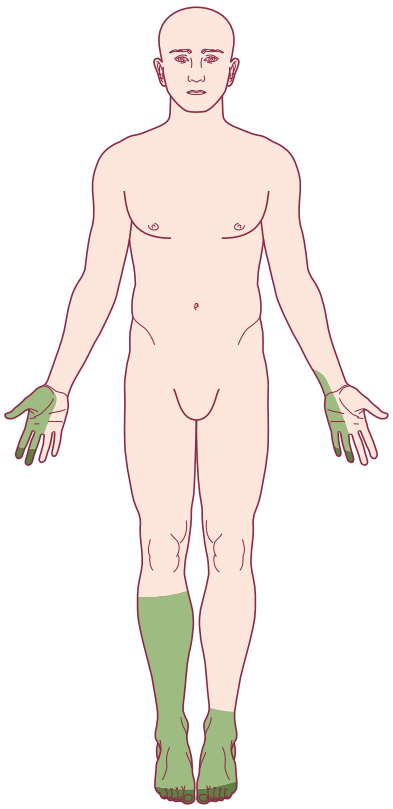


FIGURE 26–4 Mononeuropathy multiplex pattern of polyneuropathy. Mononeuropathy multiplex is a distinctive pattern, presenting as an asymmetric, stepwise progression of individual cranial or peripheral neuropathies, usually of named nerves. As time passes, a confluent pattern may develop that often is difficult to distinguish from a generalized polyneuropathy. Mononeuropathy multiplex is characteristically seen in vasculitic polyneuropathy. The pattern shown here is an asymmetric polyneuropathy with involvement of the left ulnar, right median, left distal peroneal, right saphenous, and right peroneal nerves.
(Adapted and reprinted with permission from Schaumburg, H.H., Spencer, P.S., Thomas, P.K., 1983. Disorders of peripheral nerves. FA Davis. Philadelphia.)

Box 26–3. Differential Diagnosis of Mononeuropathy Multiplex

- Vasculitis (e.g., polyarteritis nodosa, Churg–Strauss syndrome, Wegener's syndrome, hypersensitivity, cryoglobulinemia, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, chronic active hepatitis)
- Diabetes
- Inflammatory demyelinating polyneuropathy (Lewis–Sumner variant)
- Multiple entrapments (hereditary and acquired)
- Infection (e.g., Lyme, leprosy, human immunodeficiency virus)
- Infiltration (e.g., granulomatous disease [sarcoid], neoplasm [lymphoma, leukemia])

Key Question No. 4: What is the Underlying Nerve Pathology (Axonal, Demyelinating, or Mixed)?

Pathologically, injury to nerves consists of two major processes: axonal loss or demyelination. The vast majority of polyneuropathies are primarily axonal. In demyelinating polyneuropathies, the initial injury to the nerves reflects damage to or dysfunction of the Schwann cells and the myelin sheaths. As a consequence of demyelination, conduction is impaired with marked slowing of conduction velocity or frank conduction block. In establishing the differential diagnosis of a peripheral nerve disorder, the presence of demyelination is always a key finding (see later). Demyelination may be demonstrated either by nerve biopsy and pathologic examination or, more easily, by electrophysiologic testing. When nerve conduction studies demonstrate a polyneuropathy to be predominantly demyelinating, the differential diagnosis is readily narrowed to a small group of disorders (Box 26–4).

Key Question No. 5: Is there a Family History of Polyneuropathy?

For any patient with a polyneuropathy, especially when the diagnosis is not clear, particular attention must be paid to family history. There are a large number of inherited polyneuropathies. Although for most of them only symptomatic therapy is available, correct diagnosis is important for genetic counseling and prognosis, and to avoid unnecessary or inappropriate further testing and treatment. Charcot–Marie–Tooth (CMT) neuropathy refers to a group

Box 26–4. Demyelinating Polyneuropathies

Hereditary
- Charcot–Marie–Tooth, Type I (CMT1)
- Charcot–Marie–Tooth, Type IV (CMT4)
- Charcot–Marie–Tooth, X-linked (CMTX)
- Dejerine–Sottas disease*
- Refsum disease
- Hereditary neuropathy with liability to pressure palsy (HNPP)
- Metachromatic leukodystrophy
- Krabbe disease
- Adrenoleukodystrophy/adrenomyeloneuropathy
- Cockayne syndrome
- Niemann–Pick disease
- Cerebrotendinous xanthomatosis
- Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)

Acquired
- Acute inflammatory demyelinating polyradiculoneuropathy (AIDP, the most common variant of Guillain–Barré syndrome)
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
  - Idiopathic
  - Associated with human immunodeficiency virus (HIV) infection
  - Associated with MGUS (especially IgM)
  - Associated with anti-MAG antibodies
  - Associated with osteosclerotic myeloma
  - Associated with Waldenström macroglobulinemia
- Multifocal motor neuropathy with conduction block ($\pm GM_1$ antibodies)
- Diphtheria
- Toxic (i.e., amiodarone, perhexiline, arsenic, glue sniffing, buckthorn shrub poisoning)

*Dejerine–Sottas disease is a historical term used to denote a severe demyelinating neuropathy in children. The classic phenotype described a hypotonic infant with areflexia and hypertrophic nerves; on nerve conduction studies, conduction velocities were extremely slow, typically around 6 m/s. Formerly considered a distinct entity with autosomal recessive inheritance, genetic analysis has demonstrated that Dejerine–Sottas is a syndrome with either recessive inheritance or autosomal dominant inheritance with de novo mutations. The recessive forms are now incorporated into the CMT4 group. The de novo autosomal dominant forms have mutations on the same genes implicated for CMT1 (*P0, PMP22,* and *EGR2*), but with the genetic defect resulting in a much more severe demyelinating neuropathy.

of inherited disorders characterized by a chronic motor and sensory polyneuropathy. CMT accounts for the majority of inherited polyneuropathies and, in many large series, represents a significant proportion of the patients with difficult-to-diagnose polyneuropathies. Four major types of CMT are defined based on their inheritance and physiology: the demyelinating autosomal dominant form is CMT1; the axonal autosomal dominant form is CMT2; the autosomal recessive demyelinating form is CMT4; and the X-linked demyelinating form is CMTX. Within each type, there are several subtypes based on the specific genetic defect. In contrast to CMT, there are a smaller group of inherited polyneuropathies associated with defects of metabolism that have been described. Most are extremely rare and are associated with other systemic abnormalities.

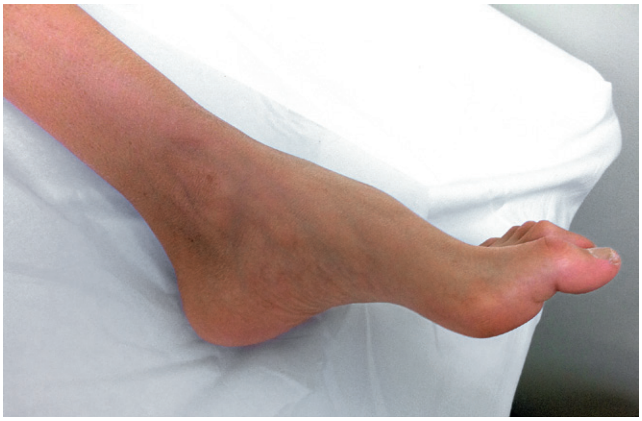


FIGURE 26–5 Pes cavus. Pes cavus is an orthopedic deformity of the foot, recognized as a foreshortened foot with a high arch and hammer toes. Pes cavus develops during childhood from the combination of intrinsic foot muscle weakness and relative preservation of the long flexors and extensor muscles in the calves. Because most polyneuropathies preferentially affect distal muscles, polyneuropathies that are present during development as a child commonly result in this deformity. As the vast majority of polyneuropathies that are present as a child are genetic, the presence of pes cavus in a patient with a peripheral neuropathy likely indicates that the neuropathy has been present since childhood and is most likely inherited.

Inherited polyneuropathies may affect certain individuals so minimally or may progress so slowly over an individual's lifetime that the person never seeks medical attention. Therefore, it often is beneficial to examine family members, both clinically and with nerve conduction studies and EMG, to help determine whether the underlying etiology of the patient's polyneuropathy is genetic. Several clinical clues, however, suggest the possibility of an inherited polyneuropathy (Figure 26–5):

- Foot deformity (pes cavus, hammer toes, high arches)
- History of a long-standing polyneuropathy (many years and often decades)
- History of very slow progression
- Few positive sensory symptoms
- Family history of "polio," "rheumatism," "arthritis," or other disorders that actually might have been inherited polyneuropathy

Key Question No. 6: Is there a History of Medical Illness or are there Signs Suggesting A Medical Illness Associated with Polyneuropathy?

A careful history and general physical examination are essential in evaluating a patient with polyneuropathy. Several medical conditions are strongly associated with polyneuropathy. Most prominent among them are diabetes and other endocrine disorders, cancer, connective tissue disorders, porphyria, vitamin and other deficiency states, and human immunodeficiency virus (HIV) infection.

Key Question No. 7: Is there any History of Occupational or Toxic Exposure To Agents Associated with Polyneuropathy?

Finally, it is always important to ask about occupational and exposure history. Among drugs, most notable are cancer chemotherapeutic agents, which frequently result in polyneuropathy that is detectable either clinically or electrically. In addition, a large number of prescription drugs, as well as over-the-counter medicines, can cause polyneuropathy. A careful review of all medicines is always important.

Asking about a patient's occupational and recreational activities occasionally elicits a toxic source for the neuropathy. One should always inquire about the patient's use of alcohol, which is one of the most frequent causes of toxic polyneuropathy.

AXONAL POLYNEUROPATHY

The underlying pathology of the vast majority of polyneuropathies is axonal degeneration, usually affecting both motor and sensory fibers. Axonal polyneuropathies include nearly all diabetic, toxic, metabolic, drug-induced, nutritional, connective tissue, and endocrine-associated polyneuropathies. In addition, there are a small number of inherited CMT neuropathies that are axonal. The autosomal dominant axonal form of CMT is now known as CMT2. CMT2 is further divided into several subtypes based on the specific genetic defect, and accounts for approximately 10–15% of the CMT inherited neuropathies.

Clinical

Clinically, the patient with an axonal polyneuropathy usually presents with a stocking-glove distribution of symptoms and signs, including distal sensory loss and weakness. Ankle reflexes usually are absent, whereas knee and upper extremity reflexes are preserved, unless the polyneuropathy is severe.

In severe cases, the pattern of abnormalities may become more complex. Sensory symptoms and signs may develop not only over the limbs but also over the anterior chest and abdomen (escutcheon sign, which is the shape of a shield), reflecting distal degeneration of the thoracic intercostal nerves, which originate from the back and run around the abdomen and chest. If this pattern is not appreciated, a mistaken impression of a spinal level may result. (*Note*: A level will only be found examining the front, not the back.) In the most extreme cases, sensory loss may develop over the top of the head due to degeneration of the distal trigeminal and cervical nerves.

Electrophysiology

Axonal polyneuropathies are associated with a characteristic pattern of nerve conduction results, provided the polyneuropathy has been present long enough for wallerian degeneration to have occurred (i.e., 3–9 days). In general, motor and sensory amplitudes decrease, with normal or only slightly slowed distal latencies, late responses, and conduction velocities. The changes are always more marked in the lower extremities, where the pathology is the greatest.

Likewise, evidence of axonal loss is found on needle EMG examination, more prominent distally than proximally, with the lower extremities more affected than the upper extremities. Of course, EMG findings are dependent on the length of time a polyneuropathy has been present. Denervation typically develops within weeks and reinnervation after weeks to months. Different patterns also develop depending on the tempo of the illness. If the process is relatively active and progressive, a combination of denervation and reinnervated motor unit action potentials (MUAPs) with decreased recruitment will be seen and again will be more prominent distally. In cases where the polyneuropathy is long-standing and only very slowly progressive, reinnervation may completely keep pace with denervation. In such cases, only reinnervated MUAPs with decreased recruitment will be seen distally, with little or no active denervation.

Most polyneuropathies have been present for several months or years before coming to evaluation. Accordingly, when a patient with an axonal polyneuropathy is first seen in the EMG laboratory, a combination of denervation and reinnervation is usually present.

Special Situations in Axonal Polyneuropathy: The Use of the Sural/Radial Amplitude Ratio in Mild Polyneuropathy

Nearly all axonal polyneuropathies are characterized by a distal pattern of abnormalities. Thus, the lower extremities are affected first and most prominently. Accordingly, the amplitude of the sural sensory study (normal or abnormal) takes on great significance in the EDX evaluation of most axonal polyneuropathies. However, interpretation of the sural amplitude has several limitations, especially in the following scenarios:

1. Younger individuals have much higher baseline sural amplitudes than older individuals. Thus, if a young patient had a sural amplitude of 30 μV, then developed an axonal polyneuropathy and the sural amplitude decreased to 15 μV, this value would still be considered normal in most EMG labs.
2. Older individuals may have low or difficult to obtain sural sensory responses at baseline. Thus, in an 80-year-old patient with numbness of the feet and a sural amplitude of 3 μV, it is difficult to know whether this value indicates a neuropathy or is simply consistent with age.
3. In obese individuals, the additional adipose tissue between the skin and the underlying nerve may result in an attenuation of the sensory nerve amplitude. Thus, in an obese patient with a sural amplitude of

5 μV, it may be difficulty to know if this value indicates a neuropathy or simply denotes a reduced amplitude from technical issues related to increased intervening adipose tissue in the lower leg.

In these situations, the use of the sural/radial amplitude ratio (SRAR) may be helpful. The SRAR is especially helpful in those patients with a "borderline normal" sural amplitude. The rationale for using the SRAR is straightforward: in a distal dying-back axonal neuropathy, the sural amplitude should be disproportionally affected compared to the radial amplitude. In the original description of this technique by Rutkove et al., a SRAR <0.40 had a specificity of 90% and a sensitivity of 90% in detecting an axonal polyneuropathy. In addition, the SRAR was less dependent on age than the sural amplitude alone, and also did not appear to be affected by body mass index (BMI). A latter study using a larger cohort of normal subjects suggested that a cutoff value of 0.4 may have been too high, and a more appropriate cutoff should be 0.21. Dropping the cutoff to 0.21 improved the specificity to 95% (i.e., reduced the number of false positives to under 5%).

Thus, the SRAR can be a useful adjunct in the EDX evaluation of axonal polyneuropathy. Of course, like all nerve conduction data, it relies on obtaining valid data. One needs to be sure that the amplitude of each nerve has been maximized and that the recording electrodes are optimally placed over each nerve. Moreover, in the rare situation wherein there is a superimposed sural or radial mononeuropathy, the SRAR cannot be considered valid for the electrodiagnosis of axonal polyneuropathy.

Special Situations in Axonal Polyneuropathy: Acute Presentation

The pattern of an acute or subacute axonal polyneuropathy is distinctly unusual. If the polyneuropathy is very acute (less than several weeks' duration) and denervation is not yet present, the only abnormality on needle EMG examination will be normal-appearing MUAPs with reduced recruitment. *However, this is the same pattern on needle EMG that occurs in an acute demyelinating polyneuropathy*. If an axonal polyneuropathy is subacute (more than several weeks but less than several months), active denervation will also be present. MUAPs again will be normal in morphology, but with reduced recruitment. These two patterns are very unusual in the EMG laboratory because very few polyneuropathies are acute or subacute, and of the ones that are acute/subacute, most are associated with demyelination and not axonal loss. Acute axonal polyneuropathies include those associated with porphyria or vasculitis and those rare cases of Guillain–Barré syndrome that are axonal and not demyelinating.

Special Situations in Axonal Polyneuropathy: Asymmetric Presentation

Nerve conduction studies and EMG are also used to assess the pattern of an axonal polyneuropathy. Nearly all axonal polyneuropathies are symmetric and distal. Any asymmetry is distinctly unusual and implies either (1) a mononeuropathy multiplex pattern or (2) a second superimposed process, such as an entrapment neuropathy or radiculopathy. Of course, patients with polyneuropathy of any kind are more susceptible to mononeuropathies at typical entrapment sites, especially median neuropathy at the wrist and ulnar neuropathy at the elbow. Any significant asymmetry found on nerve conduction studies and EMG that is not explained by an entrapment neuropathy or superimposed radiculopathy should seriously raise the possibility of an underlying mononeuropathy multiplex pattern and should lead one to consider the possibility of vasculitic polyneuropathy.

Special Situations in Axonal Polyneuropathy: Non-length-dependent Presentation

Like the finding of asymmetry, that of proximal more than distal abnormalities has important diagnostic significance in an axonal polyneuropathy. Proximal changes (e.g., paraspinal muscles, shoulder and hip girdle muscles) suggest a non-length-dependent pattern, implying either the possibility of porphyria, which characteristically affects shorter nerves first, or the combination of both peripheral nerve and nerve root pathology (i.e., a polyradiculoneuropathy). Diabetic neuropathy is the best example of a true polyradiculoneuropathy, showing abnormalities both distally and proximally.

Diabetes

In any discussion of axonal neuropathies, special mention should be made of diabetic neuropathy. Peripheral nervous system manifestations of diabetes are numerous and varied. Isolated mononeuropathies of cranial nerves (e.g., facial palsy), intercostal nerves (known as diabetic thoracoabdominal neuropathy), or peripheral nerves may occur. Several types of polyneuropathy may occur. The most common, a distal sensorimotor polyneuropathy, is a typical axonal polyneuropathy affecting both large and small sensory fibers. On EMG, however, findings of a polyradiculoneuropathy are usually present. Diabetic patients may also present with a pure autonomic polyneuropathy or a small-fiber sensory polyneuropathy, with distal burning and pain. If large sensory and motor fibers are spared, such patients will have completely normal electrodiagnostic studies. Other patients with diabetes will present with more proximal nerve syndromes, either at the root or plexus level, especially in the lower extremity (i.e., proximal diabetic neuropathy, diabetic amyotrophy, etc.). Large-fiber diabetic neuropathies usually demonstrate axonal changes on nerve conduction studies. Although most axonal polyneuropathies, *including those associated with diabetes*, have some secondary demyelination, the electrophysiologic criteria for primary demyelination are not met. Only in some cases of uremic polyneuropathy, especially when combined with diabetic polyneuropathy, do nerve conduction velocities slow sufficiently to approach or exceed the criteria set for demyelinative slowing.

BORDERLINE CASES: DIFFERENTIATION BETWEEN AXONAL AND DEMYELINATIVE SLOWING

Slowing of conduction velocity to less than 75% of the lower limit of normal is one of the fundamental electrodiagnostic criteria for establishing primary demyelination in polyneuropathy. When compound muscle action potential (CMAP) amplitudes are markedly reduced secondary to axonal loss, however, conduction velocity slowing may be seen secondary to severe axonal loss with dropout of the fastest-conducting fibers. It is in this situation, when distal CMAP amplitudes are low and conduction velocity slowing nears 75% of the lower limit of normal, that it may be difficult to differentiate between a primary demyelinating polyneuropathy and a severe axonal polyneuropathy.

In such cases, one useful technique is to compare conduction velocities recording a distal and a proximal muscle across the same segment of nerve. In the leg, the peroneal nerve is most useful for this study. Peroneal motor studies are performed stimulating below the fibular neck and at the lateral popliteal fossa and recording simultaneously from the extensor digitorum brevis (EDB), a distal muscle, and the tibialis anterior, a proximal muscle (Figure 26–6). Conduction velocities across this same segment of nerve are then compared.

In patients with demyelinating polyneuropathies, conduction velocities typically are slowed at both recording sites, with no difference between proximal and distal sites (Figure 26–7). In patients with axonal polyneuropathies, however, conduction velocities may be slowed recording the EDB but usually are normal or only mildly reduced when measured from the tibialis anterior. This distal-to-proximal gradient of conduction velocity slowing in axonal polyneuropathies may be very helpful in differentiating a primary demyelinating from axonal polyneuropathy, especially when the distal conduction velocities are near the cutoff value for demyelinative slowing.

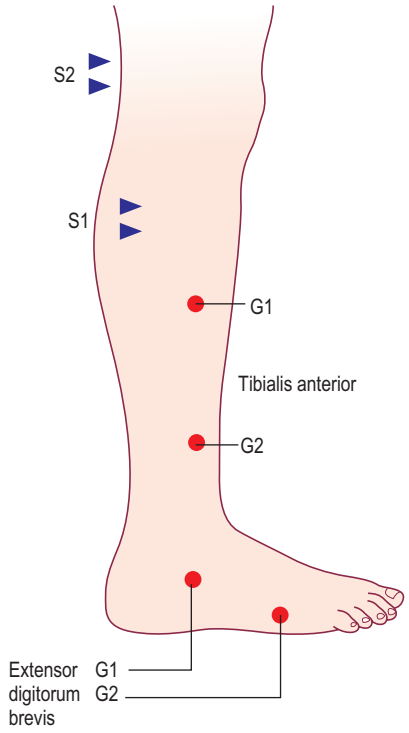


FIGURE 26–6 Recording proximal and distal muscles to differentiate axonal from demyelinative slowing. Co-recording a proximal and a distal muscle and comparing conduction velocities through the same segment of nerve may be helpful in differentiating axonal from demyelinative slowing in borderline cases. Here, recording electrodes are placed over the tibialis anterior and extensor digitorum brevis in the standard belly–tendon montage. The peroneal nerve is stimulated below the fibular neck and at the lateral popliteal fossa and conduction velocities computed across the same segment of nerve for the two recording sites.
(Reprinted with permission from Raynor, E.M., Ross, M.H., Shefner, J.M., et al., 1995. Differentiation between axonal and demyelinating neuropathies: identical segments recorded from proximal and distal muscles. Muscle Nerve 18, 402.)

DEMYELINATING POLYNEUROPATHY

For any patient with a polyneuropathy, the presence of demyelination as the primary pathology has special diagnostic significance. Nearly all polyneuropathies result in primary axonal loss, and any demyelination occurs as a secondary phenomenon. Few polyneuropathies are associated with demyelination as the primary pathologic process. Although demyelination usually is demonstrated most readily by nerve conduction studies and less often by nerve biopsy, several clinical clues may suggest primary demyelination:

- Global areflexia
- Hypertrophic nerves
- Moderate-to-severe muscle weakness with relative preservation of muscle bulk
- Motor symptoms and signs more prominent than sensory ones

On nerve conduction studies, disorders with primary demyelination are generally associated with markedly prolonged distal latencies (>130% of the upper limit of normal), markedly slowed conduction velocities (usually <75% of the lower limit of normal), and markedly prolonged or absent late responses (>130% of the upper limit of normal).

In addition, nerve conduction studies often can be used to distinguish between acquired and inherited demyelinating polyneuropathies. In a patient with an inherited condition, all myelin tends to be affected equally; thus, uniform slowing of conduction velocity occurs. Accordingly, nerve conduction studies usually are symmetric from side to side. In contrast, acquired conditions (e.g., Guillain–Barré syndrome, CIDP) are associated with patchy, often multifocal demyelination. As a result, asymmetry is found on nerve conduction studies (even in the face of clinical symmetry),

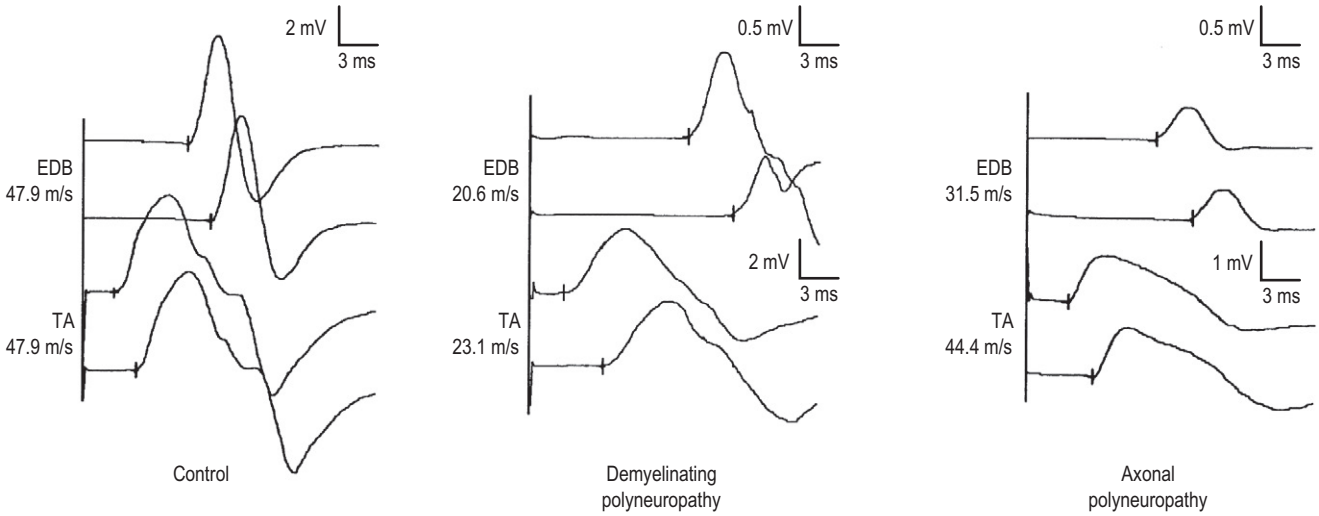
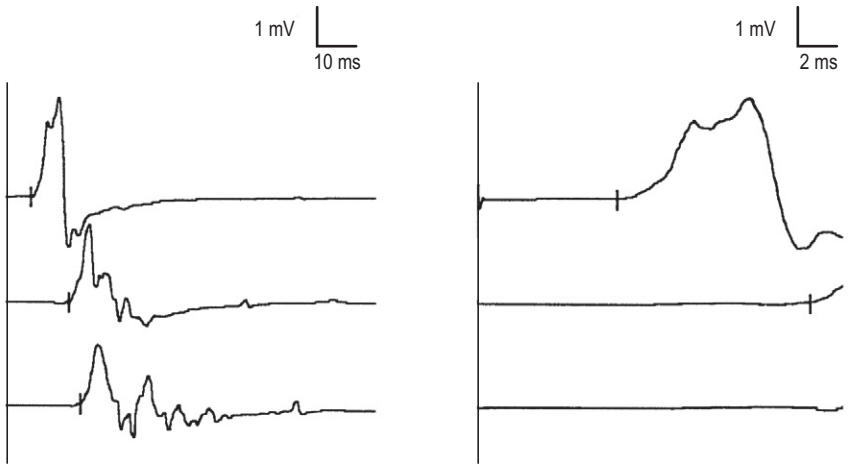


FIGURE 26–7 Proximal and distal recordings are used to differentiate demyelinative from axonal slowing. Conduction velocities below 75% of the lower limit of normal on nerve conduction studies usually imply primary demyelination. However, severe axonal polyneuropathies associated with loss of the faster fibers can approach this cutoff value, especially when distal compound muscle action potential amplitudes are very low. Comparing the conduction velocity across the same segment of nerve, recording proximal and distal muscles, can be useful in differentiating an axonal from a demyelinating polyneuropathy when conduction velocities are borderline. In normal individuals, there is no significant difference in conduction velocities when recording either the tibialis anterior (TA), a proximal muscle, or the extensor digitorum brevis (EDB), a distal muscle. In demyelinating polyneuropathies, there usually is marked slowing when recording both distal and proximal muscles. In severe axonal polyneuropathies associated with loss of the fastest axons, conduction velocity slowing may approach the cutoff in the leg value for demyelination (<30 m/s in the leg). However, conduction velocity usually is faster or normal when recording a more proximal muscle. This distal-to-proximal gradient of conduction velocity slowing and normalization of conduction velocity proximally are characteristic of axonal polyneuropathies.
(Reprinted with permission from Raynor, E.M., Ross, M.H., Shefner, J.M., et al., 1995. Differentiation between axonal and demyelinating neuropathies: identical segments recorded from proximal and distal muscles. Muscle Nerve 18, 402.)

FIGURE 26–8 Temporal dispersion in acquired demyelinating polyneuropathy. The presence of either conduction block or temporal dispersion marks a demyelinating polyneuropathy as acquired and not inherited. In the example shown here (stimulating the ulnar nerve at the wrist and below and above the elbow, recording the abductor digiti minimi muscle), there is marked temporal dispersion, at both the below-elbow and above-elbow sites. Note that when the sweep speed is set at 2 ms per division (routine setting), the proximal waveforms are off the screen.



along with evidence of conduction block and temporal dispersion. Conduction block and temporal dispersion at nonentrapment sites are key findings for differentiating acquired from inherited demyelinating polyneuropathies (Figure 26–8).

Guillain–Barré Syndrome (GBS)

Guillain–Barré syndrome is now most properly thought of as a syndrome that comprises several variants, with acute inflammatory demyelinating polyneuropathy (AIDP) being the most common in North America. GBS is an immune-mediated, rapidly progressive, predominantly motor polyneuropathy that often leads to bulbar and respiratory compromise. It is one of the most common of all neuromuscular emergencies. Although the overall prognosis is favorable in more than 80% of patients, the hospital course is frequently long, followed by a prolonged recuperation. Nerve conduction studies and EMG play an important role in the diagnosis of GBS because early recognition is necessary to begin appropriate treatment and avoid potential medical complications.

People of all ages can be affected, although GBS is most common in young adults. An antecedent event, often an upper respiratory infection or gastroenteritis, is found in approximately 60% of patients. Precipitating factors include campylobacter, cytomegalovirus, Epstein–Barr virus, and HIV infection, as well as vaccination, surgery, trauma, and malignancy (especially lymphoma).

Clinical

The classic presentation of GBS is a rapidly ascending paralysis. Many variants have also been seen, including proximal weakness, descending weakness, and the Miller–Fisher variant (ophthalmoplegia, ataxia, and areflexia). Early in the course, patients may complain of a sense of imbalance or poor coordination during walking. It is not unusual for a patient to be sent home from the emergency department with very mild gait ataxia as the only sign, only to return the next day with rapidly progressing weakness. Sensory symptoms with little objective sensory loss are common. Distal paresthesias in the fingers and toes typically are present simultaneously (an unusual finding in other polyneuropathies). A sensory level is not found. Hyporeflexia or areflexia develops early. Any weak limb with preserved reflexes should call the diagnosis of GBS into question. Bifacial weakness occurs in 50% of patients. Bulbar weakness with dysarthria and dysphagia are also frequent. Other cranial neuropathies are uncommon. Back and radicular pain occur in up to 25% of patients and may require narcotics. Autonomic dysfunction can occur. A fixed resting tachycardia is very common. Ileus, transient bladder dysfunction, arrhythmia, labile blood pressure, the syndrome of inappropriate secretion of antidiuretic hormone, and impaired thermoregulation can occur.

Most patients continue to progress for days to weeks and then experience a plateau before recovery commences. Intubation is required in one third of patients, usually between days 6 and 18. Progression beyond 4 weeks is rare for any patient with GBS.

Electrophysiology

During the first few days of the illness, all nerve conduction studies may be normal. The first changes in AIDP are often delayed, absent, or impersistent F and H responses, reflecting proximal demyelination. Indeed, pathologically, AIDP often starts at the root level as a polyradiculopathy. Later, routine motor nerve conduction studies show prolonged distal latencies, along with other evidence of segmental demyelination, especially conduction block and temporal dispersion. These changes are present in 50% of patients by 2 weeks and in 85% by 3 weeks. There is, however, a wide range of progression. Some patients have inexcitable nerves early on, due to either secondary wallerian degeneration or presumed distal demyelination. Notably, 10% of patients never fulfill criteria for acquired demyelination, sometimes because motor responses are absent. Although GBS is most often a demyelinating polyneuropathy in the form of AIDP, rare cases are associated with a similar clinical presentation but show axonal changes on nerve conduction studies. If the syndrome is pure motor and axonal, it is known as *acute motor axonal neuropathy* (AMAN). If both motor and sensory fibers are involved, the designation *acute motor sensory axonal neuropathy* (AMSAN) is used. Especially in the latter case, it is essential that these patients are screened for porphyria, which is another cause of a severe, acute axonal polyneuropathy.

To demonstrate segmental demyelination on motor nerve conduction studies, a combination of conduction block or temporal dispersion, or marked slowing of distal latencies, conduction velocities, or late responses must be seen. For acute polyneuropathies, the electrophysiologic criteria for segmental demyelination often are liberalized (Box 26–5).

Although almost 90% of patients will have motor abnormalities during the first few weeks, far fewer will have sensory nerve conduction abnormalities. Characteristically, sensory studies are normal early on. Later in the first week or two, sensory studies may show so-called *sural sparing* (i.e., the sural sensory response is normal whereas the median and ulnar sensory potentials are reduced or absent). This pattern is very unusual in the typical axonal, dying-back polyneuropathy. Many believe that sural sparing in the presence of a typical clinical picture is virtually diagnostic of AIDP. Why sural sparing occurs is not completely known, but it is likely related to the preferential, early involvement of the smaller myelinated fibers in AIDP. Although it is not intuitively obvious, the recorded sural sensory fibers are actually larger, and accordingly have more myelin, than the

Box 26–5. Electrophysiologic Criteria for Acute Demyelinating Polyneuropathy

Demonstrate at least three of the following in motor nerves:

1. Prolonged DLs (two or more nerves, not at entrapment sites)
   - DL >115% ULN (for normal CMAP amplitudes)
   - DL >125% ULN (for CMAP amplitudes <LLN)
2. CV slowing (two or more nerves, not across entrapment sites)
   - CV <90% LLN (for CMAP amplitudes >50% LLN)
   - CV <80% LLN (for CMAP amplitudes <50% LLN)
   - (*Note*: CVs are commonly preserved early in the course of acute inflammatory demyelinating polyneuropathy.)
3. Prolonged late responses: F response and H reflexes (one or more nerves)
   - >125% ULN
   - (*Note*: If distal CMAP amplitude is very low, absent F waves may not be abnormal.)
4. Conduction block/temporal dispersion (one or more nerves)
   - Unequivocal conduction block: Proximal/distal CMAP area ratio <0.50
   - Possible conduction block: Proximal/distal CMAP amplitude ratio <0.70
   - Temporal dispersion: Proximal/distal CMAP duration ratio >1.15

CMAP, compound muscle action potential; CV, conduction velocity; DL, distal latency; LLN, lower limit of normal; ULN, upper limit of normal.
Source: Adapted from Albers, J.W., Kelly, J.J., 1989. Acquired inflammatory demyelinating polyneuropathies: clinical and electrodiagnostic features. Muscle Nerve 12, 435. Reprinted by permission of John Wiley & Sons, Inc.

median and ulnar sensory fibers. The routine median and ulnar sensory potentials are recorded distally over the fingers, where the nerve diameters are more tapered than those of the sural nerve. The sural nerve actually has larger-diameter myelinated fibers where it is stimulated and recorded in the lower calf. These larger-diameter fibers presumably are relatively more resistant to the early inflammatory, demyelinating attack.

The needle EMG in early AIDP reveals the characteristic demyelinating pattern: no denervation, normal MUAP morphology, but with reduced recruitment in weak muscles. Exceptionally, somewhat larger MUAPs may be seen in early AIDP. These MUAPs are not reinnervated but occur for the same reason as does sural sparing: smaller myelinated fibers are affected first in AIDP. Thus, the normal, smaller MUAPs are blocked first because they are innervated by smaller-diameter, myelinated fibers. The normal, larger MUAPs may then be the only remaining, unblocked MUAPs. These larger MUAPs usually are not seen as individual potentials during the routine needle EMG examination. Because they are recruited last, usually with maximal contraction, they normally are buried in the interference pattern. With the smaller MUAPs blocked, however, these longer MUAPs are "uncovered" and more easily seen.

Early in the course of AIDP, there is usually no abnormal spontaneous activity at rest. The only exception may be the presence of occasional myokymic discharges. Myokymic discharges may be seen in the limbs, and especially in the face, even in the absence of clinical myokymia.

Despite the fact that AIDP has a predominantly demyelinating pathophysiology, there is always some secondary axonal loss. This leads to fibrillation potentials on needle EMG, usually developing within 2 to 5 weeks and becoming maximal at 6 to 10 weeks. Interestingly, fibrillation potentials are equally common in distal and proximal muscles, a finding that likely represents the random multifocal pathology. Fibrillation potentials may then persist for many months. After denervation, MUAPs can become more polyphasic (usually in the fourth week), followed by an increase in their amplitude and duration.

Although nerve conduction studies and EMG are principally used for diagnosis, they also are helpful in assessing prognosis. The best predictor of prognosis is the distal CMAP amplitude. Low distal CMAP amplitudes (<20% of the lower limit of normal at 3–5 weeks) are the best single predictor of a poor outcome or prolonged course. Other nerve conduction and EMG data (including the amount of fibrillation potentials) actually correlate quite poorly with prognosis. Indeed, some patients have nerve conduction results that appear to worsen despite clinical improvement. This likely represents the early recovery of fibers that previously were blocked and now are able to conduct, albeit very slowly.

Chronic Demyelinating Polyneuropathy

When a patient with a chronic polyneuropathy is found to have evidence of a primary demyelinating process on nerve conduction studies (Box 26–6), the differential diagnosis narrows considerably. However, some of the disorders that might be considered in the differential diagnosis (Box 26–4) are associated with other prominent symptoms outside of the peripheral nervous system, some of which involve the central nervous system or have an onset in early childhood. From a practical point of view, the differential diagnosis of an isolated chronic demyelinating polyneuropathy in an adult without central nervous system or systemic findings likely is limited to either an inherited polyneuropathy (most often CMT type 1A), or CIDP or one of its variants. Nerve conduction studies can often differentiate among these conditions.

Box 26–6. Electrophysiologic Criteria for Chronic Demyelinating Polyneuropathy

Demonstrate at least three of the following in motor nerves:

1. Prolonged DLs (two or more nerves, not at entrapment sites)
   DL >130% ULN
2. CV slowing (two or more nerves, not across entrapment sites)
   CV <75% LLN
3. Prolonged late responses: F response and H reflexes (one or more nerves)
   >130% ULN
   (*Note*: If distal CMAP amplitude is very low, absent F waves may not be abnormal.)
4. Conduction block/temporal dispersion (one or more nerves)
   Unequivocal conduction block: Proximal/distal CMAP area ratio <0.50
   Possible conduction block: proximal/distal CMAP amplitude ratio <0.70
   Temporal dispersion: proximal/distal CMAP duration ratio >1.15

(*Note*: These criteria are modified for inherited demyelinating polyneuropathy. At least two of the first three need to be demonstrated. Conduction block/temporal dispersion does not occur in inherited demyelinating polyneuropathies. One exception to this "rule" occurs in the severe demyelinating neuropathy of infancy and early childhood. This neuropathy was historically known in the literature as Dejerine–Sottas syndrome or HMSN-III. In these patients, the neuropathy is associated with such profound conduction velocity slowing (typically <10 m/s), there is often prominent temporal dispersion and phase cancellation resulting in dispersed, lower amplitude waveforms with proximal stimulation; however, the area does not drop >50% between distal and proximal stimulation sites.)

CMAP, compound muscle action potential; CV, conduction velocity; DL, distal latency; LLN, lower limit of normal; ULN, upper limit of normal.
Source: Adapted from Albers, J.W., Kelly, J.J., 1989. Acquired inflammatory demyelinating polyneuropathies: clinical and electrodiagnostic features. Muscle Nerve 12 (6), 435–451. Reprinted by permission of John Wiley & Sons, Inc.

Charcot–Marie–Tooth Neuropathy

Charcot–Marie–Tooth (CMT) is a group of inherited neuropathies that is comprised of several major types (CMT1, CMT2, CMT4, and CMTX) based on inheritance pattern (dominant, recessive, or X-linked) and whether the primary pathology is located in the myelin or axon. Each of these

CMT types are further divided based on their specific molecular and genetic findings. More than 40 different genes and loci associated with CMT have been identified. The most common type is CMT1, which accounts for approximately 40–50% of all patients with CMT. CMT1 comprises a group of demyelinating neuropathies, are among the most common demyelinating neuropathies seen in the EMG laboratory, and are by far the most common inherited demyelinating neuropathies. In the past, CMT1 was referred to in the literature as hereditary motor sensory neuropathy type I (HMSN-I), peroneal muscular atrophy, and hypertrophic or onion-bulb neuropathy of childhood. CMTX comprises a group of X-linked demyelinating neuropathies that account for approximately 10–15% of CMT cases. Rarely, females present with milder symptoms. Lastly, CMT4 encompasses a group of autosomal recessive demyelinating neuropathies which are extremely rare and unlikely to be encountered clinically.

Clinical

CMT is a slowly progressive, distal, motor more than sensory, neuropathy associated with pes cavus and hammer toes. Scoliosis and other skeletal deformities occur in some patients. The demyelinating types are CMT1, CMT4, and CMTX and may be associated with hypertrophic nerves. Sensory symptoms are uncommon, although mild sensory signs are usually discovered through careful examination. There are no cranial nerve signs in the more common CMT1 and CMTX phenotypes. CMT predominantly affects the intrinsic foot and lower leg anterior compartment musculature resulting in the typical appearance of distal leg wasting. The distal weakness results in prominent foot drops and a steppage gait. Later, the impairment spreads to the distal thighs and intrinsic hand muscles. Claw hands may develop. Ankle reflexes are always absent, and, in well-established cases, all reflexes are unobtainable. The onset is commonly in early childhood, typically presenting as a foot deformity or delay in achievement of motor milestones. Other patients may present in the first decades of life. Some patients are affected so minimally, however, that they may not come to medical attention until middle age or later.

Genetics

The genetics of the demyelinating CMT types are heterogeneous. In CMT1, the inheritance is autosomal dominant. At present, there are six subtypes of CMT1 (CMT1A, 1B, 1C, 1D, 1E, and 1F). The most common form is CMT1A which accounts for approximately 70–80% of all CMT1 cases. The genetic defect is a duplication error of a 1.5-megabase DNA region at chromosome 17p11.2. This region contains the peripheral myelin protein gene *PMP22* (this is the same gene location at which a deletion error results in hereditary neuropathy with liability to pressure palsies). Isolated patients without any family history have been found to have the same duplication, implying that some cases may be due to a *de novo* mutation. The second most common CMT1 is CMT1B which accounts for appropriately 10% of CMT1 cases. CMT1B is caused by a point mutation in the myelin protein zero (*MPZ*) gene on chromosome 1. The other CMT1 subtypes are extremely rare, each representing less than 1% of CMT1. While phenotypic differences between families with CMT1A and CMT1B is small, among large groups, patients with CMTIB are found to be more severely affected than patients with type IA, and have slower conduction velocities. DNA testing for the common CMT1 subtypes is widely commercially available.

CMT4, the autosomal recessive demyelinating type, is very rare. In contrast, CMTX, the X-linked form, is more common and occasionally seen in the EMG laboratory. The genetic defect in the most common form of CMTX, CMTX1, is a mutation of the gap-junction protein 1 gene (*GJB1*) which codes for connexin-32. Connexin-32 is important in forming the gap junctions in myelin at the paranodal regions.

Pathology and Imaging

The cerebrospinal fluid protein level is elevated in more than half of all patients with the demyelinating forms of CMT. Pathology of peripheral nerve shows segmental demyelination and Schwann cell proliferation with onion-bulb formation. Unmyelinated fibers are not affected. Imaging of the lumbar spine may show enlargement of the lumbosacral nerve roots and, in exceptional cases, may result in spinal stenosis.

Prognosis

The prognosis in many cases is relatively benign. Although rare patients eventually may require a wheelchair, most remain ambulatory with the use of simple bracing and have little impairment of functional strength.

Electrophysiology

In the demyelinating CMT neuropathies, nerve conduction studies show marked slowing of conduction velocity, usually below 75% of the lower limit of normal. Slowing is uniform in all nerves, without evidence of temporal dispersion or conduction block. Motor responses may be very low or absent in the lower extremities. In nearly all cases, slowing can be demonstrated in the upper extremities (median motor conduction velocity <38 m/s). Most patients with CMT1A have conduction velocities in the range of 20–25 m/s in the upper extremities. Patients with CMT1B, however, often have even slower velocities, in the range of 15 m/s or slower. In contrast, males with CMTX may have conduction velocities that are somewhat faster (e.g., 25–38 m/s). In females with CMTX, some may have a peripheral neuropathy clinically, but the conduction velocities are only slightly slow or are in the normal range.

There often is little correlation between the degree of slowing and the clinical symptoms. Maximal slowing evolves during the first 3 to 5 years, after which there is little change. Slowing has been documented in patients as young as 6 months. Distal latencies may increase during the first 10 years. Sensory studies are usually abnormal and

generally show low or absent amplitudes. As in most demyelinating polyneuropathies, there is some secondary axonal loss. Indeed, it is the secondary axonal loss that leads to the weakness and disability. Accordingly, EMG typically shows evidence of distal reinnervation, often with little spontaneous activity. Nerve conduction studies are extremely helpful in early diagnosis. Indeed, if a patient who is tested at several months of age or older has no clinical signs of CMT and normal conduction velocities, the diagnosis of a demyelinating form of CMT is essentially excluded.

Chronic Inflammatory Demyelinating Polyneuropathy

Clinical

CIDP is an acquired, demyelinating, motor and sensory neuropathy that is presumed to be immune mediated. All ages can be affected, but most patients present in their fifth to sixth decade. Both proximal and distal muscles are affected, and the clinical presentation is usually symmetric. The time course in CIDP is longer than AIDP (>6 weeks) and may follow a monophasic progression, a stepwise progression, or a relapsing and remitting course. Early in the illness, it may be impossible to differentiate AIDP from the initial presentation of CIDP. Patients with CIDP generally progress slowly (over weeks to months), with the major disability usually a gait disturbance. Areflexia or hyporeflexia is the rule. Large-fiber sensory loss (touch, vibration, position sense) is more common than small-fiber loss (pain, temperature). A Romberg sign is commonly present. Tremor may also be seen, especially in the upper extremities. Significant bulbar or respiratory weakness is unusual.

Etiology

CIDP may be idiopathic or may occur in association with HIV infection, osteosclerotic myeloma, Waldenström macroglobulinemia, lymphoma, monoclonal gammopathy of undetermined significance, or antibodies to myelin-associated glycoprotein (MAG). Therefore, all patients should undergo blood tests, including serum protein electrophoresis, immunoelectrophoresis, and tests for antibodies to MAG and HIV. Patients should undergo a skeletal survey to look for osteosclerotic myeloma and any patient who is found to have a monoclonal protein, should have further hematologic evaluation to identify a possible plasma cell dyscrasia.

Pathology

Cerebrospinal fluid studies commonly reveal protein elevation in the absence of a pleocytosis (except in HIV-associated CIDP, where a lymphocytic pleocytosis is common). Pathologic examination may demonstrate segmental demyelination with perivascular or diffuse mononuclear infiltration of nerve, without vasculitis, although many biopsies show nonspecific changes.

Prognosis

CIDP is an important diagnosis to recognize because patients may improve with plasma exchange, intravenous immunoglobulin (IVIG), or immunosuppressive therapy. Idiopathic CIDP may respond to prednisone, azathioprine (Imuran®), mycophenolate mofetil (CellCept®), cyclophosphamide (Cytoxan®), cyclosporine, or plasma exchange. In CIDP associated with monoclonal immunoglobulin M (IgM) antibodies, rituximab (Rituxan®) may be helpful. In patients whose CIDP is associated with osteosclerotic myeloma, surgery or radiation therapy directed at the plasmacytoma may result in improvement of the neuropathy.

Electrophysiology

On nerve conduction studies and EMG, CIDP is a chronic demyelinating polyneuropathy with secondary axonal features. Evidence of primary demyelination is present, with markedly prolonged distal latencies (>130% of the upper limit of normal), markedly slowed conduction velocities (<75% of the lower limit of normal), and markedly prolonged or absent late responses (>130% of the upper limit of normal). Because CIDP usually is a multifocal process affecting different segments of nerve differently, nerve conduction abnormalities often are asymmetric, despite the symmetric clinical presentation. Most importantly, there is usually conduction block, temporal dispersion, or both, marking the polyneuropathy as acquired.

Secondary axonal changes are the rule. Distal CMAP and sensory nerve action potential (SNAP) amplitudes are reduced, usually more markedly in the lower extremities. Needle EMG shows evidence of chronic and ongoing axonal loss with the typical neuropathic pattern: fibrillation potentials and long, large, polyphasic MUAPs with reduced recruitment. Because CIDP is actually a polyradiculoneuropathy, changes are often also seen in proximal muscles, including the paraspinal muscles.

Idiopathic CIDP and its variants usually display similar findings on nerve conduction studies and EMG. The only exceptions are multifocal motor neuropathy with conduction block (MMNCB, discussed in the following section) and some cases of anti-MAG polyneuropathy. Anti-MAG CIDP typically is a very slowly progressive, predominantly sensory polyneuropathy and is more common in older patients, especially men. Patients usually present with gait ataxia and marked large-fiber sensory loss. Some patients have a prominent action tremor. Although electrical studies demonstrate an acquired, demyelinating, motor and sensory polyneuropathy, often the most prominent change is markedly prolonged distal latencies (sometimes referred to as a distal myelinopathy). Anti-MAG polyneuropathy should be considered in any patient with a demyelinating polyneuropathy, especially when the distal latencies are prolonged out of proportion to the other abnormalities. Most anti-MAG polyneuropathies are associated with an IgM monoclonal protein.

Multifocal Motor Neuropathy with Conduction Block

In the early 1990s, attention was brought to patients with pure motor neuropathies, often associated with antiganglioside antibodies (especially anti-GM_1). A monoclonal protein was not present. These patients presented with a pure lower motor neuron syndrome, clinically similar to the progressive muscular atrophy variant of amyotrophic lateral sclerosis (ALS). However, their electrophysiologic studies

showed evidence of an acquired segmental demyelinating neuropathy with conduction block along motor nerves, similar to CIDP, although sensory nerves were minimally affected or completely spared. It was unclear whether these patients were a variant of CIDP or represented a unique syndrome. The recognition of this disorder, multifocal motor neuropathy with conduction block (MMNCB), now has important therapeutic and prognostic implications because most of these patients are treated successfully with intravenous immunoglobulin; cyclophosphamide or rituximab therapy have been used successfully in some refractory cases. It often falls to the electromyographer to make the differentiation between ALS, which usually is fatal, and MMNCB, which responds to immunomodulation.

Clinical

Patients with MMNCB present with progressive, asymmetric weakness and wasting, often affecting the distal upper extremity muscles first. Most patients are younger than 50 years, which is younger than patients with typical ALS. Males are more commonly affected than females. In some cases, it may be possible to detect weakness in the distribution of named motor nerves with sparing of other nerves in the same myotome (clinical multifocal motor neuropathy). This pattern is not seen in ALS or its progressive muscular atrophy variant, in which the entire myotome is characteristically affected at the same time. Occasional patients will have prominent weakness but without wasting, a finding usually associated with pure demyelination. Definite upper motor neuron signs are always absent, although retained or inappropriately brisk reflexes for the degree of weakness and wasting may be seen. Bulbar function and sensation are characteristically spared, although mild or transient sensory symptoms may be present.

Many believe that this disorder is a variant of CIDP. However, the asymmetry, upper extremity predominance, relative absence of sensory findings, and typical lack of response to prednisone all suggest the possibility of a unique disorder that differs from the usual presentation of CIDP.

Electrophysiology

Findings on motor nerve conduction studies in MMNCB often are similar to those seen in CIDP. There may be evidence of demyelinative slowing, including markedly prolonged latencies, slowed conduction velocities, and prolonged late responses. *The characteristic finding, however, is that of conduction block, temporal dispersion, or both, along the motor nerves*.

The precise electrophysiologic definition of conduction block remains controversial (see Chapter 3), and much of the interest in defining conduction block is due to this disorder. From results of computer simulation models, a drop in proximal CMAP area of more than 50% always signifies conduction block and cannot be explained by temporal dispersion alone. However, any abrupt drop in CMAP area or amplitude, especially over a short segment, usually signifies conduction block. Of course, conduction block across a known entrapment site (e.g., ulnar nerve at the elbow, peroneal nerve at the fibular neck) cannot be used to diagnose MMNCB or any other acquired demyelinating polyneuropathy.

Because MMNCB is potentially treatable and ALS is usually fatal, an exhaustive search for conduction blocks often is undertaken. Although such testing is worthwhile, it should be done only in patients with predominantly lower motor symptoms and signs. Patients with MMNCB do not have unequivocal upper motor signs (i.e., spasticity, extensor plantar responses, pathologic hyperreflexia) or bulbar dysfunction. Even if strict criteria for conduction block are not met, any markedly slowed conduction velocity or distal latency (excluding entrapment sites and recording from nerves where the recorded muscle is severely atrophic), or markedly prolonged F responses, should seriously put into question the diagnosis of ALS. Electrophysiologic evidence of demyelination does not occur in ALS.

In the search for conduction block, more proximal segments of nerve may be studied (e.g., stimulating axilla, Erb's point, cervical roots). In exceptional cases, conduction blocks may be demonstrated only proximally. However, conduction blocks in MMNCB typically are present distally in the routine segments of nerve usually studied. One must always remember that with proximal stimulation, technical problems become more marked, especially the problem of ensuring supramaximal stimulation. If supramaximal stimulation is not achieved proximally, a mistaken impression of a conduction block may occur. In addition, the normal effects of temporal dispersion become more marked when longer distances are studied. When patients with ALS are studied proximally, some drop in amplitude and area may occur, but a drop in area of more than 50% is never seen. Last, stimulation of proximal segments also carries the inherent problem of co-stimulation of adjacent nerves. This is especially true for the median and ulnar nerves, where collision studies are needed to exclude the contribution to the CMAP from proximal stimulation of adjacent nerves (see Chapter 30).

In MMNCB, sensory studies are usually completely normal (though mild sensory abnormalities have been seen). Indeed, sensory studies usually are normal, even if performed across the same segment of nerve where a motor conduction block is present (Figure 26–9). Of course, any sensory abnormalities should also put into question the diagnosis of ALS, unless there is a known secondary process resulting in a superimposed polyneuropathy.

Needle EMG findings characteristically show decreased recruitment of MUAPs in weak muscles as a result of proximal conduction blocks. As in CIDP, secondary axonal changes are not unusual; denervating potentials and reinnervated MUAPs are present in most patients.

ELECTROPHYSIOLOGIC EVALUATION OF POLYNEUROPATHY

The electrophysiologic evaluation of a polyneuropathy varies with its severity. In general, nerve conduction studies and EMG should progress from distal to proximal (from

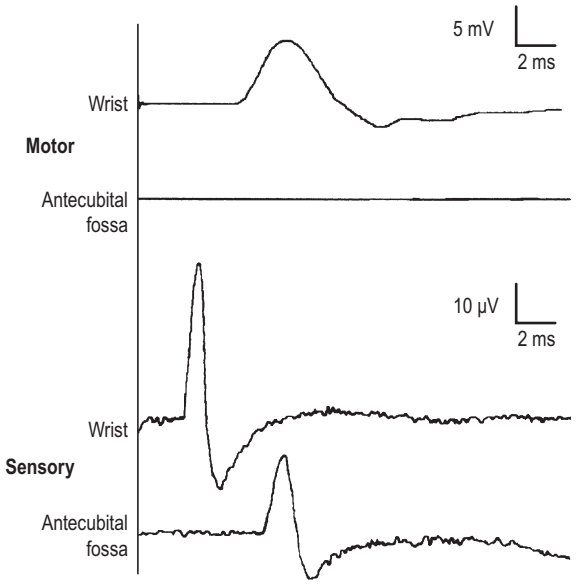


FIGURE 26–9 Motor conduction block in multifocal motor neuropathy with conduction block (MMNCB). Patients with MMNCB characteristically display conduction block of motor fibers, but often with complete sparing of sensory fibers, even through the same segment of nerve. Shown here are results of median nerve conduction studies in a patient with MMNCB, with the wrist and antecubital fossa stimulated and the abductor pollicis brevis muscle **(top)** for motor studies and the index finger **(bottom)** for sensory studies co-recorded. Note the complete block of motor conduction with intact sensory conduction. The amount of amplitude drop in the proximal sensory potential is within the normal range expected for the effects of normal temporal dispersion and phase cancellation for sensory potentials.

longer to shorter) nerves. In severe polyneuropathies, all responses may be absent distally in the lower extremities; in such cases nerve conduction studies must rely on the upper extremities. Testing should continue proximally from the lower to the upper extremities until normal or minimally affected nerves/muscles are encountered. As mentioned earlier, the goal of the electrophysiologic study is to confirm the presence of a polyneuropathy; assess its pattern and severity; determine whether motor, sensory, or a combination of fibers are involved; and, most importantly, assess whether the underlying pathology is primarily axonal loss or demyelination.

Nerve Conduction Studies

Nerve conduction studies should begin with motor conduction studies in a lower extremity (Box 26–7). The routine peroneal and tibial motor studies are performed along with their F responses. If motor responses are absent recording the usual distal muscles (i.e., EDB, abductor hallucis brevis), peroneal motor studies can be performed using the tibialis anterior, a more proximal muscle, for recording. Likewise, tibial motor studies can be performed proximally recording the soleus, using the same montage as for the H reflex. (*Note*: In this situation, only one stimulation site [i.e., the popliteal fossa] is possible; thus, an amplitude and distal latency can be obtained, but not a conduction velocity.) After the motor studies are completed in a lower extremity, one should obtain a lower extremity sensory response, either the sural or superficial peroneal, and often both. Averaging may be required, especially in polyneuropathy, where the responses may be very small. At least one motor and one sensory nerve conduction study should be performed in the contralateral leg to assess symmetry. In general, amplitude differences of more than 50% comparing side to side are considered abnormal (i.e., a 50% drop from the higher side to the lower; or a 100% increase from the lower side to the higher). Finally, in the lower extremities, the soleus H reflex can be performed. In most polyneuropathies where the ankle reflex is absent, so too is the H reflex, so the study adds little additional information. The H reflex, however, is more helpful in the assessment of very early polyneuropathies. Mild prolongation of the H reflex latency may be one of the first abnormalities seen in mild or early polyneuropathy.

After the lower extremity studies, an upper extremity is conducted. If only the lower extremities are studied, any abnormalities found could be just as consistent with the diagnosis of lumbosacral plexopathies as with that of polyneuropathy. In the upper extremity, median and ulnar motor conduction studies are performed first, with their F

Box 26–7. Recommended Nerve Conduction Study Protocol for Polyneuropathy

Routine motor conduction studies:

1. Peroneal study, recording extensor digitorum brevis and stimulating ankle, below fibular neck, and lateral popliteal fossa
2. Tibial study, recording abductor hallucis brevis and stimulating ankle and popliteal fossa
3. Median study, recording abductor pollicis brevis and stimulating wrist and antecubital fossa
4. Ulnar study, recording abductor digiti minimi and stimulating wrist and below and above elbow

Routine sensory studies:

1. Sural SNAP, stimulating calf and recording posterior ankle
2. Median SNAP, stimulating wrist and recording digit 2
3. Ulnar SNAP, stimulating wrist and recording digit 5
4. Radial SNAP, stimulating forearm and recording snuffbox

Late responses:

1. F responses: median, ulnar, peroneal, and tibial
2. Soleus H reflexes

Special considerations:

- All of the above studies are performed on one side. In addition, in each extremity on the contralateral side, one motor and sensory study should be performed to assess symmetry. If there is a clinical suggestion of asymmetry, more nerves on the contralateral side should be studied.
- The yield of demonstrating conduction block and other evidence of demyelination increases as additional motor nerves or segments are studied. In selected patients, either the contralateral routine motor nerves can be studied or proximal stimulation studies can be performed.
- In borderline cases, comparing the ratio of the maximal radial sensory amplitude to the maximal sural sensory amplitude can be helpful. A ratio <0.21 is supportive of the electrical diagnosis of an axonal polyneuropathy.

SNAP, sensory nerve action potential.

responses. Their respective sensory studies are performed next. In axonal polyneuropathy, the median and ulnar sensory responses, although abnormal, usually are better preserved than the sural and superficial peroneal responses in the legs. Of course, one must ensure that these sensory responses are not abnormal secondary to a local entrapment neuropathy. In this regard, measuring the radial sensory response often is helpful, being much less commonly involved in entrapment neuropathy. Comparing the maximal radial sensory amplitude to the maximal sural amplitude can be especially useful (see discussion of the SRAR above). Any ratio <0.21 is supportive of the diagnosis of an axonal polyneuropathy. As with the lower extremities, comparison of one motor and sensory nerve from side to side should be performed to assess symmetry. If there is a clear clinical asymmetry, comparison of more nerves is indicated.

When looking for conduction block and other electrophysiologic evidence of demyelination, it is often worthwhile to study additional nerves. The formal criteria for a demyelinating polyneuropathy are based on finding a number of different abnormalities (Boxes 26-5 and 26-6). If these criteria are only partially met, a more extensive search is warranted to try to secure the electrodiagnosis of a demyelinating neuropathy.

Electromyographic Approach

The EMG strategy in polyneuropathy (Box 26–8) is similar to that of the nerve conduction studies. Distal and proximal muscles of at least one upper and lower extremity must be sampled. In polyneuropathy, there is a characteristic distal-to-proximal gradient of neuropathic changes (lower extremity more affected than upper extremity; legs more affected than thighs; hands more affected than arms). It is very unusual for any polyneuropathy to affect the gluteal muscles or the muscles of the upper arm and shoulder girdle. Important exceptions to this include AIDP, which is a polyradiculoneuropathy, as well as other neuropathies with a proximal predominance, including porphyria and some diabetic neuropathies. As in the nerve conduction studies, it is worthwhile to compare a contralateral muscle in each limb to assess symmetry. In cases in which there is a clinical suggestion of asymmetry, more muscles should be sampled, especially in the distribution of the asymmetry.

Although the intrinsic foot muscles are the most distal muscles, they are best avoided in the EMG evaluation of polyneuropathy. First, examination of these muscles is often painful for most patients to tolerate. Second, activation of these muscles is usually difficult or nearly impossible (especially the tibial-innervated foot muscles), making any assessment of MUAPs difficult. Finally and most importantly, some denervation and reinnervation are commonly found in normal patients, especially in the EDB muscle. Presumably, repetitive trauma over time from shoes, walking, and running injures the distal nerves in the feet. Any EMG abnormality in those muscles must always be interpreted with caution and compared from side to side. In general, the best distal muscles to sample are those in the lower calf, especially the extensor hallucis longus and flexor digitorum longus.

For evaluation of polyneuropathy, the needle EMG is clearly the more sensitive part of the electrophysiologic study. Although the typical polyneuropathy shows distal abnormalities on both nerve conduction studies and EMG, in some mild polyneuropathies the only abnormal findings may be those present on the EMG. The loss of only a few axons may result in fibrillation potentials that are easily seen on the EMG but may cause little appreciable change on the motor and sensory nerve conduction studies. To emphasize this point, take the example of mild neuropathy wherein 10% of the fibers have been lost. A sural sensory amplitude that had been 20 μV drops to 18 μV (normal >6 μV), and a tibial motor amplitude that had been 10 mV drops to 9 mV (normal >4 mV). Thus, the nerve conduction studies still are interpreted as "normal." However, within the extensor hallucis longus muscle, there may be 200 motor units (i.e., 200 axons). Each motor unit may be composed of 50 muscle fibers. Thus, if 10% of the fibers are lost (20 axons), 20 × 50 = 1000 muscle fibers will be fibrillating and easily appreciated on needle EMG.

Box 26–8. Recommended Electromyography Protocol for Polyneuropathy

Lower extremity routine muscles:
1. Extensor hallucis longus
2. Tibialis anterior
3. Soleus/medial gastrocnemius
4. Quadriceps
5. Gluteal muscles or tensor fascia latae

Upper extremity routine muscles:
1. First dorsal interosseous
2. Extensor indicis proprius
3. Forearm muscles (pronator teres or flexor carpi radialis)
4. Biceps brachii
5. Medial deltoid

Special considerations:
- At a minimum, the above muscles should be studied on one side. In addition, in each extremity on the contralateral side, one muscle should be sampled to assess symmetry. If there is a clinical suggestion of asymmetry, additional muscles on the contralateral side should be studied.
- It is best to avoid the intrinsic foot muscles because denervation and reinnervation are commonly present in normal individuals.
- If abnormalities are found in the proximal muscles (e.g., glutei, biceps brachii), the paraspinal muscles should be sampled as well.

EXAMPLE CASES

In the following polyneuropathy example cases, we use the history, physical examination, and EDX study to answer the seven key questions about the polyneuropathy illustrated in the case. By doing so, the differential diagnosis is narrowed to a much smaller number of disorders, and subsequent evaluation and treatment proceeds in a more directed and logical way.

Case 26–1

History and Physical Examination

A 45-year-old woman was referred for numbness and tingling in the legs. She had been well until 6 months previously, when bilateral numbness began in the toes. Over the next several months, the numbness spread to above the ankles and was associated with pins-and-needles paresthesias. She described her feet as feeling like wooden blocks. More recently, numbness spread to the calves, with some tingling in the fingertips. She noted some difficulty opening jars, buttoning buttons, and turning keys.

On examination, there was mild atrophy of the intrinsic foot muscles bilaterally, especially of both extensor digitorum brevis muscles. Muscle strength testing was normal in all extremities. Ankle reflexes were absent bilaterally. Both knee reflexes were present but hypoactive. The upper extremity reflexes were normal and symmetric. Sensory testing demonstrated decreased vibration at both ankles. Sensation to light touch and pinprick was decreased below the knees bilaterally and in the fingers of both hands. There was no Romberg sign. Gait and coordination were normal. She had no family history of polyneuropathy, and no significant medical illnesses.

Summary

The history in this case is quite typical for polyneuropathy: a slow progression over several months and an onset that cannot be clearly dated. Symptoms began distally in the feet and slowly spread up the legs. A length-dependent pattern subsequently developed; the fingertips became involved at the same time as the upper calves (i.e., because the length from the cervical spinal cord to the fingertips is approximately the same length from the lumbosacral spinal cord to the upper calf).

Symptoms in this case are predominantly sensory, including altered sensation and pins-and-needles paresthesias distally. Likewise, the examination shows decreased vibration and pinprick sensation distally in a stocking-glove distribution. Although the symptoms are predominantly sensory, there is evidence of some motor dysfunction on examination. There is atrophy of the EDB muscle bilaterally. The ankle reflexes are absent, whereas knee and upper extremity reflexes are intact, a common finding in a distal polyneuropathy.

Based on the history and physical examination, it appears likely that the patient has a symmetric polyneuropathy involving predominantly large sensory fibers (decreased light touch and vibration). However, there also is some involvement of both motor and small sensory (decreased pinprick) fibers.

Nerve conduction studies are performed in the right lower and upper extremities, and some studies are done on the contralateral side to assess symmetry. Most of the abnormalities are noted in the lower extremity studies. The peroneal motor study shows a low amplitude, but without any prominent drop of amplitude on proximal stimulation, with a normal distal latency and slightly slowed conduction velocities. Similar findings occur in the tibial motor studies: low amplitudes, normal distal

CASE 26–1. Nerve Conduction Studies

Nerve Stimulated	Stimulation Site	Recording Site	Amplitude Motor = mV; Sensory = µV			Latency (ms)			Conduction Velocity (m/s)			F Wave latency (ms)		
			RT	LT	NL	RT	LT	NL	RT	LT	NL	RT	LT	NL
Median (m)	Wrist	APB	6.2	5.8	≥4	3.5	3.2	≤4.4				31	32	≤31
	Antecubital fossa	APB	6.1	5.8		7.3	7.2		52	50	≥49			
Ulnar (m)	Wrist	ADM	7.3		≥6	3.1		≤3.3				32		≤32
	Below elbow	ADM	7.2			6.4			55		≥49			
	Above elbow	ADM	7.2			8.3			53		≥49			
Median (s)	Wrist	Index finger	13	12	≥20	3.4	3.3	≤3.5	50	51	≥50			
Ulnar (s)	Wrist	Little finger	7		≥17	3.1		≤3.1	49		≥50			
Tibial (m)	Ankle	AHB	3.2	2.8	≥4	5.7	5.6	≤5.8				57	56	≤56
	Popliteal fossa	AHB	2.5	2.2		12.1	11.7		39	41	≥41			
Peroneal (m)	Ankle	EDB	1.1		≥2	6.2		≤6.5				NR		≤56
	Below fibula	EDB	0.9			12.6			39		≥44			
	Lateral popliteal fossa	EDB	0.8			15.3			37		≥44			
Sural (s)	Calf	Posterior ankle	NR	NR	≥6			≤4.4			≥40			

m = motor study; s = sensory study; R = right; LT = left; NL = normal; NR = no response; APB = abductor pollicis brevis; ADM = abductor digiti minimi; AHB = abductor hallucis brevis; EDB = extensor digitorum brevis.

Note: All sensory latencies are peak latencies. All sensory conduction velocities are calculated using onset latencies. The reported F wave latency represents the minimum F wave latency.

CASE 26–1. Electromyography

Muscle	Insertional Activity	Spontaneous Activity		Voluntary Motor Unit Action Potentials				
		Fibrillation Potentials	Fasciculations	Activation	Recruitment	Configuration		
						Duration	Amplitude	Polyphasia
Right extensor hallucis longus	↑	+3	0	NL	↓↓	+2	+2	+2
Right tibialis anterior	↑	+2	0	NL	↓↓	+2	+1	+1
Right medial gastrocnemius	↑	+2	0	NL	↓↓	+2	+1	+1
Right vastus lateralis	NL	+1	0	NL	↓	+1	+1	NL
Right gluteus medius	NL	0	0	NL	NL	NL	NL	NL
Right first dorsal interosseous	↑	+2	0	NL	↓↓	+2	+1	+1
Right indicis proprius	↑	+1	0	NL	↓	+1	+1	+1
Right pronator teres	NL	0	0	NL	↓	+1	NL/+1	NL/+1
Right biceps brachii	NL	0	0	NL	NL	NL	NL	NL
Right medial deltoid	NL	0	0	NL	NL	NL	NL	NL
Left tibialis anterior	↑	+2	0	NL	↓↓	+2	+2	+2
Left biceps brachii	NL	0	0	NL	NL	NL	NL	NL

↑ = increased; ↓ = slightly reduced; ↓↓ = moderately reduced; NL = normal.

latencies, and borderline slowed conduction velocities. The tibial F responses are slightly prolonged. Although the peroneal F responses are absent, this finding is of unclear significance because peroneal F responses are absent or difficult to obtain in some normal individuals. The sural sensory responses are absent bilaterally.

The motor studies in the lower extremities are consistent with axonal loss: amplitudes are low; velocities and latencies are normal to slightly slowed. The tibial and sural responses are symmetric from side to side. In the upper extremities, the motor studies are completely normal and symmetric. However, the sensory studies show low-amplitude responses with normal latencies and borderline slowed conduction velocities. These abnormalities again are consistent with axonal loss.

On the nerve conduction studies, there is a clear distal predominance of abnormalities, which are more prominent in the lower extremities than the upper. In addition, the nerve conduction studies are fairly symmetric comparing side to side.

Moving on to the needle EMG, the distal muscles of the right leg show fibrillation potentials and large, long, polyphasic MUAPs with reduced recruitment. As more proximal muscles are sampled, however, the amount of fibrillation potentials decreases and the motor unit potential changes are not as marked. When the gluteus medius, a very proximal muscle, is sampled, no abnormalities are seen.

In the upper extremities, a similar distal-to-proximal pattern is present. The first dorsal interosseous and extensor indicis proprius are fibrillating with large MUAPs and decreased recruitment. However, the pronator teres shows no fibrillation potentials and only borderline enlarged MUAPs. More proximally, at the biceps and deltoid, MUAPs and spontaneous activity are normal. Comparing two contralateral muscles, the tibialis anterior and biceps brachii, the findings are symmetric.

At this point we are ready to form our electrophysiologic impression.

IMPRESSION: *There is electrophysiologic evidence of an active and chronic sensorimotor distal, axonal polyneuropathy.*

We now have all the information needed to answer the seven key questions about the polyneuropathy in this case:

Key Neuropathy Questions	Answers
Temporal course	Subacute/Chronic; slowly progressive
Fiber types involved	Sensory (large and small fiber) > motor
Pattern	Symmetric; stocking glove
Pathology	Axonal, active and chronic
Family history	No
Associated medical illness	No
Toxic/Occupational exposure	No

With this information, the case can be further analyzed and other key questions answered.

Does the Clinical–Electrophysiologic Correlation Make Sense?

The key point in this case is the similar pattern of abnormalities that emerges from the clinical data, nerve conduction studies, and EMG. All reveal a length-dependent, distal predominance of findings. In addition, there is no significant asymmetry on physical examination, nerve conduction studies, or EMG.

The polyneuropathy involves both sensory and motor fibers. The history and examination indicate abnormalities of sensation, which correlate with the abnormal sensory responses found on the nerve conduction studies. Although the patient has very few motor complaints, minor motor signs are found on the physical examination, and there is clear evidence of motor dysfunction on both nerve conduction studies and EMG.

Does the Underlying Nerve Pathology Help Limit the Differential Diagnosis?

The pattern on nerve conduction studies is clearly one of axonal loss, which is symmetric, involving both sensory and motor fibers. Both fibrillation potentials and large, long MUAPs are seen on EMG, which are signs of acute and chronic axonal loss, respectively. On nerve conduction studies, amplitudes are generally reduced with normal or slightly prolonged latencies, conduction velocities, and late responses, the electrophysiologic findings of axonal loss. There is no conduction block or markedly slowed latency or conduction velocity to suggest demyelination.

The overall picture in this case is one of a typical, subacute to chronic, axonal polyneuropathy. Such a picture could be seen in a multitude of different axonal polyneuropathies. Toxic, metabolic, endocrine, and drug-induced causes should be carefully considered. Because there is no electrophysiologic evidence of demyelination to suggest one of the demyelinating polyneuropathies, several possibilities have been eliminated from the differential diagnosis. Likewise, the need for certain laboratory tests has been obviated. For instance, there would be little point in obtaining a skeletal survey looking for an osteosclerotic myeloma or in performing an anti-MAG antibody test, both of which would be indicated in a patient with a chronic demyelinating polyneuropathy, while it would certainly make sense to screen for diabetes, thyroid dysfunction, and B_{12} deficiency.

Case Follow-up

The patient underwent routine blood screening for diabetes, thyroid disease, vitamin deficiencies, connective tissue disease, and a monoclonal protein. No abnormality was discovered. On repeat questioning, she admitted to heavy alcohol intake for many years, which she had been reluctant to admit initially. She was treated symptomatically and advised to discontinue alcohol and improve her nutrition.

Case 26–2

History and Physical Examination

A 68-year-old woman gradually developed numbness of the left fourth and fifth digits over several weeks. A month later, she developed similar numbness on her inner thighs bilaterally, which then spread to her outer thighs and then down her legs. A similar sensation then developed around her lower back and abdomen. This was followed by numbness of the remainder of the left hand and then of the entire right hand. She had no complaints of weakness, bowel or bladder difficulties, or visual changes. However, her gait had become very unsteady. Her past medical history was notable for mild rheumatoid arthritis and a 40-pack per year history of smoking.

Examination showed normal cranial nerve function. Eye movements were full. There was no facial weakness. Corneal response and facial sensation were normal. Motor examination revealed full strength in all limbs. Sensory examination revealed a profound loss of vibration in all four extremities and impaired joint position sense in the lower extremities. Pinprick and temperature sensation were reduced in a patchy distribution over the extremities. Pseudoathetosis was present in the upper extremities. Reflexes were diffusely absent. Gait was grossly ataxic, and a Romberg sign was present.

Summary

The history and examination in this case suggest a polyneuropathy, but one very different from the stocking-glove, length-dependent polyneuropathy described in Case 26–1. In this patient, the history is one of an asymmetric, stepwise progression of symptoms, compatible with a mononeuropathy multiplex pattern. This type of presentation would be distinctly unusual for any toxic, metabolic, endocrine, drug-induced, or inherited polyneuropathy, all of which are typically symmetric and distal.

The examination is notable only for sensory abnormalities, mostly involving large sensory fibers. All reflexes are absent, and there is profound loss of vibration and joint position sense in all four extremities. With patchy loss of pin and temperature sense, there must be an element of small-fiber sensory loss as well.

The combination of findings suggests that the person has severe sensory denervation. Pseudoathetosis is an important sign, usually signifying markedly impaired joint position sense. Normally when a patient places the hands and arms straight out with the eyes closed, there is very little movement. A patient with severe sensory loss, who does not know where his or her limbs are in space, will display athetotic movements of the fingers and sometimes of the hands and wrists. In addition, patients with severe sensory loss will often have a Romberg sign, as is present in this case. Finally, gait may be very unstable and ataxic from sensory loss alone. This underscores that gait ataxia is not always a cerebellar problem but may represent dysfunction of the sensory pathways, either in the spinal cord (i.e., dorsal columns) or in the peripheral

CASE 26–2. Nerve Conduction Studies

Nerve Stimulated	Stimulation Site	Recording Site	Amplitude Motor = mV; Sensory = µV			Latency (ms)			Conduction Velocity (m/s)			F Wave latency (ms)		
			RT	LT	NL	RT	LT	NL	RT	LT	NL	RT	LT	NL
Median (m)	Wrist	APB	6.5	7.2	≥4	3.4	3.2	≤4.4				25	27	≤31
	Antecubital fossa	APB	6.4	7.0		6.9	6.6		57	59	≥49			
Ulnar (m)	Wrist	ADM	6.7		≥6	2.7		≤3.3				28		≤32
	Below elbow	ADM	6.2			5.7			60		≥49			
	Above elbow	ADM	6.0			7.5			55		≥49			
Median (s)	Wrist	Index finger	7	9	≥20	3.2	3.0	≤3.5	52	54	≥50			
Ulnar (s)	Wrist	Little finger	3	NR	≥17	2		≤3.1	55		≥50			
Radial (s)	Forearm	Snuffbox	5	7	≥15	2.8	2.8	≤2.9	54	54	≥50			
Tibial (m)	Ankle	AHB	10	11	≥4	4.8	4.5	≤5.8				52	51	≤56
	Popliteal fossa	AHB	8.2	7		9.4	9.0		54	55	≥41			
Peroneal (m)	Ankle	EDB	4.9		≥2	5.2		≤6.5				49		≤56
	Below fibula	EDB	4.4			9.3			44		≥44			
	Lateral popliteal fossa	EDB	4.4			11.3			50		≥44			
Sural (s)	Calf	Posterior ankle	3	10	≥6	4.0	3.6	≤4.4	39	52	≥40			

m = motor study; s = sensory study; RT = right; LT = left; NL = normal; NR = no response; APB = abductor pollicis brevis; ADM = abductor digiti minimi; AHB = abductor hallucis brevis; EDB = extensor digitorum brevis.

Note: All sensory latencies are peak latencies. All sensory conduction velocities are calculated using onset latencies. The reported F wave latency represents the minimum F wave latency.

CASE 26–2. Electromyography

Muscle	Insertional Activity	Spontaneous Activity		Voluntary Motor Unit Action Potentials				
		Fibrillation Potentials	Fasciculations	Activation	Recruitment	Configuration		
						Duration	Amplitude	Polyphasia
Right extensor hallucis longus	NL	0	0	NL	NL	NL	NL	NL
Right tibialis anterior	NL	0	0	NL	NL	NL	NL	NL
Right medial gastrocnemius	NL	0	0	NL	NL	NL	NL	NL
Right vastus lateralis	NL	0	0	NL	NL	NL	NL	NL
Right gluteus medius	NL	0	0	NL	NL	NL/+1	NL	NL
Right first dorsal interosseous	NL	0	0	NL	NL	NL	NL	NL
Right indicis proprius	NL	0	0	NL	NL	NL	NL	NL
Right pronator teres	NL	0	0	NL	NL	NL	NL	NL
Right biceps brachii	NL	0	0	NL	NL	NL	NL	NL
Right medial deltoid	NL	0	0	NL	NL	NL	NL	NL
Left tibialis anterior	NL	0	0	NL	NL	NL	NL	NL
Left biceps brachii	NL	0	0	NL	NL	NL	NL	NL

NL = normal.

nerves. Notably, the patient's motor system is completely normal. Although this observation will have to be confirmed with nerve conduction studies and EMG, clinically the symptoms and signs suggest predominantly sensory dysfunction with an asymmetric presentation.

This sensory asymmetry is subsequently found on the nerve conduction studies. Nearly all sensory responses are abnormal. The median sensory responses are bilaterally low, with normal latencies and conduction velocities. The right ulnar sensory potential is very low, and on the left it is unobtainable. Both radial sensory potentials are low. In the lower extremity, however, the sural potential is low on the right but normal on the left. Those sensory potentials that are abnormal have normal to slightly slowed latencies and conduction velocities, all within the range of axonal loss. The asymmetry of the sural sensory potential is a key finding that would not be expected in a typical length-dependent distal axonal polyneuropathy.

The motor studies in the upper and lower extremities are completely normal. Thus, at the end of the nerve conduction studies, an unusual situation is found: the abnormalities are asymmetric and appear limited to the sensory system.

Moving on to the EMG, the study is entirely normal and shows no evidence of denervation or reinnervation of the proximal or distal muscles of the upper or lower extremities. The recruitment is normal in all muscles tested. In combination with the nerve conduction studies, the EMG study excludes involvement of the motor fibers. EMG is the most sensitive way to detect subtle motor involvement. If only a few motor axons are lost, denervation can usually be seen on EMG, although no appreciable change is seen on the motor conduction studies.

At this time we are ready to make a diagnosis.

IMPRESSION: *The electrophysiologic findings are consistent with an asymmetric, sensory neuropathy or sensory neuronopathy.*

We now have all the information needed to answer the seven key questions about the polyneuropathy in this case:

Key Neuropathy Questions	Answers
Temporal course	Subacute; stepwise
Fiber types involved	Restricted to sensory (large > small fiber)
Pattern	Asymmetric
Pathology	Axonal, asymmetric, sensory
Family history	No
Associated medical illness	Rheumatoid arthritis
Toxic/Occupational exposure	Smoking

With this information, the case can be further analyzed and other key questions answered.

Does the Pure Sensory Involvement Narrow the Differential Diagnosis?

This case is distinctly unusual. The history, physical examination, nerve conduction studies, and EMG show a disorder restricted to the sensory system; the motor system is completely spared. Both large and small sensory fibers are involved. The large-fiber sensory dysfunction has led to the impaired vibration and joint position sense, loss of reflexes, Romberg sign, pseudoathetosis, and gait ataxia. There is minor, small-fiber sensory involvement, demonstrated by pinprick and temperature sense loss.

Because nearly all polyneuropathies have some motor as well as sensory findings, especially on nerve conduction studies and EMG, this particular case is exceptional. Because of the asymmetry and the fact that the upper extremities are as equally involved as the lower extremities, the pattern suggests a sensory neuronopathy, a disorder of the dorsal root ganglia, the primary sensory neuron. Sensory neuronopathies are quite rare. In some cases, a sensory neuronopathy may be part of a larger neurodegenerative disorder. For instance, Friedreich's ataxia and some other chronic spinocerebellar degenerations can have an associated sensory neuronopathy. In acute or subacute cases such as this one, however, sensory neuronopathies usually are associated with only a few distinct disorders. They may be paraneoplastic neuronopathies, often associated with a small cell carcinoma of the lung. In a subset of these cases, an anti-HU antibody will be present. Sensory neuronopathies may also be seen in patients with Sjögren's syndrome and related connective tissue disorders. In addition, sensory neuronopathy may be seen as a postinfectious process, a sequela of pyridoxine (vitamin B_6) intoxication, or as an isolated autoimmune process.

In this patient, who has rheumatoid arthritis and a long history of smoking, one must investigate both the possibility of Sjögren's syndrome associated with rheumatoid arthritis or a paraneoplastic sensory neuronopathy from an underlying, yet unrecognized carcinoma. The subsequent workup and evaluation should be very different from that indicated in the distal axonal sensorimotor polyneuropathy of Case 26–1.

Case Follow-up

Subsequent evaluation for Sjögren's syndrome was negative, and there was no history of pyridoxine ingestion. A chest X-ray film showed a hilar mass that on biopsy proved to be small cell carcinoma. Anti-HU antibodies were present in the blood.

Case 26–3

History and Physical Examination

A 65-year-old man was referred for evaluation of fever, progressive weight loss, and recent numbness and weakness of several months' duration. Three weeks previously,

abrupt pain developed in the left posterior thigh, followed by a foot drop and numbness over the dorsum of the foot and lateral leg. One week ago, a similar episode occurred in the right leg. The day before the examination, pain developed in the left medial arm, followed by weakness of hand grip and numbness involving the ring and little fingers of the left hand.

Examination showed a cachectic, ill-appearing man. Muscle bulk was diminished in the anterolateral compartment of the left leg. Marked bilateral foot drops were present. The left first dorsal interosseous, abductor digiti minimi (ADM), and flexor digitorum profundus to digits 4 and 5 were markedly weak. However, strength testing of the left extensor indicis proprius, abductor pollicis brevis (APB), and flexor pollicis brevis was normal. Reflexes were absent at the ankles but otherwise were normal. Sensation was diminished in the left hypothenar region and fourth and fifth digits. There was a stocking-pattern loss to all sensory modalities in the legs that was somewhat more prominent on the dorsum of both feet.

Summary

In this case, the history suggests some type of systemic illness, manifested by fever and weight loss followed by a progressive polyneuropathy. The polyneuropathy, however, has an unusual presentation: an asymmetric, stepwise progression of numbness and weakness, heralded by the abrupt onset of pain. The entire neurologic history is acute; the first event occurred only 3 weeks ago. Although exact localization is not possible from the history alone, it appears that left peroneal fibers were affected 3 weeks ago (foot drop and numbness), followed by a similar event on the right side 1 week ago. One day ago, the left ulnar fibers became involved, with numbness of the ring and little fingers and weakness of grip.

On examination, there are bilateral foot drops, correlating with the patient's symptoms 1 and 3 weeks ago. In the left leg, some atrophy has developed as well. In the left hand, there are abnormalities in the ulnar nerve distribution, including weakness of the first dorsal interosseous, ADM, and flexor digitorum profundus muscles. The weakness, along with decreased sensation over the left hypothenar region and fourth and fifth digits, clearly suggests involvement of the left ulnar nerve. Distal muscles that are innervated by different nerves (i.e., the extensor indicis proprius, APB, and flexor pollicis brevis) are all normal. This preferential involvement of only certain distal muscles would not occur in a typical distal axonal polyneuropathy. Rather, the history and examination thus far suggest involvement of isolated named nerves. Sensory examination in the lower extremities shows a stocking loss to all modalities that is somewhat more prominent on the dorsum of the feet. Recall that

CASE 26–3. Nerve Conduction Studies

Nerve Stimulated	Stimulation Site	Recording Site	Amplitude Motor = mV; Sensory = µV			Latency (ms)			Conduction Velocity (m/s)			F Wave latency (ms)		
			RT	LT	NL	RT	LT	NL	RT	LT	NL	RT	LT	NL
Median (m)	Wrist	APB	5.2	5.4	≥4	4.2	4.0	≤4.4				30	28	≤31
	Antecubital fossa	APB	5.0	5.1		7.4	7.0		56	59	≥49			
Ulnar (m)	Wrist	ADM	11.2	12	≥6	3.1	3.2	≤3.3				28	28	≤32
	Below elbow	ADM	11.2	11.2		6.1	6.5		60	55	≥49			
	Above elbow	ADM	11.2	11		7.8	8.3		60	57	≥49			
Median (s)	Wrist	Index finger	34	32	≥20	3.3	3.2	≤3.5	55	55	≥50			
Ulnar (s)	Wrist	Little finger	24	22	≥17	2.9	2.9	≤3.1	58	56	≥50			
Tibial (m)	Ankle	AHB	4.2	2.1	≥4	5.7	6.0	≤5.8				56	56	≤56
	Popliteal fossa	AHB	3.8	1.7		11.9	12.4		40	39	≥41			
Peroneal (m)	Ankle	EDB	0.2	0.3	≥2	6.2	6.4	≤6.5				NR	NR	≤56
	Below fibula	EDB	0.2	0.2		11.0	11.5		41	39	≥44			
	Lateral popliteal fossa	EDB	0.2	0.2		13.5	14		40	40	≥44			
Peroneal (s)	Lateral calf	Lateral ankle	NR	NR	≥6			≤4.4			≥40			
Sural (s)	Calf	Posterior ankle	12	3	≥6	4.1	4.2	≤4.4	45	46	≥40			

m = motor study; s = sensory study; RT = right; LT = left; NL = normal; NR = no response; APB = abductor pollicis brevis; ADM = abductor digiti minimi; AHB = abductor hallucis brevis; EDB = extensor digitorum brevis.

Note: All sensory latencies are peak latencies. All sensory conduction velocities are calculated using onset latencies. The reported F wave latency represents the minimum F wave latency.

CASE 26–3. Electromyography

Muscle	Insertional Activity	Spontaneous Activity		Voluntary Motor Unit Action Potentials				
		Fibrillation Potentials	Fasciculations	Activation	Recruitment	Configuration		
						Duration	Amplitude	Polyphasia
Right extensor hallucis longus	NL	0	0	NL	↓↓↓	NL	NL	NL
Right tibialis anterior	↑	0	0	NL	↓↓↓	NL	NL	NL
Right medial gastrocnemius	NL	0	0	NL	NL	NL	NL	NL
Right tibialis posterior	NL	0	0	NL	NL	NL	NL	NL
Right vastus lateralis	NL	0	0	NL	NL	NL	NL	NL
Right gluteus medius	NL	0	0	NL	NL	NL	NL	NL
Left tibialis anterior	↑	+2	0	NL	↓↓↓	NL	NL	NL
Left medial gastrocnemius	↑	+1	0	NL	↓↓	NL	NL	NL
Left tibialis posterior	↑	+1	0	NL	↓↓	NL	NL	NL
Left vastus lateralis	NL	0	0	NL	NL	NL	NL	NL
Left short head biceps femoris	↑	+2	0	NL	↓↓↓	NL	NL	NL
Right abductor pollicis brevis	NL	0	0	NL	NL	NL	NL	NL
Right first dorsal interosseous	NL	0	0	NL	NL	NL	NL	NL
Right pronator teres	NL	0	0	NL	NL	NL	NL	NL
Right biceps brachii	NL	0	0	NL	NL	NL	NL	NL
Right medial deltoid	NL	0	0	NL	NL	NL	NL	NL
Left abductor pollicis brevis	NL	0	0	NL	NL	NL	NL	NL
Left first dorsal interosseous	NL	0	0	NL	↓↓↓	NL	NL	NL
Left flexor digitorum profundus (V)	NL	0	0	NL	↓↓↓	NL	NL	NL
Left biceps brachii	NL	0	0	NL	NL	NL	NL	NL

↑= increased; ↓↓ = moderately reduced; ↓↓↓ = markedly reduced; NL = normal; V = digit five.

the dorsum of the feet receive their sensory innervation from the peroneal nerves.

The history and physical examination tell us that the patient, who is probably systemically ill, had the asymmetric presentation of what appears to be a left peroneal neuropathy 3 weeks ago, a right peroneal neuropathy 1 week ago, and a left ulnar neuropathy 1 day ago.

Because the clinical findings are asymmetric, the assessment of symmetry will be an important part of the nerve conduction studies and EMG. In the lower extremities, both peroneal motor conduction studies show very low amplitudes, with normal latencies and slightly slowed conduction velocities. This pattern of abnormalities is classic for an axonal loss lesion. When the tibial motor conduction studies are performed, however, a normal result is found on the right side, but a low-amplitude response is present on the left. The distal latencies are normal, but the conduction velocities are borderline slowed. Thus, there is evidence of axonal loss in the left tibial nerve. When the lower extremity sensory studies are performed, both peroneal sensory responses are absent, a finding that correlates well with the loss of feeling over the dorsum of the feet. The sural responses, however, are asymmetric: abnormal on the left but intact on the right. The asymmetric sural sensory and tibial motor responses are important findings. Such would not be expected in a typical distal dying-back axonal polyneuropathy. Furthermore, the abnormal tibial and peroneal

findings on the left side suggest that the foot drop may be secondary to a more proximal lesion. Thus, at the end of the lower extremity nerve conduction studies, there is definite evidence of bilateral peroneal neuropathies as well as a left tibial neuropathy.

Median motor conduction studies are performed bilaterally and are completely normal and symmetric. Next, ulnar motor conduction studies are performed bilaterally and are normal and symmetric. At this point, one may question why the left ulnar motor study is completely normal, yet the patient has weakness in the ulnar distribution. Recall that the left ulnar lesion is only 1 day old, so not enough time has passed for wallerian degeneration to have occurred. In this hyperacute period, nerve conduction studies remain normal. Likewise, when the median and ulnar sensory conduction studies are performed, they also are normal and symmetric bilaterally, with normal latencies and conduction velocities. Once again, there is a paradoxical finding of numbness in the ulnar distribution clinically, yet a normal ulnar sensory potential. This unusual combination of findings (clinical sensory loss with normal sensory potential in the distribution of numbness) can only occur in one of three situations: (1) a hyperacute axonal lesion, (2) proximal demyelination, or (3) any lesion proximal to the dorsal root ganglion. In the present case, it is most likely that the sensory response is normal because of the time course of the lesion (i.e., not enough time has passed for wallerian degeneration to have occurred).

On EMG, the right leg is sampled first. Recall that the right leg was clinically affected 1 week ago and that nerve conduction studies in the right leg showed only low peroneal motor and sensory amplitudes. The right leg shows no evidence of active denervation, and all MUAPs are normal. However, MUAP recruitment is markedly reduced in two peroneal-innervated muscles: the extensor hallucis longus and the tibialis anterior. The tibial-innervated muscles are normal, as are the more proximal muscles: the vastus lateralis and gluteus medius. Putting together the right leg nerve conduction studies and needle EMG, we see the pattern of an acute peroneal neuropathy. Enough time has passed for wallerian degeneration to have occurred, resulting in abnormal nerve conduction studies, but it remains too early to see signs of denervation or reinnervation. This is the classic acute axonal pattern: the only abnormality on EMG is decreased recruitment of normal appearing MUAPs

When the left leg is sampled, there is clear evidence of active denervation, both in peroneal- and tibial-innervated muscles including the short head of the biceps femoris, which is above the popliteal fossa. Involvement of the short head of the biceps femoris, along with the abnormal peroneal and tibial motor and peroneal and sural sensory nerve conduction studies, suggests that the lesion is in the sciatic nerve. Once again, the MUAPs are normal in morphology with a reduced recruitment pattern. This is the classic subacute axonal pattern: enough time has passed for wallerian degeneration to have occurred, resulting in abnormal nerve conduction studies; enough time also has passed for denervation to be seen on the needle examination. However, it remains too early for reinnervation. This particular pattern occurs after several weeks but before several months have passed.

In the clinically unaffected right upper extremity, all muscles are normal. However, in the left upper extremity, where the patient had ulnar motor and sensory loss on physical examination yet normal ulnar nerve conduction studies, we find decreased recruitment in ulnar-innervated muscles. Of note, there are no fibrillation potentials or reinnervated MUAPs. When other non-ulnar C8-innervated muscles are sampled (e.g., APB), they are normal. Putting together the clinical examination, nerve conduction studies, and EMG in the left upper extremity, it is apparent that a hyperacute axonal ulnar neuropathy is present. Not enough time has passed (only 1 day) for wallerian degeneration, denervation, or reinnervation to have occurred. The only abnormality is decreased recruitment in weak muscles.

Therefore, at this time we are ready to make a diagnosis.

IMPRESSION: *The electrophysiologic findings are consistent with a mononeuropathy multiplex pattern, with a hyperacute left ulnar neuropathy, acute right peroneal neuropathy, and subacute left sciatic neuropathy.*

We now have all the information needed to answer the seven key questions about the polyneuropathy in this case:

Key Neuropathy Questions	Answers
Temporal course	Subacute, stepwise progressive
Fiber types involved	Motor and sensory
Pattern	Asymmetric, multiple nerves
Pathology	Axonal, asymmetric, multiple nerves
Family history	No
Associated medical illness	Underlying fever, weight loss
Toxic/Occupational exposure	No

With this information, the case can be further analyzed and other key questions answered. This case demonstrates the major clinical and electrophysiologic findings of a mononeuritis multiplex pattern. The clinical presentation is distinctive: an asymmetric stepwise progression of individual mononeuropathies. Nerve conduction studies and EMG, if performed early in the disease, typically will demonstrate evidence of asymmetry. The

presence of asymmetry excludes the typical toxic, metabolic, endocrine, drug-induced, and genetic polyneuropathies that result in a symmetric, dying-back, stocking-glove pattern of abnormalities.

Does the Time Course of the Polyneuropathy Fit with the Electrophysiologic Data?

Mononeuritis multiplex is one of the few polyneuropathies that may present acutely over a short period of time. Knowing the duration of symptoms and the tempo of the polyneuropathy is essential to interpret the nerve conduction studies and EMG properly. As demonstrated in this case, if a patient is studied within 1 week of an acute event, nerve conduction studies and EMG findings will be completely normal, with the exception of decreased recruitment of MUAPs in weak muscles (hyperacute axonal pattern). If studies are performed after 1 week but before several weeks, nerve conduction studies will be abnormal, but EMG findings will be similar (acute axonal pattern). If the study is performed after several weeks but not before months, abnormal nerve conduction studies will be found along with fibrillation potentials on EMG. MUAPs will remain normal in morphology but will show decreased recruitment (subacute axonal pattern). These patterns are not seen in the typical, slowly progressive polyneuropathy. By the time a patient with a typical polyneuropathy reaches the EMG laboratory, there are usually nerve conduction study abnormalities and evidence of denervation and reinnervation on EMG.

What is the Differential Diagnosis of Mononeuropathy Multiplex?

In this particular case, in which the history suggests a coexistent systemic illness, the possibility of systemic vasculitis, especially polyarteritis nodosa, should be strongly considered. Polyarteritis nodosa is a neurologic emergency, requiring prompt diagnosis and treatment to prevent infarction of other nerves or internal organs (e.g., kidney, bowel, heart). The next logical step in such a patient would be to perform a nerve and muscle biopsy as soon as possible, looking for evidence of vasculitis. In this case, the best nerve to biopsy would be the left sural nerve, the side that was abnormal on nerve conduction studies. Note that a muscle should be chosen for biopsy that was not studied on EMG, because of the possibility of the needle creating an inflammatory reaction, which could confuse the biopsy findings.

As in this case, the typical vasculitic mononeuropathy multiplex pattern is asymmetric and purely axonal in nature, showing no electrophysiologic evidence of demyelination. Although vasculitis is the most common cause of mononeuropathy multiplex, the differential diagnosis of mononeuropathy multiplex includes other conditions (Box 26-3), among them a variant of CIDP, which in this case is excluded by the lack of demyelination on nerve conduction studies, as well as diabetes, multiple entrapments, and infectious and infiltrative lesions.

Case Follow-up

Blood testing showed a markedly elevated ESR of 110 mm/h, and mild elevation of the liver function tests. A left sural nerve and lateral gastrocnemius muscle biopsy were performed. Both showed fibrinoid necrosis surrounding small and medium sized arterial blood vessels with an inflammatory infiltrate within the vessel walls. The diagnosis of polyarteritis nodosa was made. The patient was treated with a combination of high dose oral steroids and cyclophosphamide.

Case 26–4

History and Physical Examination

A 32-year-old woman was admitted for progressive weakness and numbness. She had been well until 3 weeks ago, when she developed diarrhea and fever that persisted for several days, and remitted. Ten days ago, she developed pins-and-needles paresthesias in both feet and both hands. Those symptoms were followed by clumsiness of gait and progressive weakness of both arms and legs.

Examination was notable for bifacial weakness and a mild, diffuse quadriparesis. Reflexes were trace in the arms and absent in the legs. A mild distal sensory loss to pinprick, light touch, and vibration was present in both upper and lower extremities.

Summary

In this case, there is a rapidly progressive, subacute polyneuropathy that developed several days after an infectious illness. The history and physical examination provide clear evidence of both motor and sensory dysfunction. However, the pattern is unusual: pins-and-needles paresthesias in the hands and feet at the same time. That combination does not occur in typical distal, length-dependent polyneuropathies, in which symptoms first develop in the feet and only later in the hands after the polyneuropathy has reached the mid-shins. The examination is notable for the lack of reflexes and the predominant motor findings, with minor sensory findings. These clinical findings, along with development of paresthesias simultaneously in the hands and feet, are suggestive of a demyelinating polyneuropathy.

Nerve conduction studies show completely normal motor studies in the upper and lower extremities. All amplitudes are normal, with intact conduction velocities and distal latencies. There is no evidence on proximal stimulation to suggest conduction block. However, all F responses are notably absent, despite the normal distal amplitudes and conduction velocities. This particular pattern of normal distal motor conduction studies with absent late responses is strongly suggestive of proximal demyelination, either at the plexus or root level.

The results of the sensory conduction studies are quite unusual: both sural potentials are normal bilaterally, but the median and ulnar sensory amplitudes are low. Such a pattern does not occur in the typical distal, length-dependent polyneuropathy. This pattern of "sural sparing"

CASE 26–4. Nerve Conduction Studies

Nerve Stimulated	Stimulation Site	Recording Site	Amplitude Motor = mV; Sensory = µV			Latency (ms)			Conduction Velocity (m/s)			F Wave latency (ms)		
			RT	LT	NL	RT	LT	NL	RT	LT	NL	RT	LT	NL
Median (m)	Wrist	APB	5.4	6.0	≥4	4.1	3.8	≤4.4				NR	NR	≤31
	Antecubital fossa	APB	5.0	6.0		7.3	7.0		56	55	≥49			
Ulnar (m)	Wrist	ADM	10.2		≥6	3.1		≤3.3				NR		≤32
	Below elbow	ADM	10.2			6.6			57		≥49			
	Above elbow	ADM	10.2			8.3			59		≥49			
Median (s)	Wrist	Index finger	3	4	≥20	3.5	3.4	≤3.5	54	53	≥50			
Ulnar (s)	Wrist	Little finger	5		≥17	2.9		≤3.1	45		≥50			
Tibial (m)	Ankle	AHB	5.7	4.2	≥4	5.8	5.6	≤5.8				NR	NR	≤56
	Popliteal fossa	AHB	4.8	4.0		11.7	11.6		42	41	≥41			
Peroneal (m)	Ankle	EDB	5.2		≥2	5.6		≤6.5				NR		≤56
	Below fibula	EDB	5.0			11.2			44		≥44			
	Lateral popliteal fossa	EDB	5.0			13.4			45		≥44			
Sural (s)	Calf	Posterior ankle	23	18	≥6	4.2	4.1	≤4.4	45	47	≥40			

m = motor study; s = sensory study; RT = right; LT = left; NL = normal; NR = no response; APB = abductor pollicis brevis; ADM = abductor digiti minimi; AHB = abductor hallucis brevis; EDB = extensor digitorum brevis.

Note: All sensory latencies are peak latencies. All sensory conduction velocities are calculated using onset latencies. The reported F wave latency represents the minimum F wave latency.

CASE 26–4. Electromyography

Muscle	Insertional Activity	Spontaneous Activity		Voluntary Motor Unit Action Potentials				
		Fibrillation Potentials	Fasciculations	Activation	Recruitment	Configuration		
						Duration	Amplitude	Polyphasia
Right extensor hallucis longus	NL	0	0	NL	↓↓	NL	NL	NL
Right tibialis anterior	NL	0	0	NL	↓↓	+1	+1	NL
Right medial gastrocnemius	NL	0	0	NL	↓↓	+1	+1	NL
Right vastus lateralis	NL	0	0	NL	↓↓	NL	NL	NL
Right gluteus medius	NL	0	0	NL	↓	NL	NL	NL
Right first dorsal interosseous	NL	0	0	NL	↓↓	NL	NL	NL
Right indicis proprius	NL	0	0	NL	↓↓	NL	NL	NL
Right pronator teres	NL	0	0	NL	↓↓	NL	NL	NL
Right biceps brachii	NL	0	0	NL	↓↓	NL	NL	NL
Right medial deltoid	NL	0	0	NL	↓↓	NL	NL	NL
Left tibialis anterior	NL	0	0	NL	↓↓	+1	+1	NL
Left biceps brachii	NL	0	0	NL	↓↓	NL	NL	NL

↓ = slightly reduced; ↓↓ = moderately reduced; NL = normal.

in this clinical setting strongly suggests a diagnosis of Guillain–Barré syndrome.

On needle EMG, there is no evidence of denervation in any muscle, and most muscles show moderately decreased recruitment. In general, MUAP morphology is normal. However, the tibialis anterior and medial gastrocnemius appear to have slightly large, slightly long-duration MUAPs.

At this point we are ready to form our impression.

IMPRESSION: *The electrophysiologic findings are consistent with an acute, demyelinating, sensorimotor polyneuropathy.*

We now have all the information needed to answer the seven key questions about the polyneuropathy in this case:

Key Neuropathy Questions	Answers
Temporal course	Acute
Fiber types involved	Motor and sensory
Pattern	Non-length-dependent, symmetric; bilateral cranial nerve 7
Pathology	Demyelination, with sural sparing
Family history	No
Associated medical illness	Gastrointestinal infection 10 days earlier
Toxic/Occupational exposure	No

With this information, the case can be further analyzed and other key questions answered. This patient demonstrates many of the classic clinical and electrophysiologic findings of Guillain–Barré syndrome, specifically the AIDP variant, which is the most common. AIDP usually presents as a postinfectious disorder, with rapidly progressive weakness and loss of reflexes. Sensory paresthesias are common, but sensory loss is relatively less common on examination.

What is the Significance of Absent F Responses?

On nerve conduction studies, absent or impersistent F responses usually are the earliest finding in AIDP, signifying proximal demyelination. AIDP typically starts as a polyradiculopathy, with demyelination occurring at the root level. Absent or impersistent F responses may be the only abnormality noted during the first few days of the illness. Other evidence of demyelination (i.e., prolonged distal latencies, slowed conduction velocities, conduction block) may take several weeks to develop.

What is the Significance of "Sural Sparing"?

Like the results of the motor conduction studies, all sensory potentials usually are normal during the first few days of the illness. Near the end of the first week or so, however, the unusual pattern of sural sparing may occur in some patients. In this pattern, the sural response is normal, yet the upper extremity median and ulnar sensory responses are abnormal. This pattern occurs because of the preferential involvement of the smaller myelinated fibers early in AIDP. The sural fibers, recorded in the lower calf, are actually larger and more myelinated than the median and ulnar sensory fibers recorded over the digits. The median and ulnar nerves are recorded very distally, where the nerves have tapered in diameter and thus are ensheathed with less myelin.

What is the Significance of Large Motor Unit Action Potentials if the Neuropathy is Acute?

The EMG is quite distinctive in early AIDP. The needle examination usually is completely normal, with the exception of decreased recruitment of MUAPs, which results from proximal conduction block of motor fibers. In pure demyelination, there is no denervation or reinnervation. The only abnormality is decreased recruitment in weak muscles. Of course, in most cases of AIDP, some secondary axonal loss will eventually develop, leading to some denervation and reinnervation later on EMG.

In some cases of AIDP, however, slightly large MUAPs may be seen early on, as noted in the tibialis anterior and medial gastrocnemius in this patient. Although one might first consider the possibility that reinnervation is present from some preexisting condition, such a finding is sometimes seen in early AIDP. The mechanism is similar to that of sural sparing. In every muscle, there is a normal range of MUAP size. When a muscle first contracts, the smaller, type I MUAPs have the lowest threshold and are the first to fire. As more force is generated, these MUAPs fire faster as more MUAPs are brought in. With increasing force, larger MUAPs begin to fire; at maximum contraction, the largest MUAPs fire. These large, type II MUAPs are innervated by the largest axons and hence have the greatest amount of myelin. Usually, these largest MUAPs are not seen individually during the EMG examination. By the time these MUAPs are recruited, a full interference pattern is already present, obscuring the identification of the individual MUAPs. In some cases of AIDP, however, the smaller MUAPs, innervated by the smaller myelinated fibers, are blocked earlier, leaving only the larger, unblocked MUAPs, which are more readily seen. Thus, in such cases the larger, normal MUAPs have been "uncovered" and their presence does not necessarily imply that reinnervation is present.

Case Follow-up

The patient underwent a lumbar puncture that showed an elevated CSF protein of 110 mg/dl but without a pleocytosis. She was treated with 5 days of IVIG at a dose of 400 mg/kg per dose. By the third treatment, she showed improvement in her strength. Upon completion of the full course of IVIG, she was discharged to a rehabilitation facility. She subsequently made a complete recovery over the next 6 weeks.

Case 26–5

History and Physical Examination

A 52-year-old man was referred for progressive numbness and weakness of 6 months' duration. The patient first noted the insidious onset of pins-and-needles paresthesias in his toes bilaterally 6 months ago, followed by slow progression up his feet and calves. Recently, a pins-and-needles sensation developed in the fingertips. More recently, difficulty with dexterity developed, along with a tendency to trip with walking.

Examination was notable for a stocking-glove loss of vibration and pinprick sense. Reflexes were diffusely hypoactive and absent at the ankles. Mild distal weakness and atrophy were present on motor examination. A Romberg sign was present. Gait was moderately ataxic.

Summary

Both the history and physical examination in this case strongly suggest a typical distal stocking-glove polyneuropathy. In many ways, the clinical information is not unlike that seen in Case 26–1, a stocking-glove, axonal polyneuropathy. Like most polyneuropathies, this one is slowly progressive; symptoms began distally in the toes and slowly advanced proximally. Physical examination reveals evidence of motor and sensory involvement, including both large (vibration) and small (pinprick) sensory fibers. The only unusual clinical aspect of the case is the presence of diffusely hypoactive reflexes. In most stocking-glove polyneuropathies, the upper extremity reflexes are preserved.

On nerve conduction studies, an unusual pattern is found. In the lower extremities, the tibial motor conduction studies show a marked drop in amplitude stimulating at the popliteal fossa, much more of a drop than would normally be expected. In addition, the tibial distal latencies are markedly prolonged, more than 200% of the upper limit of normal, with markedly slowed conduction velocities and absent late responses. Similar findings are present in the peroneal motor conduction study. Both sural sensory responses are absent.

In the upper extremities, the median motor studies show normal amplitudes distally. With proximal stimulation on the right, however, there is a marked drop of amplitude, from 6.4 to 1.2 mV. The distal latencies are markedly prolonged, and the conduction velocities are markedly slow. Both median F responses are absent. Thus, the results of the median motor conduction studies are clearly asymmetric; there is evidence of conduction block on the right but not on the left. The ulnar motor conduction study also shows a marked drop in amplitude between the wrist and below-elbow sites, with a markedly prolonged latency and very slow conduction velocity. Again, the F responses are absent. Both the median and ulnar sensory potentials are present, but they are low in amplitude with prolonged peak latencies and markedly slowed conduction velocities.

CASE 26–5. Nerve Conduction Studies

Nerve Stimulated	Stimulation Site	Recording Site	Amplitude Motor = mV; Sensory = µV			Latency (ms)			Conduction Velocity (m/s)			F Wave latency (ms)		
			RT	LT	NL	RT	LT	NL	RT	LT	NL	RT	LT	NL
Median (m)	Wrist	APB	6.4	7.2	≥4	8.4	6.5	≤4.4				NR	NR	≤31
	Antecubital fossa	APB	1.2	5.8		15.9	13.4		24	26	≥49			
Ulnar (m)	Wrist	ADM	4.6		≥6	6.7		≤3.3				NR		≤32
	Below elbow	ADM	2.2			14.9			22		≥49			
	Above elbow	ADM	2.2			20.1			19		≥49			
Median (s)	Wrist	Index finger	3	5	≥20	4.5	4.1	≤3.5	32	37	≥50			
Ulnar (s)	Wrist	Little finger	5		≥17	3.7		≤3.1	34		≥50			
Tibial (m)	Ankle	AHB	4.2	3.2	≥4	12.5	10.2	≤5.8				NR	NR	≤56
	Popliteal fossa	AHB	0.5	0.2		24.4	23.3		21	19	≥41			
Peroneal (m)	Ankle	EDB	3.1		≥2	9.5		≤6.5				NR		≤56
	Below fibula	EDB	1.0			20.6			18		≥44			
	Lateral popliteal fossa	EDB	0.5			25.9			19		≥44			
Sural (s)	Calf	Posterior ankle	NR	NR	≥6			≤4.4			≥40			

m = motor study; s = sensory study; RT = right; LT = left; NL = normal; NR = no response; APB = abductor pollicis brevis; ADM = abductor digiti minimi; AHB = abductor hallucis brevis; EDB = extensor digitorum brevis.

Note: All sensory latencies are peak latencies. All sensory conduction velocities are calculated using onset latencies. The reported F wave latency represents the minimum F wave latency.

CASE 26–5. Electromyography

Muscle	Insertional Activity	Spontaneous Activity		Voluntary Motor Unit Action Potentials				
		Fibrillation Potentials	Fasciculations	Activation	Recruitment	Configuration		
						Duration	Amplitude	Polyphasia
Right extensor hallucis longus	↑	+2	0	NL	↓↓	+2	+2	+1
Right tibialis anterior	↑	+1	0	NL	↓↓	+1	+1	+1
Right medial gastrocnemius	↑	+1	0	NL	↓↓	+1	+1	+1
Right vastus lateralis	NL	0	0	NL	↓↓	+1	+1	+1
Right gluteus medius	NL	0	0	NL	↓	NL	NL	NL
Right first dorsal interosseous	↑	+1	0	NL	↓	+1	+2	+1
Right extensor indicis proprius	↑	0	0	NL	↓	NL/+1	+1	NL/+1
Right pronator teres	NL	0	0	NL	↓	NL/+1	NL/+1	NL
Right biceps brachii	NL	0	0	NL	NL	NL	NL	NL
Right medial deltoid	NL	0	0	NL	NL	NL	NL	NL
Left tibialis anterior	↑	+1	0	NL	↓↓	+2	+2	+1
Left biceps brachii	NL	0	0	NL	NL	NL	NL	NL

↑ = increased; ↓ = slightly reduced; ↓↓ = moderately reduced; NL = normal.

Thus, at the end of the nerve conduction studies, there is clear evidence of a sensorimotor polyneuropathy with demyelinating features. First, the distal motor latencies are markedly prolonged, many of which are more than 130% of the upper limit of normal. Second, conduction velocities are markedly slowed, nearly all less than 75% of the lower limit of normal. Third, all the late responses are absent. Finally, and possibly most importantly, there is clear evidence of conduction block in multiple nerves and asymmetry (comparing the left and right median motor studies). These latter abnormalities are consistent with an acquired demyelinating polyneuropathy.

On needle EMG, there is evidence of distal denervation in the legs and arms, although it is more pronounced in the legs. Likewise, MUAPs are large, long, and polyphasic with decreased recruitment, more prominently in the lower extremities. All of the findings on needle EMG have a clear distal-to-proximal gradient.

At this time, we are ready to formulate our electrophysiologic impression.

IMPRESSION: *The electrophysiologic findings are consistent with a chronic sensorimotor, demyelinating polyneuropathy with secondary axonal features. In addition, the presence of asymmetry and conduction block strongly suggests an acquired condition.*

We now have all the information needed to answer the seven key questions about the polyneuropathy in this case:

Key Neuropathy Questions	Answers
Temporal course	Subacute – chronic progressive
Fiber types involved	Motor and sensory
Pattern	Symmetric, stocking glove
Pathology	Demyelination with conduction block and asymmetry
Family history	No
Associated medical illness	No
Toxic/Occupational exposure	No

With this information, the case can be further analyzed and other key questions answered.

How Does One Distinguish between an Inherited and Acquired Demyelinating Neuropathy?

Although the history and physical examination first suggested nothing more than a typical, distal, axonal polyneuropathy, nerve conduction studies demonstrated

unequivocal evidence of primary demyelination. The presence of primary demyelination narrows the differential diagnosis considerably. There are literally hundreds of causes of axonal polyneuropathies but very few causes of primary demyelination. In addition, the presence of asymmetry and conduction block on proximal stimulation strongly suggests an acquired condition. Asymmetry and conduction block are not seen in the various inherited demyelinating polyneuropathies, such as Charcot–Marie–Tooth polyneuropathy. An exception to this rule may occur in hereditary neuropathy with liability to pressure palsies (HNPP), a condition in which conduction blocks or other evidence of demyelination are typically seen at entrapment sites, and the findings can be asymmetric.

Although conduction blocks are found in multiple nerves in the present case, one might question the right ulnar motor conduction study, in which a conduction block was present between the wrist and below-elbow sites. However, such a drop in amplitude between the two sites may be a normal finding when a Martin–Gruber anastomosis is present. Remember, whenever an ulnar motor conduction study shows an apparent conduction block in the forearm, one must exclude the possibility of a Martin–Gruber anastomosis. Of course, in this particular case, many other nerves also showed conduction block on proximal stimulation, so it was not essential to exclude a Martin–Gruber anastomosis in this case.

Do the Electrophysiologic Findings of Acquired Demyelination Help Guide the Subsequent Evaluation?

The results of the nerve conduction studies and EMG have narrowed the differential diagnosis considerably. Although such findings may be seen in Guillain–Barré syndrome, the clinical history in this case is too long. The likely diagnosis is CIDP. With this knowledge one can proceed to a more appropriate workup, including blood studies for serum protein and immunoprotein electrophoresis and anti-MAG antibodies; a bone survey looking for osteosclerotic myeloma; and possible consideration of an HIV-associated neuropathy. Because the electrophysiologic examination shows an acquired demyelinating polyneuropathy, numerous other tests looking for toxic-, metabolic-, or endocrine-related causes of polyneuropathies would not be indicated, although amiodarone and rare toxins can cause a demyelinating neuropathy.

Case Follow-up

The patient underwent a lumbar puncture which showed a markedly elevated CSF protein of 400 mg/dl without a pleocytosis. Blood studies were negative for HIV, monoclonal proteins, and the anti-MAG antibody. A skeletal survey, however, showed a sclerotic lesion in the vertebral body of L3. Biopsy showed osteosclerotic myeloma. The patient was referred to oncology and was subsequently treated with chemotherapy and radiation.

Case 26–6

History and Physical Examination

A 35-year-old man was referred for a 2-year history of slowly progressive foot drops. The patient reported having been extremely healthy and active until 2 years ago, when he noted progressive tripping during walking. Both legs were affected. There were no sensory complaints and no history of pain.

Examination revealed wasting of the distal leg and foot muscles, with a prominent foot drop bilaterally. Pes cavus was present. All reflexes were absent. There was a subtle stocking loss of sensation to vibration and light touch. Nerves were palpable and enlarged.

Summary

This case is one of progressive, bilateral foot drops. Although the history might suggest a pure motor syndrome, subtle evidence of sensory loss is found on examination. There are several other unusual findings as well.

First is the presence of pes cavus. Pes cavus is an orthopedic deformity of the foot, recognized as a foreshortened foot with a high arch and hammer toes. Pes cavus develops during childhood from the combination of intrinsic foot muscle weakness and relative preservation of the long flexors and extensor muscles in the calves. Because most polyneuropathies preferentially affect distal muscles, polyneuropathies that are present during childhood development commonly result in this deformity. Accordingly, pes cavus in a patient with polyneuropathy usually means that the polyneuropathy has been present since childhood and likely is inherited. One might ask why the patient reports only a 2-year history if pes cavus suggests that the polyneuropathy is of long standing. This situation is not uncommon in inherited polyneuropathies. Because these polyneuropathies often are very mild and progress slowly, patients may not notice any symptoms or seek medical attention until middle age or later. Thus, in many cases, a patient with an inherited polyneuropathy that is, in fact, of longstanding duration reports a history of only several months or years of dysfunction. Of course, some inherited polyneuropathies are more debilitating, and patients present with symptoms in infancy or early childhood. Also note that pes cavus does not always signify a polyneuropathy, but can also be seen in longstanding conditions such as familial spastic paraparesis, slow-growing spinal cord tumors, and local orthopedic disorders.

The second unusual finding is the presence of areflexia on examination. In the typical axonal, stocking-glove polyneuropathy, usually only the ankle reflexes are absent. Global areflexia suggests a demyelinating polyneuropathy.

Third is the unusual finding of palpable and enlarged nerves on physical examination. Nerve hypertrophy may occur if the nerve is infiltrated or infected (as in leprosy), but it is most commonly seen as a sequela of chronic demyelination. Enlarged nerves are characteristic of inherited demyelinating CMT polyneuropathies.

CASE 26–6. Nerve Conduction Studies

Nerve Stimulated	Stimulation Site	Recording Site	Amplitude Motor = mV; Sensory = µV			Latency (ms)			Conduction Velocity (m/s)			F Wave latency (ms)		
			RT	LT	NL	RT	LT	NL	RT	LT	NL	RT	LT	NL
Median (m)	Wrist	APB	6.5	7.2	≥4	8.9	9.2	≤4.4				47	44	≤31
	Antecubital fossa	APB	6.2	7.0		17.5	18.2		21	20	≥49			
Ulnar (m)	Wrist	ADM	7.2		≥6	7.2		≤3.3				44		≤32
	Below elbow	ADM	7.0			16.2			18		≥49			
	Above elbow	ADM	6.9			21.2			20		≥49			
Median (s)	Wrist	Index finger	2	3	≥20	5.2	5.4	≤3.5	22	21	≥50			
Ulnar (s)	Wrist	Little finger	NR		≥17			≤3.1			≥50			
Tibial (m)	Ankle	AHB	2.0	1.5	≥4	12.2	13.3	≤5.8				95		≤56
	Popliteal fossa	AHB	1.6	1.1		27.8	29.9		16	15	≥41			
Peroneal (m)	Ankle	EDB	0.8		≥2	10.5		≤6.5				NR		≤56
	Below fibula	EDB	0.7			22.3			17		≥44			
	Lateral popliteal fossa	EDB	0.5			28.9			15		≥44			
Sural (s)	Calf	Posterior ankle	NR	NR	≥6			≤4.4			≥40			

m = motor study; s = sensory study; RT = right; LT = left; NL = normal; NR = no response; APB = abductor pollicis brevis; ADM = abductor digiti minimi; AHB = abductor hallucis brevis; EDB = extensor digitorum brevis.

Note: All sensory latencies are peak latencies. All sensory conduction velocities are calculated using onset latencies. The reported F wave latency represents the minimum F wave latency.

CASE 26–6. Electromyography

Muscle	Insertional Activity	Spontaneous Activity		Voluntary Motor Unit Action Potentials				
		Fibrillation Potentials	Fasciculations	Activation	Recruitment	Configuration		
						Duration	Amplitude	Polyphasia
Right extensor hallucis longus	NL	+1	0	NL	↓↓	+2	+2	+1
Right tibialis anterior	NL	0	0	NL	↓↓	+2	+2	NL
Right medial gastrocnemius	NL	0	0	NL	↓↓	+2	+1	+1
Right vastus lateralis	NL	0	0	NL	↓	+1	+1	NL
Right gluteus medius	NL	0	0	NL	NL	NL/+1	NL	NL
Right first dorsal interosseous	NL	0	0	NL	↓↓	+1	+1	NL
Right extensor indicis proprius	NL	0	0	NL	↓	NL/+1	NL/+1	NL
Right pronator teres	NL	0	0	NL	NL	NL	NL	NL
Right biceps brachii	NL	0	0	NL	NL	NL	NL	NL
Right medial deltoid	NL	0	0	NL	NL	NL	NL	NL
Left tibialis anterior	NL	0	0	NL	↓↓	+2	+1	+1
Left biceps brachii	NL	0	0	NL	NL	NL	NL	NL

↓ = slightly reduced; ↓↓ = moderately reduced; NL = normal.

The nerve conduction studies demonstrate many abnormalities. In the lower extremities, the motor responses have low amplitudes, with markedly prolonged latencies and slowed conduction velocities. The right tibial F response is markedly prolonged. Both sural potentials are absent. Notably, side-to-side comparisons show no significant asymmetry. In addition, there is no abnormal drop in amplitude on proximal stimulation to suggest conduction block. The median and ulnar motor conduction studies show normal amplitudes, but with markedly prolonged distal latencies and markedly slowed conduction velocities. In addition, the late responses are extremely prolonged. The median sensory potentials are quite low in amplitude, with slowed latencies and conduction velocities. The ulnar sensory potential is absent.

On needle EMG, denervation is absent except very distally in the extensor hallucis longus muscle. MUAPs are reinnervated, however, with decreased recruitment that is more prominent distally and worse in the legs than in the arms.

At this point, we are ready to form our electrophysiologic impression.

IMPRESSION: *The electrophysiologic findings are consistent with a sensorimotor demyelinating polyneuropathy with secondary axonal loss. The lack of asymmetry or conduction block suggests an inherited disorder.*

We now have all the information needed to answer the seven key questions about the polyneuropathy in this case:

Key Neuropathy Questions	Answers
Temporal course	Chronic (in addition, the pes cavus suggests a problem dating back to childhood)
Fiber types involved	Motor ≫ sensory
Pattern	Distal, symmetric
Pathology	Demyelination without asymmetry or conduction block
Family history	Need to check
Associated medical illness	No
Toxic/Occupational exposure	No

With this information, the case can be further analyzed and other key questions answered. The clinical examination showing pes cavus and palpable nerves suggests an inherited demyelinating polyneuropathy, most likely some form of Charcot–Marie–Tooth. The nerve conduction studies provide unequivocal evidence of primary demyelination: markedly prolonged latencies, markedly slowed conduction velocities, and markedly prolonged or absent late responses.

How Does One Distinguish between an Inherited and Acquired Demyelinating Neuropathy?

In inherited disorders, all myelin is equally affected. Hence, there is uniform slowing of conduction without asymmetry and without the presence of conduction block or temporal dispersion. Although several of the Charcot–Marie–Tooth polyneuropathy types are primarily demyelinating, there are always secondary axonal changes, demonstrated by the low motor and sensory amplitudes on nerve conduction studies and by evidence of denervation and reinnervation on needle EMG.

Charcot–Marie–Tooth polyneuropathy typically presents very slowly, often with more prominent motor than sensory symptoms and signs. With careful testing, however, sensory abnormalities are always found on examination, and they are also present on nerve conduction studies.

What is the Appropriate Laboratory Evaluation in this Patient?

For this patient, it would be appropriate to obtain blood DNA testing to look for the duplication error on chromosome 17 that is associated with the most common type of demyelinating Charcot–Marie–Tooth polyneuropathy, CMT1A. Note that many of the antibody and other studies routinely obtained in cases of CIDP need not be performed in this case, because the combination of clinical and electrophysiologic data point clearly to an inherited, demyelinating polyneuropathy.

Case Follow-up

The patient underwent DNA testing for CMT1A, which showed a duplication error in chromosome 17p11.2. He was fitted for bilateral ankle foot orthoses and referred to physical therapy. Genetic counseling was advised.

Suggested Readings

Albers, J.W., Donofrio, P.D., McGonagle, T.K., 1985. Sequential electrodiagnostic abnormalities in acute inflammatory demyelinating polyradiculoneuropathy. Muscle Nerve 8, 528.

Albers, J.W., Kelly, J.J., 1989. Acquired inflammatory demyelinating polyneuropathies: clinical and electrodiagnostic features. Muscle Nerve 12, 435.

Barohn, R.J., Kissel, J.T., Warmolts, J.R., et al., 1989. Chronic inflammatory demyelinating polyradiculoneuropathy: clinical characteristics, course, and recommendations for diagnostic criteria. Arch Neurol 46, 878.

Bird, T.D., 2012. Charcot–Marie–Tooth Hereditary Neuropathy Overview. http://www.ncbi.nlm.nih.gov/books/NBK1358/

Bromberg, M.B., 1991.Comparison of electrodiagnostic criteria for primary demyelination in chronic polyneuropathy. Muscle Nerve 14, 968.

Chalk, CH., Windebank, A.J., Kimmel, D.W., et al., 1992. The distinctive clinical features of paraneoplastic sensory neuronopathy. Can J Neurol Sci 19, 346.

Donofrio, P.D., Albers, J.W., 1990. AAEM minimonograph no. 34: polyneuropathy: classification by nerve

conduction studies and electromyography. Muscle Nerve 13, 889.
England, J.D., Gronseth, G.S., Franklin, G., et al., 2009. Evaluation of distal symmetric polyneuropathy: the role of laboratory and genetic testing (an evidence-based review). Muscle Nerve 39 (1), 116–125.
Esper, G.J., Nardin, R.A., Benatar, M., et al., 2005. Sural and radial sensory responses in healthy adults: diagnostic implications for polyneuropathy. Muscle Nerve 31 (5), 628–632.
Gabreeels-Festen, A., 2002. Dejerine-Sottas syndrome grown to maturity: overview of genetic and morphological heterogeneity and follow-up of 25 patients. J Anat 200, 341–356.
Griffin, J.W., Li, C.Y., Ho, T.W., et al., 1996. Pathology of the motor-sensory axonal Guillain–Barré syndrome. Ann Neurol 39, 17–28.
Horwich, M.S., Cho, L., Porro, R.S., et al., 1977. Subacute sensory neuronopathy: a remote effect of carcinoma. Ann Neurol 2, 7.
Lewis, R.A., Sumner, A.J., 1980. Electrodiagnostic distinctions between chronic acquired and familial demyelinative neuropathies. Neurology 30, 371.
Malinow, K., Yannakakis, G.D., Glusman, S.M., et al., 1986. Subacute sensory neuronopathy secondary to dorsal root ganglionitis in primary Sjögrens syndrome. Ann Neurol 20, 535.
McKann, G.M., Cornblath, D.R., Griffin, J.W., et al., 1993. Acute motor axonal neuropathy: a frequent cause of acute flaccid paralysis in China. Ann Neurol 33, 333–342.
Pareyson, D., Scaioli, V., Laurà, M., 2006. Clinical and electrophysiological aspects of Charcot–Marie–Tooth disease. NeuroMol Med 8 (1–2), 3–22.
Plante-Bordeneuve, V., Said, G., 2002. Dejerine-Sottas disease and hereditary demyelinating polyneuropathy of infancy. Muscle Nerve 26 (5), 608–621.
Raynor, E.M., Ross, M.H., Shefner, J.M., et al., 1995. Differentiation between axonal and demyelinating neuropathies: identical segments recorded from proximal and distal muscles. Muscle Nerve 18, 402.
Reilly, M.M., Shy, M.E., 2009. Diagnosis and new treatments in genetic neuropathies. J Neurol Neurosurg Psychiatry 80 (12), 1304–1314.
Rutkove, S.B., Kothari, M.J., Raynor, E.M., et al., 1997. Sural/radial amplitude ratio in the diagnosis of mild axonal polyneuropathy. Muscle Nerve 20 (10), 1236–1241.
Saporta, A.S., Sottile, S.L., Miller, L.J., et al., 2011. Charcot–Marie–Tooth disease subtypes and genetic testing strategies. Ann Neurol 69 (1), 22–33.
Schaumburg, H.H., Spencer, P.S., Thomas, P.K., 1983. Disorders of peripheral nerves. FA Davis, Philadelphia.
Sterman, A.B., Schaumburg, M.D., Asbury, A.K., 1980. The acute sensory neuronopathy syndrome: a distinct clinical entity. Ann Neurol 7, 354.