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A Structured Approach to the Diagnosis of Peripheral Nervous System Disorders

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ABSTRACT

PURPOSE OF REVIEW: **Neuroanatomic localization and pattern recognition can be used to diagnose both focal lesions and generalized disorders of the peripheral nervous system. This article describes the nature and pattern of sensory and motor deficits associated with lesions of specific spinal nerve roots, plexus, or peripheral nerves. It also describes the patterns of sensory and motor deficits that suggest multifocal or generalized disorders of the motor neurons, sensory neurons, and peripheral nerves.**

RECENT FINDINGS: **The pattern of sensory and motor deficits may be used to distinguish lesions of the peripheral nervous system from those of the central nervous system. The spinal roots, nerve plexus, and peripheral nerves supply specific muscles and receive sensory input from distinctive cutaneous regions. Focal lesions of these structures therefore produce characteristic patterns of sensory and motor deficits. Multifocal or generalized disorders of the peripheral nervous system may be distinguished by categorizing their sensory and motor involvement, proximal and distal predominance, and degree of symmetry. Serum tests, CSF analysis, electrodiagnostic studies, MRI, ultrasound, nerve biopsy, and skin biopsy have unique roles in the diagnosis of suspected neuromuscular disorders.**

SUMMARY: **A structured approach to the diagnosis of nerve and motor neuron disorders can lead to hypothesis-driven diagnostic testing. Ancillary tests should be reserved for cases in which confirming or refuting a diagnosis will change patient management.**

INTRODUCTION

The peripheral nervous system consists of the motor, sensory, and autonomic neural elements that have extensions outside of the brain and spinal cord. Motor neurons are located in the anterior gray matter of the spinal cord and are often referred to as anterior horn cells. Their axons traverse the nerve roots into the peripheral nerves and communicate with the muscle at the neuromuscular junction. Sensory neurons

are located in the dorsal root ganglia, which are located posteriorly just outside the intervertebral foramina.

Dorsal and ventral roots travel through the intervertebral foramina and fuse to form the spinal nerves. The anterior primary rami form the brachial and lumbosacral plexus, which terminate in the peripheral nerves. Each of these neuroanatomic structures is responsible for providing motor input to specific muscles or receiving sensory input from specific areas in the extremities or the afferent arcs of the deep tendon reflexes. When a patient has right-sided focal weakness, the responsible lesion could be anywhere along the motor pathway from the left motor cortex down through the decussation at the medullary pyramids, in the corticospinal tracts, or in the peripheral structures summarized above. For example, isolated weakness of the right abductor pollicis brevis may be related to a central nervous system (CNS) lesion or a peripheral lesion involving the C8 or T1 anterior horn cells, corresponding ventral roots, lower trunk of the brachial plexus, medial cord of the brachial plexus, median nerve, neuromuscular junction, or the muscle itself. This list can be whittled down dramatically by adding a second clinical abnormality, such as numbness over the palmar aspect of the right index finger. The combination of those findings would make a right median mononeuropathy significantly more likely than the other possible localizations. This is the classic strategy of neuroanatomic localization; the clinician uses the physical examination and a knowledge of functional neuroanatomy to identify where the involved pathways overlap.

Disorders of the peripheral nervous system may be focal, multifocal, or generalized, but the classic strategies of neuroanatomic localization work best with focal lesions. In generalized disorders of the peripheral nervous system, the innervations of individual muscles become less important than recognizing patterns, such as whether the weakness and numbness are distal or proximal, whether symptoms are symmetric between limbs, or whether cranial or autonomic nerves are involved.

A rational approach to a patient with sensory or motor symptoms answers the following questions about the clinical presentation:

- **Does it localize to the CNS or to the peripheral nervous system?**
- **Can it localize to a single named peripheral nervous system structure?**
- **If it is multifocal or generalized:**
  - **Does it involve sensory loss or weakness, or both?**
  - **Is it primarily proximal or distal, or both?**
  - **Is it symmetric or asymmetric?**
- **Is it acute or subacute in onset?**

Often, the answers to these questions will narrow the differential diagnosis enough so that the judicious use of ancillary testing can verify a specific diagnosis.

CENTRAL OR PERIPHERAL NERVOUS SYSTEM

One of the first tasks of the clinician is to use the history and physical examination to distinguish disorders of the peripheral nervous system from

disorders of the CNS. In addition to appreciation of upper motor neuron and lower motor neuron signs on examination, a number of localization clues can be useful in distinguishing central versus peripheral lesions (TABLE 1-1).

- **Lesions in the brain and brainstem rarely cause pain. A notable exception is central poststroke pain. This is a rare late effect of ischemic stroke, usually in the thalamus, and is characterized by contralateral hyperalgesia and allodynia. The presence of pain with neuropathic features (eg, burning, tingling, electric shock–like sensation) in the affected limb(s) should prompt the examiner to consider a peripheral etiology.**
- **Hyporeflexia in a symptomatic limb suggests a peripheral lesion, whereas brisk reflexes in a symptomatic limb suggest a central lesion.**
- **If all the signs and symptoms are in a single limb, both central and peripheral localizations are possible. Hemibody symptoms suggest a central localization; no single lesion in the peripheral nervous system can cause isolated symptoms affecting an arm and leg on the same side of the body.**
- **If a patient has deficits in both strength and pain/temperature sensation in the same limb and no other abnormalities, the lesion is either in the brain or the peripheral nervous system, not in the spinal cord.**
- **Patients with ascending sensory loss in both lower extremities may have either a spinal cord lesion or a polyneuropathy. Peripheral polyneuropathy causes length-dependent symptoms and signs, so by the time the sensory loss spreads up above the knee, the distal upper extremities are usually involved as well. Sensory loss that spreads up from the feet to the groin or trunk without any upper extremity involvement is almost always related to spinal cord pathology.**

TABLE 1-1

Distinguishing Central From Peripheral Nervous System Lesions

Features Consistent With Any Central Nervous System Localization

- Brisk reflexes in an affected limb
- Increased tone in an affected limb
- Sensory or motor symptoms limited to two limbs on the same side of the body
- Weakness of extensors in the upper extremity
- Weakness of flexors in the lower extremity

Features Consistent With a Spinal Cord Localization

- Sensory loss in both legs with a sensory level on the trunk
- Decreased pinprick sensation on one side, weakness and diminished proprioception on the other side

Features Consistent With a Peripheral Localization

- Axial or limb pain
- Diminished reflexes in an affected limb
- Weakness and diminished pain sensation in the same limb are not due to a spinal cord lesion and are due to either a peripheral or brain/brainstem lesion
- Sensory loss that involves the hands and feet but not the trunk

- Patients with upper extremity weakness due to a CNS lesion often have preferential involvement of the extensors, such as the triceps and wrist and finger extensor muscles. Although rare, a proximal radial mononeuropathy could also affect these muscles. To rule that out, it is useful to test the strength of the brachioradialis, which will be reduced in a proximal radial mononeuropathy but relatively spared (along with the other upper extremity flexors) in a CNS lesion.
- Patients with leg weakness due to a CNS lesion often have preferential weakness of the flexors, such as the iliopsoas, hamstrings, and tibialis anterior. No single peripheral lesion could affect all of these muscles in isolation.

KEY POINTS

- The presence of neuropathic pain in an affected limb is more suggestive of a peripheral nervous system lesion than a central nervous system lesion.
- Features that suggest a central nervous system lesion rather than a peripheral nervous system lesion include a sensory level on the trunk, hyperreflexia, hemibody symptoms, weakness of extensors in an arm, and weakness of flexors in a leg.
- Neuralgic amyotrophy may appear to localize to multiple nerves in the same limb rather than a specific part of the brachial plexus.

FOCAL SYMPTOM PATTERN

The first question to ask is whether the sensory and motor signs and symptoms can localize to a single named nervous system structure. The spinal nerve roots, nerve plexus, and most peripheral nerves contain both afferent somatic sensory nerve fibers and efferent motor fibers. Lesions of these structures may cause distinctive patterns of pain, sensory loss, and weakness.

Radiculopathy

A careful neurologic examination coupled with an understanding of the neuroanatomic functions of the spinal nerve roots may yield a very specific localization. TABLE 1-2 and TABLE 1-3 summarize the sensory and motor findings associated with lesions at each level.[1] Sensory symptoms often precede motor symptoms in cervical and lumbar radiculopathy. This should be considered in a patient with axial and radicular pain who presents with a dermatomal pattern of sensory loss.

The most common mechanisms of spinal nerve root compression are intervertebral disk herniation and spondylosis.[2] Less common causes include synovial cysts, osteomyelitis and diskitis, vertebral fracture, bony malignant disease, epidural hematoma, infectious radiculitis, or infiltrative disease of the meninges. The presence of systemic symptoms may raise suspicion for some of these less common mechanisms.

Plexopathy

The brachial and lumbosacral plexus are anatomically protected compared to the spinal nerve roots but may be susceptible to trauma, structural abnormalities, neoplastic infiltration, or inflammatory processes (TABLE 1-4 and TABLE 1-5).

Neuralgic amyotrophy (also known as idiopathic brachial plexitis or Parsonage-Turner syndrome) is an uncommon disorder characterized by subacute onset of pain, weakness, and sensory loss. Although it is usually referred to as a plexopathy, neuralgic amyotrophy may present with multiple disparate mononeuropathies in the same limb rather than dysfunction of a focal region of the brachial plexus.[3]

Neurogenic thoracic outlet syndrome is a controversial and likely overdiagnosed condition in which the lower trunk or C8 and T1 nerve roots are injured or compressed by certain anatomic defects, such as an extra rib. It presents with aching pain along the medial aspect of the upper extremity and weakness of the intrinsic hand muscles.[4]

In patients with breast or lung cancer, the mechanisms of brachial plexopathy include trauma during surgery, metastatic spread of tumor (which most

TABLE 1-2 **Sensory, Motor, and Reflex Distributions of the Upper Extremity Roots**[a]

Structure	Principal Muscles Involved	Sensory Distribution	Diminished Reflexes
C5 root	Rhomboids[b] Supraspinatus[b] Infraspinatus[b] Deltoid[b] Brachioradialis[b] Biceps	Lateral upper arm	Biceps, brachioradialis
C6 root	Supraspinatus Infraspinatus Deltoid Brachioradialis[b] Triceps Flexor carpi radialis[b] Extensor carpi radialis[b] Pronator teres[b]	Lateral forearm and hand, first two digits	Biceps, brachioradialis
C7 root	Triceps[b] Flexor carpi radialis[b] Extensor carpi radialis[b] Pronator teres[b] Extensor digitorum[b] Flexor digitorum[b] Flexor pollicis longus[b]	Centermost portion of the distal dorsal forearm and third digit	Triceps
C8 root	Triceps Extensor indicis[b] Flexor pollicis longus[b] Abductor pollicis brevis[b] Interossei[b]	Fourth and fifth digits and medial hand	None
T1 root	Abductor pollicis brevis[b] Interossei[b]	Medial forearm	None

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[b] Muscle may be more prominently involved.

commonly affects the lower trunk), and radiation injury. Tumor infiltration is more likely to cause pain than radiation injury.[5]

Mononeuropathy

Most mononeuropathies occur at specific entrapment sites, regions where specific nerves are relatively unprotected or susceptible to stretch or compression due to day-to-day use or repetitive trauma. The most common entrapment sites are the median nerve at the carpal tunnel, the ulnar nerve at the elbow, the radial nerve at the spiral groove, and the fibular (peroneal) nerve at the fibular head (TABLE 1-6 and TABLE 1-7).[6] Most of these cause both sensory and motor manifestations. Other causes of focal nerve injury include acute trauma, ischemia, compression or invasion by tumor, infection, irradiation, or injury due to cold.

Sensory, Motor, and Reflex Distributions of the Lower Extremity Roots[a] TABLE 1-3

Structure	Principal Muscles Involved	Sensory Distribution	Diminished Reflexes
L2 root	Iliopsoas[b] Adductor longus[b]	Anterior thigh	None
L3 root	Iliopsoas[b] Quadriceps[b] Adductor longus[b]	Medial thigh, knee	Patellar
L4 root	Quadriceps[b] Adductor longus[b] Tibialis anterior	Medial lower leg	Patellar
L5 root	Gluteus medius[b] Hamstrings Tibialis anterior[b] Extensor digitorum[b] Peroneus longus[b] Tibialis posterior[b]	Lateral lower leg, dorsal foot	None
S1 root	Gluteus maximus[b] Hamstrings[b] Gastrocnemius[b] Peroneus longus Extensor digitorum Tibialis posterior	Posterior/lateral lower leg, plantar aspect of foot	Ankle

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[b] Muscle may be more prominently involved.

The most common mononeuropathies to cause a pure motor syndrome are those that affect a nerve that does not have a sensory component. Examples include the suprascapular nerve, the anterior interosseous nerve, or the posterior interosseous nerve. Occasionally, entrapment of a mixed nerve, such as the ulnar nerve or fibular (peroneal) nerve, may spare the fascicles involved in sensation. In these cases, the distribution of the weakness is most helpful in localizing the lesion. A pure motor syndrome that follows more of a myotomal pattern, with denervation in the distribution of individual spinal roots, has been reported as a complication of intrathecal chemotherapy or radiation therapy near the spinal roots.[7] In theory, injury or infiltration of the ventral spinal roots can cause a pure motor radiculopathy, but this is rare.

TABLE 1-4 **Sensory, Motor, and Reflex Distributions of the Upper Extremity Plexus**[a]

Structure	Principal Muscles Involved	Sensory Distribution	Diminished Reflexes
Upper trunk	Supraspinatus[b] Infraspinatus[b] Deltoid[b] Brachioradialis[b] Biceps[b] Triceps Pronator teres Extensor carpi radialis Flexor carpi radialis	Lateral upper arm and forearm and first one to two digits	Biceps, brachioradialis
Lower trunk	Triceps Extensor digitorum[b] Extensor indicis[a] Flexor digitorum profundus[b] Flexor pollicis longus[b] Abductor pollicis brevis[b] Interossei[b]	Medial forearm and hand, fourth and fifth digits	None
Middle trunk	Triceps[b] Flexor carpi radialis[b] Extensor carpi radialis[b] Pronator teres[b] Extensor digitorum[b] Flexor digitorum[b] Flexor pollicis longus[b]	Centermost portion of the distal forearm and third digit	Triceps

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Some peripheral nerves have no motor component. A focal lesion involving one of these will result in isolated sensory loss in the distribution of that nerve. Examples in the upper extremity include the superficial radial nerve and the medial and lateral antebrachial cutaneous nerves. Examples in the lower extremity include the lateral femoral cutaneous nerve, the saphenous nerve, and the sural nerve. It is not uncommon for focal mononeuropathies of mixed nerves to preferentially involve the sensory fascicles. A median mononeuropathy caused by carpal tunnel syndrome, for example, commonly presents with wrist pain and sensory loss in the palmar aspect of the first three or four digits. Patients may not develop the characteristic thenar weakness until late in the course of the disease.

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Structure	Principal Muscles Involved	Sensory Distribution	Diminished Reflexes
Lateral cord	Biceps[b] Pronator teres[b] Flexor carpi radialis[b] Flexor digitorum[b] Flexor pollicis longus[b]	Lateral forearm, palmar hand and first three digits	Biceps
Medial cord	Flexor digitorum[b] Flexor pollicis longus[b] Abductor pollicis brevis[b] Interossei[b]	Medial forearm and hand, fourth and fifth digits	None
Posterior cord	Deltoid[b] Teres minor[b] Brachioradialis[b] Triceps[b] Extensor carpi radialis[b] Extensor digitorum[b] Extensor indicis[b]	Dorsal aspect of upper arm, forearm, lateral hand, and the first three digits	Triceps, brachioradialis

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[b] Muscle may be more prominently involved.

MULTIFOCAL OR GENERALIZED SYMPTOM PATTERN

In patients with multifocal or generalized symptoms that appear to localize to the peripheral nervous system, the next questions to ask are whether the symptoms involve sensory loss or weakness, or both; whether they are proximal or distal, or both; and whether they are symmetric or asymmetric (FIGURE 1-1).

MIXED SENSORY AND MOTOR SYMPTOM PATTERN

Most disorders of nerves, spinal roots, and plexus are characterized by both sensory and motor involvement. The differential diagnosis can be narrowed further by recognizing the pattern of signs and symptoms.

Proximal Asymmetric

Proximal asymmetric weakness and sensory loss are usually due to a polyradiculopathy, polyradiculoneuropathy, or radiculoplexopathy. This pattern is particularly suggestive of diabetic lumbosacral radiculoplexus neuropathy, also known as diabetic amyotrophy, which presents with subacute progressive asymmetric pain and weakness, most prominently affecting the proximal lower extremity muscles. Most patients have superimposed weight loss and autonomic dysfunction. The severity of the symptoms does not correlate with the severity of the diabetes, and, in fact, glycemic dysregulation may be mild at the time of diagnosis.[8] For more information on diabetic lumbosacral radiculoplexus neuropathy, refer to the article "Diabetes and Metabolic Disorders and the Peripheral Nervous System" by Christopher H. Gibbons, MD, MMSc, FAAN,[9] in this issue of *Continuum*. Other causes of proximal asymmetric sensorimotor symptoms include meningeal disorders, such as carcinoma, lymphoma, sarcoidosis, or infections, which may infiltrate multiple nerves, roots, and regions of the plexus.

TABLE 1-5 **Sensory, Motor, and Reflex Distributions of the Lower Extremity Plexus**[a]

Structure	Principal Muscles Involved	Sensory Distribution	Diminished Reflexes
Lumbar plexus	Iliopsoas Quadriceps Adductor longus	Anterior thigh, medial and lateral thigh, medial lower leg	Patellar
Lower lumbosacral plexus	Gluteus medius Gluteus maximus Hamstrings Tibialis anterior Extensor digitorum Peroneus longus Tibialis posterior Gastrocnemius	Posterior thigh, lateral lower leg, all of foot	Ankle

[a] Modified with permission from London ZN.[1] © 2019 American Academy of Neurology.

Proximal and Distal Symmetric

Peripheral nervous system disorders that involve proximal muscles are usually related to involvement of nerve roots (polyradiculopathy). Symmetric proximal and distal involvement strongly suggests involvement of both nerve roots and the distal peripheral nerves (polyradiculoneuropathy).

Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) presents with acroparesthesia followed by symmetric ascending weakness and areflexia, usually developing over 1 to 2 weeks. The weakness usually affects proximal and distal limb muscles symmetrically and may involve muscles involved in facial expression, speech, swallowing, neck flexion, breathing, and, occasionally, eye movements. Sensory loss is common but usually mild. Most patients report axial and radicular pain. Patients often develop dysautonomia, characterized by sinus tachycardia or labile blood pressure. Ninety percent of patients reach their nadir by 4 weeks.[10] For more information on AIDP, refer to the article "Guillain-Barré Syndrome" by Kazim A. Sheikh, MBBS,[11] in this issue of *Continuum*.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) causes slowly progressive proximal and distal weakness, areflexia, and sensory loss. Progression continues for more than 8 weeks after symptom onset. Unlike AIDP, CIDP does not usually affect cranial nerves or muscles of respiration. For more information on CIDP, refer to the article "Chronic Inflammatory Demyelinating Polyradiculoneuropathy and Its Variants" by Kelly Gwathmey, MD,[12] in this issue of *Continuum*.

Proximal and Distal Asymmetric

The presence of significant asymmetry in a patient with prominent distal weakness suggests a mononeuritis multiplex, which is defined by damage to at least two named peripheral nerves, most often not at entrapment sites. The most common mechanism is vasculitis, inflammatory destruction of the vasa nervorum, and resultant ischemic nerve injury. The clinical course is usually acute or stuttering, with significant pain and sensory and motor deficits in discrete peripheral nerve distributions.[13] Over time, mononeuritis multiplex may affect so many nerves that the pattern becomes symmetric, a pattern referred to as confluent mononeuritis multiplex.

Even when only one nerve is involved, the conditions that predispose patients to mononeuritis multiplex should be considered if no evidence of trauma is present, the involved nerve is not susceptible to entrapment, or the injury is not at the common entrapment site (**CASE 1-1**).

Mononeuritis multiplex may occur in isolation (nonsystemic vasculitic neuropathy) or may occur as a manifestation of eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis, microscopic polyangiitis, or polyarteritis nodosa. Other systemic inflammatory disorders, such as rheumatoid arthritis, Sjögren syndrome, and systemic lupus erythematosus (SLE) can predispose patients to mononeuritis multiplex.[14] For more information about vasculitic and other autoimmune axonal neuropathies, refer to the article "Peripheral Neuropathies Associated with Vasculitis and Autoimmune Connective Tissue Disease" by Chafic Karam, MD,[15] in this issue of *Continuum*.

Other causes of multiple mononeuropathies include lymphoma, diabetes, hepatitis, or human immunodeficiency virus (HIV). Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) is a rare variant of

KEY POINTS

- **Injuries to nerve roots and mixed nerves, both of which contain both sensory and motor components, may present with pain or sensory symptoms without weakness.**
- **Chronic inflammatory demyelinating polyradiculoneuropathy progresses for more than 8 weeks after symptom onset. Unlike acute inflammatory demyelinating polyradiculoneuropathy, it is generally not associated with dysautonomia, weakness of cranial muscles, or dyspnea.**
- **Mononeuritis multiplex affects named nerves but not necessarily at the common entrapment sites.**

CIDP that causes a chronic sensorimotor mononeuropathy multiplex with involvement of individual nerves asymmetrically, distal more than proximal and upper limbs more than lower limbs.[16] Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal dominant disorder characterized by recurrent painless mononeuropathies following compression or trivial trauma.[17]

Distal Symmetric

Distal symmetric involvement is consistent with a length-dependent polyneuropathy. The differential diagnosis is based on the relative sensory and motor involvement.

DISTAL SYMMETRIC POLYNEUROPATHY. The most common pattern of generalized peripheral nerve dysfunction is aptly referred to as distal symmetric polyneuropathy. This term is preferred over the less specific terms neuropathy, peripheral neuropathy, and polyneuropathy, which are often used interchangeably but fail to exclude focal or multifocal processes.

TABLE 1-6 Sensory, Motor, and Reflex Distributions of the Upper Extremity Nerves[a]

Structure	Principal Muscles Involved	Sensory Distribution	Diminished Reflexes
Dorsal scapular	Rhomboids[b]	None	None
Suprascapular	Supraspinatus[b] Infraspinatus[b]	None	None
Musculocutaneous	Biceps[b]	Lateral forearm	Biceps
Axillary	Deltoid	Lateral shoulder	None
Radial			
Superficial sensory nerve at the wrist	None	Dorsal hand and first three digits	None
Posterior interosseous	Extensor digitorum[b] Extensor indicis[b]	None	None
At the spiral groove	Brachioradialis[b] Extensor carpi radialis[b] Extensor digitorum[b] Extensor indicis[b]	Dorsal hand and first three digits	Brachioradialis
At the axilla	Triceps[b] Brachioradialis[b] Extensor carpi radialis[b] Extensor digitorum[b] Extensor indicis[b]	Dorsal aspect of upper arm, forearm, lateral hand, and the first three digits	Brachioradialis, triceps

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Distal symmetric polyneuropathy is sensory predominant, with little or no motor involvement until later in the course of the illness when patients may have mild distal lower extremity weakness. Patients often experience neuropathic pain, paresthesia, or sensory loss that starts in the toes and feet because of length-dependent axonal injury. As the disease progresses, the sensory symptoms move proximally. Around the time that sensory abnormalities reach the knees, patients may also begin to experience paresthesia, pain, or sensory loss in the fingertips. Sensory symptoms then proceed proximally in the upper extremities. Loss of deep tendon reflexes occurs in a length-dependent pattern. When present, motor involvement also starts distally, with weakness of the toe flexor and extensor muscles. Atrophy of the intrinsic foot muscles, such as the extensor digitorum brevis, may be found before clinically significant weakness.

Patients with distal symmetric polyneuropathy may note mild sudomotor dysfunction on directed questioning (reduced sweating in the feet or increased sweating more proximally). However, more significant autonomic neuropathy,

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Structure	Principal Muscles Involved	Sensory Distribution	Diminished Reflexes
Median			
Anterior interosseous	Flexor pollicis longus[b] Flexor digitorum profundus 1-2[b]	None	None
At the carpal tunnel	Abductor pollicis brevis[b]	Palmar first through third digits	None
At the elbow	Pronator teres[b] Flexor carpi radialis[b] Flexor pollicis longus[b] Flexor digitorum profundus 1-2[b] Abductor pollicis brevis[b]	Palmar hand and first through third digits	None
Ulnar			
At the wrist	Interossei[b] Interossei[b]	Palmar aspect of fourth and fifth digits	None
At the elbow	Flexor digitorum profundus 4-5[b]	Medial hand, fourth and fifth digits	None

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[b] Muscle may be more prominently involved.

including orthostatic hypotension, prominent sexual dysfunction, or gastroparesis, is unusual and suggests specific disorders (eg, diabetes or amyloidosis).

Most distal symmetric polyneuropathies have a chronic time course with slow progression. Most patients with this pattern have diabetes, prediabetes, or idiopathic neuropathy. Although uncommon, vitamin B_{12} deficiency and paraproteinemia (monoclonal gammopathy) should be excluded in all patients.[18] Other common causes of distal symmetric polyneuropathy include toxicity due to specific chemotherapeutic agents and chronic alcohol use.[18]

Distal symmetric polyneuropathy with motor greater than sensory involvement suggests a distinct differential diagnosis. The most common cause of this pattern is Charcot-Marie-Tooth disease (CMT), also known as hereditary motor sensory neuropathy. Other diagnostic clues for CMT include a young age of onset, a positive family history, and high arches and hammer toes related to long-standing atrophy of intrinsic foot muscles. For more information on Charcot-Marie-Tooth disease, refer to the article "Charcot-Marie-Tooth Disease

TABLE 1-7 Sensory, Motor, and Reflex Distributions of the Lower Extremity Nerves[a]

Structure	Principal Muscles Involved	Sensory Distribution	Diminished Reflexes
Femoral			
Above inguinal ligament	Iliopsoas Quadriceps	Medial thigh and lower leg	Patellar
Below inguinal ligament	Quadriceps	Medial thigh and lower leg	Patellar
Obturator	Adductor longus	Medial thigh	None
Sciatic	Hamstrings Tibialis anterior Extensor digitorum Peroneus longus Tibialis posterior Gastrocnemius	Lateral lower leg, all of foot	Ankle
Fibular (peroneal)			
Deep	Tibialis anterior Extensor digitorum	First dorsal webspace	None
Superficial	Peroneus longus	Lateral lower leg, dorsal aspect of foot	None
Common	Tibialis anterior Extensor digitorum Peroneus longus	Lateral lower leg, dorsal aspect of foot	None
Tibial	Tibialis posterior Gastrocnemius	Plantar aspect of foot	Ankle

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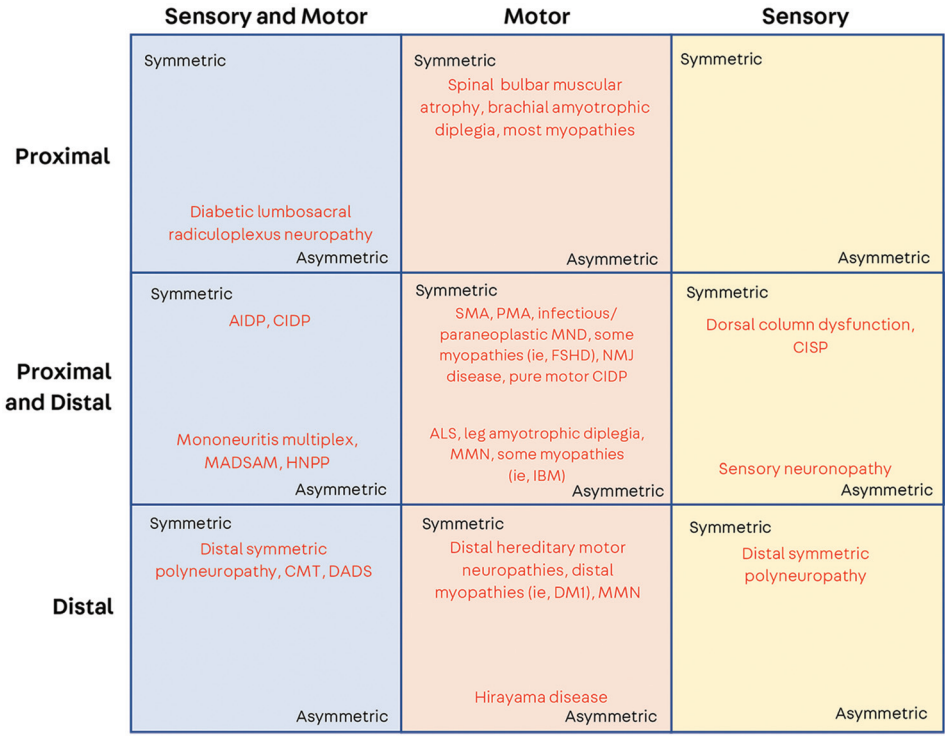

FIGURE 1-1

A pattern recognition approach for multifocal or generalized sensory and motor symptoms. In each of the nine squares, diagnoses at the top tend to be symmetric, whereas diagnoses at the bottom tend to be asymmetric.

AIDP = acute inflammatory demyelinating polyradiculoneuropathy; ALS = amyotrophic lateral sclerosis; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; CISP = chronic immune sensory polyradiculoneuropathy; CMT = Charcot-Marie-Tooth disease; DADS = distal acquired demyelinating symmetric neuropathy; DM1 = myotonic dystrophy type 1; FSHD = facioscapulohumeral dystrophy; HNPP = hereditary neuropathy with liability to pressure palsies; IBM = inclusion body myositis; MADSAM = multifocal acquired demyelinating sensory and motor neuropathy; MMN = multifocal motor neuropathy; MND = motor neuron disease; NMJ = neuromuscular junction; PMA = progressive muscular atrophy; SMA = spinal muscular atrophy.

and Other Hereditary Neuropathies" by Christopher J. Klein, MD, FAAN,[19] in this issue of *Continuum*.

Distal acquired demyelinating symmetric (DADS) neuropathy, a variant of CIDP, is a rare cause of motor greater than sensory distal symmetric polyneuropathy. DADS is a chronic inflammatory neuropathy characterized by symmetric distal weakness and sensory loss, often with tremor.[20] Many patients have an IgM monoclonal gammopathy that binds to myelin-associated glycoprotein (MAG).

PURE MOTOR SYMPTOM PATTERN

Widespread weakness without significant sensory loss or pain localizes best to disorders of the motor neurons, motor nerves, neuromuscular junctions, or the muscles themselves. A summary of distinguishing features of pure motor syndromes can be found in TABLE 1-8.

Proximal and Distal Symmetric

Proximal greater than distal symmetric weakness is usually due to a myopathy or, less commonly, a disorder of neuromuscular junction transmission. Diagnostic

KEY POINTS

- **Mononeuritis multiplex is usually an axonal process, but multifocal acquired demyelinating sensory and motor neuropathy and hereditary neuropathy with liability to pressure palsies are multifocal demyelinating neuropathies.**
- **Distal symmetric polyneuropathy usually begins to involve the distal upper extremities around the time that the lower extremity sensory symptoms progress to the level of the knees.**
- **Clinical features that should raise suspicion for a hereditary cause of neuropathy include young age of onset, family history, and high arches and hammer toes.**

clues supporting a myopathy include myalgia, elevated serum creatine kinase, and supportive EMG findings. Myasthenia gravis often causes ptosis, diplopia, and dysarthria and dysphagia, although isolated limb weakness is rare. Fatigability is a diagnostic clue, and electrodiagnostic studies and the presence of anti–acetylcholine receptor antibodies confirm the diagnosis. Lambert-Eaton myasthenic syndrome (LEMS) also causes proximal greater than distal weakness with fatigue; other symptoms and signs of LEMS include reduced or absent reflexes that augment following brief exercise and autonomic dysfunction (particularly dry mouth). Cranial nerve involvement is uncommon. Although transient improvement in strength is seen following brief exercise, most patients subjectively report severe fatigue. Identification of antibodies reactive to voltage-gated calcium channels and electrodiagnostic studies confirm the diagnosis. Botulism is a syndrome in which the neurotoxin from the bacterium *Clostridium botulinum* causes irreversible inhibition of acetylcholine release at the presynaptic nerve terminals. Botulism presents with ocular and bulbar weakness (usually with dilated poorly reactive pupils) that progresses to symmetric descending flaccid paralysis throughout the trunk and extremities. Patients may have blurry vision and paresthesia but rarely have true sensory loss. Symmetric

CASE 1-1

A 37-year-old woman with 6 months of fatigue, arthralgia, and chronic cough presented to clinic 1 month after the sudden onset of right footdrop and severe pain in her lower leg and foot. She had no history of trauma to the leg or back.

On examination, she had severe weakness of right ankle dorsiflexion but normal eversion and inversion strength. Sensation was diminished in a patchy distribution in her feet, most prominently in a nummular area on the dorsum of her right foot between the first and second toe. Nerve conduction studies showed asymmetric sural sensory nerve action amplitudes, lower on the left. The right fibular (peroneal) compound muscle action potential (CMAP) amplitude was very low, without any conduction slowing across the knee. Needle EMG showed active denervation in the right tibialis anterior but was otherwise normal. Left sural nerve biopsy showed endoneurial vessels with evidence of vessel wall infarction and transmural infiltration by inflammatory cells.

COMMENT

This patient had vasculitic mononeuritis multiplex. The initial clinical picture was consistent with a focal mononeuropathy of the left deep fibular (peroneal) nerve, which is not a common entrapment mononeuropathy. The sudden onset, severe pain, bilateral sensory signs, and abnormal sural nerve conduction studies further raised suspicion that this was the initial presentation of mononeuritis multiplex, and the nerve biopsy confirmed evidence of vasculitis. Additional serologic testing may have helped determine if the patient's weight loss, arthralgia, and cough were manifestations of a systemic vasculitis, such as granulomatosis with polyangiitis.

motor neuronopathies also cause this pattern of weakness, although less commonly than myopathies and neuromuscular junction disorders.

Rarely, CIDP may present with a pure motor syndrome characterized by symmetric proximal and distal weakness without sensory loss or pain.

Spinal muscular atrophy (SMA) is an autosomal recessive motor neuronopathy that usually presents in infancy or childhood. It is a pure lower motor neuron

Multifocal or Generalized Pure Motor Syndromes

TABLE 1-8

Localization/Disease	Pattern of Weakness	Distinguishing Clinical Features
Myopathy	Proximal predominant greater than distal predominant or multifocal	Variable
Neuromuscular junction		
Myasthenia gravis	Eyelids, eye movements, face, bulbar with or without limb involvement	Fatigability
Lambert-Eaton myasthenic syndrome	Lower extremity predominant	Hyporeflexia potentiated by exercise, dysautonomia
Motor neuron		
Amyotrophic lateral sclerosis	Limb or bulbar onset	Upper motor neuron signs, pseudobulbar affect, weight loss, frontotemporal dysfunction
Brachial amyotrophic diplegia	Bilateral proximal arms	No progression to other body segments for >12–18 months
Leg amyotrophic diplegia	One or both legs	No progression to other body segments for >12–24 months
Spinal muscular atrophy	Limb, bulbar and respiratory	Autosomal recessive inheritance pattern, infant or childhood onset
Spinal bulbar muscular atrophy (Kennedy disease)	Bulbar and proximal	Face and tongue fasciculations, gynecomastia, X-linked recessive inheritance pattern
Hirayama disease	Unilateral or bilateral hand and forearm	Young men, progresses for years then stabilizes, minipolymyoclonus, cold paresis
Infectious	Segmental or generalized	Acute or subacute onset, encephalitis, signs of systemic infection
Paraneoplastic	Segmental or generalized	Subacute onset, association with nonmotor paraneoplastic syndromes
Nerve		
Multifocal motor neuropathy	Distal upper extremity, weakness in the distribution of individual nerves; no bulbar or respiratory involvement	Weakness more than atrophy early in the course
Pure motor chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	Symmetric proximal and distal weakness; no bulbar or respiratory involvement	Reduced or absent reflexes

disease, presenting with progressive limb, bulbar, and respiratory weakness without spasticity or hyperreflexia. It is classified as type 1, 2, 3, or 4, depending on the age of onset and expected rate of progression. Type 1 has the earliest onset and most severe course, whereas type 4 is diagnosed after age 18 and is not necessarily fatal. It is important to distinguish SMA (a condition for which effective molecular therapy now exists) from other causes of isolated childhood weakness, such as congenital myopathies, muscular dystrophies, and congenital myasthenic syndromes. For more information on SMA, refer to the article "Spinal Muscular Atrophy" by Jessica Rose Nance, MD,[21] in this issue of *Continuum*.

In an adult with progressive proximal and distal weakness, progressive muscular atrophy should be suspected. Progressive muscular atrophy is a degenerative motor neuron disease only involving lower motor neurons. Most patients with this pattern eventually develop upper motor neuron signs, consistent with amyotrophic lateral sclerosis (ALS). Rarely, patients with ALS will present with bilateral proximal arm weakness without prominent upper motor neuron involvement (known as brachial amyotrophic diplegia).

Spinal bulbar muscular atrophy (also known as Kennedy disease) is an X-linked recessive trinucleotide repeat disorder that affects men between the fourth and seventh decades of life. Spinal bulbar muscular atrophy is a pure lower motor neuron disorder that has a predilection for the lower cranial nerves. Patients often present with dysarthria more than dysphagia and fasciculations of the tongue and lower face. Proximal limb weakness typically follows, along with atrophy and hyporeflexia in the upper arms and hip girdle. It is slowly progressive, with disability accumulating over many years or decades. The genetic defect is in the androgen receptor gene, so patients often have systemic features such as gynecomastia, impaired sexual function, or infertility.[22] Diabetes mellitus is also common. Unlike ALS, a substantial proportion of patients with spinal bulbar muscular atrophy also have a sensory neuropathy, which may be clinical or subclinical. For more information on spinal bulbar muscular atrophy, refer to the article "Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases" by Colin Quinn, MD, and Lauren Elman, MD,[23] in this issue of *Continuum*.

Proximal and Distal Asymmetric

Proximal and distal weakness that is asymmetric is usually due to a neurogenic disorder, with the exception of inclusion body myositis, which presents with asymmetric weakness that preferentially involves deep finger flexors and knee extensor muscles. The most common cause of this pattern of weakness is ALS.

ALS most often presents with progressive asymmetric painless weakness affecting both proximal and distal muscles, although distal muscles are affected first. ALS has a variable presentation, especially early in the course, and no sensitive biomarker is available to identify the majority of cases. The time course of symptoms, presence or absence of coincident upper motor neuron signs, and pattern of weakness are the most useful clinical features for differentiating ALS from other motor neuron disorders or mimics.

ALS is a progressive, invariably fatal, neurodegenerative disease. It is usually sporadic, but familial cases are well described and some sporadic cases appear to be associated with genetic mutations. Apoptosis of the lower motor neurons

causes degeneration of the motor axons and denervation of the muscles supplied by those axons. This leads to fasciculations, weakness, and atrophy in the affected muscles. ALS presents with limb onset in about two-thirds of cases and bulbar onset in about one-third of cases.[24] Weakness may begin asymmetrically but characteristically spreads to other limbs or regions of the brain over months. ALS does not cause pain, but intermittent muscle cramps are common. Patients often lose a significant amount of body weight, in part because of muscle loss and dysphagia. Involvement of the lower cranial motor nerves is common, but the motor neurons supplying the extraocular muscles are spared.

Among the degenerative diseases that affect the lower motor neurons, ALS is unique in that it also causes dysfunction of the upper motor neurons that run from the motor cortex through the brainstem and into the spinal cord corticospinal tracts. Involvement of the corticobulbar tracts can cause emotional lability, characterized by crying or laughing with minimal stimulus. This is known as pseudobulbar affect and represents a dysregulation of motor output of emotion rather than a mood disorder.[25] Patients may note increased yawning. Upper motor neuron involvement causes spasticity, which may present as limb stiffness causing gait dysfunction and impaired mobility out of proportion to the weakness. Upper motor neuron signs that may be found on examination include spastic dysarthria, spasticity in the limbs, hyperreflexia, frontal release signs (such as a palmomental reflex), and primitive reflexes (such as Babinski and Hoffman signs.)

Impaired cognition and behavioral problems are common in ALS, with as many of 50% of patients having some form of frontotemporal dysfunction and 15% of patients meeting strict criteria for frontotemporal dementia.[26]

Although ALS typically spreads to involve all limbs, regional variants have been described. Brachial amyotrophic diplegia is a pure lower motor neuron disorder that leads to progressive weakness limited to the upper extremities for at least 12 to 18 months. It may start asymmetrically, but most cases progress to being symmetric. Brachial amyotrophic diplegia is characterized by early proximal arm involvement, as opposed to typical ALS, in which weakness of the intrinsic hand muscles may be noted first. The flail leg variant of ALS, also known as leg amyotrophic diplegia, presents with pure lower motor neuron involvement limited to one or both lower extremities for at least 12 to 24 months. Both brachial amyotrophic diplegia and leg amyotrophic diplegia are associated with atrophy and diminished or absent reflexes in the affected limbs. Both may eventually progress to involve other body segments or upper motor neurons, at which point the clinical picture may resemble classic ALS. Life expectancy is generally greater in brachial amyotrophic diplegia and leg amyotrophic diplegia than in patients who presented with a more rapid progression between body segments. A minority of patients never develop weakness beyond a single body segment, in which case the disease is disabling but may not be fatal.[27] For more information on ALS, refer to the article "Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases" by Colin Quinn, MD, and Lauren Elman, MD,[23] in this issue of *Continuum*.

Infectious motor neuronopathies also present with asymmetric proximal and distal weakness. Poliomyelitis is an infection of the spinal cord caused by the poliovirus. The poliovirus has a predilection for motor neurons, leading to acute asymmetric and patchy flaccid paralysis with or without bulbar and respiratory

KEY POINTS

- Spinal bulbar muscular atrophy may cause fasciculations in the face or tongue, signs of androgen deficiency (including gynecomastia), and slowly progressive bulbar and proximal weakness.
- The pseudobulbar affect seen in patients with amyotrophic lateral sclerosis represents dysregulation of emotional output rather than a mood disorder.
- Overt dementia is not common in amyotrophic lateral sclerosis, but up to half of patients will have some impaired cognition or behavioral problems.
- Brachial amyotrophic diplegia and leg amyotrophic diplegia present with painless flaccid weakness starting in one body segment, which may or may not eventually progress to involve other body segments or cause upper motor neuron pathology.

CASE 1-2

A 35-year-old man presented with 2 years of left thumb weakness that had not improved following carpal tunnel release surgery. Following surgery, he developed progressive weakness of both hands and had to quit his job scooping ice cream. He did not have any pain or sensory loss.

On examination, he had no facial or bulbar weakness. He had mild atrophy and a few fasciculations in his left thenar eminence, but otherwise bulk appeared normal. Strength was 4/5 for left elbow flexion, wrist flexion, finger flexion, and thumb abduction. He could not fully extend the third and fourth fingers on the right hand. Otherwise, strength was full. Sensation was intact throughout, and reflexes were diminished but not absent throughout.

Nerve conduction studies were significant for conduction block in several upper extremity motor nerves (FIGURE 1-2[33]). Active denervation was seen in some of the intrinsic hand muscles on the left, and decreased recruitment was seen in the left biceps and right finger extensors. GM1 ganglioside antibody testing was negative.

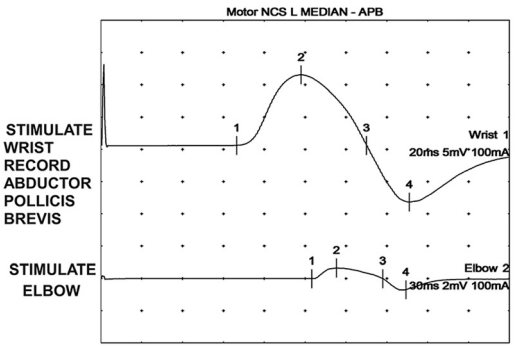

FIGURE 1-2
Nerve conduction studies showing partial conduction block with proximal stimulation in a patient with multifocal motor neuropathy.
APB = abductor pollicis brevis; L = left; NCS = nerve conduction study.
Reprinted with permission from Russell JW, Zilliox LA, Continuum (Minneap Minn).[33] © 2014 American Academy of Neurology.

COMMENT

This case highlights many of the classic features of multifocal motor neuropathy (MMN), and how it can be differentiated from amyotrophic lateral sclerosis (ALS). The patient presented with slowly progressive focal asymmetric arm weakness without sensory symptoms. The weakness was in the distribution of named nerves (left median and right radial) but with variable weakness of different finger extensors, suggesting differential fascicular involvement. A motor neuron disease such as ALS would more typically present with a myotomal pattern of weakness. MMN does not affect bulbar and facial muscles, whereas ALS eventually does. Patients with ALS usually have significant atrophy and fibrillations in the clinically affected muscles; the relative absence of these features suggests that some of his weakness was caused by demyelination rather than axonal loss. GM1 ganglioside antibodies are not sensitive, and a positive test is not necessary to make the diagnosis of MMN in the correct clinical and electrodiagnostic setting.

weakness. The polio vaccine became available in 1955, and the disease has been eradicated in the United States. The last case of wild-type poliomyelitis that originated in the United States was in 1979, and the last time a traveler with polio was identified in the United States was in 1993.[28] In 2019, there were 176 cases of wild-type polio worldwide.[29]

A poliolike illness has been associated with West Nile virus infection. A small percentage of patients with West Nile viremia will develop encephalitis, with or without an acute regional flaccid paralysis. Sensory loss in the affected limbs is common.

Enterovirus D68 infections have been increasing worldwide since an outbreak in 2014. Although most patients only develop a mild respiratory illness, the virus is associated with acute flaccid myelitis in a minority of patients.[30]

Very rarely, patients may develop a motor neuron disease as part of a paraneoplastic syndrome, presenting with subacute-onset asymmetric upper limb weakness, with or without upper motor neuron involvement.[31] This may co-occur with nonmotor manifestations such as sensory neuronopathy. It is a difficult diagnosis to make because the clinical features are nonspecific, and patients often have no known tumor history at the time of presentation.

Distal Symmetric

Distal symmetric weakness is most commonly due to hereditary motor neuropathies. Axonal forms of CMT and juvenile forms of ALS have significant phenotypic and genotypic overlap with hereditary spastic paraplegia.[32]

Some myopathies, such as myotonic dystrophy type 1, primarily affect the distal muscles. A careful sensory examination can usually distinguish a distal myopathy from a distal symmetric polyneuropathy. The extensor digitorum brevis muscle is often weak and atrophic in sensorimotor neuropathy but relatively spared in most distal myopathies.

Distal Asymmetric

Distal asymmetric weakness should raise concern for ALS, particularly if reflexes are preserved or brisk. Several other disorders cause distal asymmetric weakness and should be excluded.

Multifocal motor neuropathy (MMN) is an acquired disorder of the motor nerves presenting with progressive asymmetric limb weakness and characterized by multifocal conduction block on nerve conduction studies. The underlying mechanism is an immune attack at the nodes of Ranvier. It can easily be mistaken for ALS, but it is important to distinguish between the two conditions because MMN is a treatable and nonlethal condition. In MMN, the lesions are at the level of the peripheral nerve rather than the cell body in the anterior horn cell, so weakness and atrophy are more likely to follow a pattern of multiple mononeuropathies rather than a myotomal pattern as would be seen in ALS. For example, a patient with ALS who has interosseous weakness will likely also have ipsilateral weakness of thumb abduction because both are derived from the C8 and T1 nerve roots and have motor neurons in the same level of the spinal cord. Patients with MMN often have differential weakness of muscles that share a myotome but are supplied by different nerves or even different nerve fascicles (CASE 1-2). Because MMN causes conduction failure at the nodes of Ranvier, it may cause weakness out of proportion to atrophy, especially early in the course of the disease.[34] Typically, patients with MMN will have diminished

KEY POINTS

- Systemic infections with West Nile Virus and specific enteroviruses may cause a poliolike illness characterized by flaccid paralysis with or without encephalitis.
- The extensor digitorum brevis muscle may atrophy in sensorimotor distal symmetric polyneuropathy but is often relatively spared in distal myopathies.
- The weakness in amyotrophic lateral sclerosis tends to follow a myotomal pattern, whereas the weakness in multifocal motor neuropathy may be in the distribution of specific peripheral nerves.
- Early in the course of multifocal motor neuropathy, patients may have significant weakness with little or no atrophy, suggesting that the motor axons are still intact.

deep tendon reflexes in affected muscles and should not have bulbar or respiratory involvement. For more information on MMN, refer to the article "Chronic Inflammatory Demyelinating Polyradiculoneuropathy and Its Variants" by Kelly Gwathmey, MD,[12] in this issue of *Continuum*.

Hirayama disease, or monomelic amyotrophy, is not a neurodegenerative disease of the motor neurons but an unusual form of cervical myelopathy that has a predilection for the motor neurons. Patients are often young men of Asian descent. Forward displacement of the posterior cervical dural sac with neck flexion causes cord compression or venous congestion that preferentially damages the C7, C8, and T1 anterior horn cells on one or both sides (CASE 1-3). Patients usually present with progressive painless weakness in the hand and forearm, with sparing of the brachioradialis. Distinctive clinical manifestations include cold paresis and an irregular tremor (minipolymyoclonus) with finger extension. Weakness is progressive at first, but the disease plateaus within 5 years and does not spread to other body segments.[35]

CASE 1-3

A 19-year-old man presented for evaluation of weakness in his right hand that had slowly progressed over the previous 2 years. He was a casual bodybuilder and had been able to maintain excellent muscle bulk everywhere in his body other than the right forearm and hand. Recently, he had noticed fasciculations in some of the intrinsic hand muscles. He did not report any sensory loss or pain, other than a propensity for the hand to cramp at night.

On examination, he had mild atrophy of the right hand and weakness of all intrinsic hand muscles on the right, including the interossei and thumb abductors. Electrodiagnostic testing showed low-amplitude median and ulnar compound muscle action potentials (CMAPs). On needle EMG, evidence of active denervation in the right abductor pollicis brevis, flexor pollicis longus, first dorsal interosseus, and extensor indicis was seen.

MRI of the cervical spine showed focal atrophy of the cord from C5 through C7 vertebral levels. Dynamic MRI with the neck in flexion showed the posterior dura with anterior displacement and compression of the cord. The flow voids in the posterior epidural space during neck flexion were exaggerated, and a crescent-shaped enhancing epidural space extending from C4 to T2 was seen.

COMMENT

Slowly progressive hand weakness in one limb could, in theory, be caused by a single lesion of the C8 nerve root or lower trunk of the brachial plexus. However, the lack of pain or sensory loss would be unusual and should raise suspicion for focal injury to the lower cervical motor neurons. The dynamic MRI findings described in this case are classic findings in Hirayama disease, a rare juvenile-onset myelopathy with a predilection for the lower cervical anterior horn cells. Although it is often known as monomelic amyotrophy, a significant minority of patients eventually develop symptoms in the contralateral arm.

PURE SENSORY SYMPTOM PATTERN

Sensory dysfunction without significant weakness localizes best to the spinal cord sensory tracts, the dorsal root ganglia, the sensory nerves, or small unmyelinated nerves. Most clinically significant lesions will cause static sensory loss in a fixed distribution. When patients present with episodic migrating paresthesia, a neurologic etiology is rarely identified.

Proximal and Distal Symmetric

The central projections of the sensory neurons travel through the dorsal columns and the spinothalamic tracts. Disruption of these tracts from trauma, disk disease, infection, or toxic-metabolic syndromes leads to sensory loss and pain below the level of the lesion. A focal injury to the dorsal columns in the lower parts of the spinal cord may affect the lower extremities only, mimicking a distal symmetric polyneuropathy. If the cervical dorsal columns are disrupted, patients may report generalized sensory loss. Patients with cervical cord involvement may also report electric shock–like sensations traveling down their spines with neck flexion (the Lhermitte phenomenon).

Isolated dorsal column dysfunction may lead to impaired position sense and two-point discrimination with relatively preserved pain sensation. This is helpful in differentiating this condition from polyneuropathy, in which proprioception is usually spared relative to other primary sensory modalities.

The dorsal columns are often involved as part of a more extensive myelopathy. A careful history and motor examination may reveal bowel and bladder retention, hyperreflexia, or spasticity.

Proximal and Distal Asymmetric

All peripheral sensory nerves are derived from neurons located within the dorsal root ganglia. Certain infectious, inflammatory, and metabolic disorders are known to preferentially damage these sensory neurons. Because these conditions may affect any dorsal root ganglion, the sensory loss does not conform to the typical length-dependent pattern seen in most distal symmetric polyneuropathies. Sensory loss may be asymmetric and may affect proximal areas before distal areas, including the upper extremities, face, and trunk. Special sensory modalities may be affected, and pain is common. The sensory loss in the limbs is often profound, leading to gait and limb ataxia. Patients may have pseudoathetosis, adventitious movements of their distal extremities caused by markedly impaired proprioception. The examiner may initially note weakness on confrontational testing, but strength may normalize when the patient looks at the limb that is being tested, using visual cues to overcome their lack of proprioception. Deep tendon reflexes are reduced or absent.

This clinical presentation is strongly suggestive of a sensory neuronopathy but is nonspecific as to cause. About 20% of cases occur as part of a paraneoplastic syndrome associated with small cell lung cancer, lymphoma, adenocarcinoma, or neuroblastoma.[36] Paraneoplastic sensory neuronopathy tends to be rapidly progressive and may co-occur with other paraneoplastic disorders. Other etiologies include Sjögren syndrome, toxicity related to cisplatin or other chemotherapies, pyridoxine overdose, or HIV infection, although in many cases it is idiopathic.

Wartenberg migratory sensory neuritis, a poorly understood multifocal sensory neuropathy, presents with sudden-onset fixed numbness of one or more cutaneous nerves with or without preceding pain in the distribution of the

KEY POINTS

- Hirayama disease (monomelic amyotrophy) presents in young men with unilateral or bilateral hand weakness that progresses for years and then plateaus.
- Proprioception is often involved early in disorders affecting the dorsal columns and late in disorders affecting the peripheral nerves.
- Patients with sensory neuronopathy may initially appear weak on confrontational testing but are able to generate full power when they look at the limb being tested.
- Sensory neuronopathy may be idiopathic or associated with Sjögren syndrome, a paraneoplastic syndrome, human immunodeficiency virus, or pyridoxine overdose.

affected nerve(s). The cause of Wartenberg migratory sensory neuritis is unknown. An autoimmune etiology has been suggested, but immunomodulatory therapy does not appear to be beneficial.[37]

A small percentage of patients with small fiber neuropathy present with a non–length-dependent syndrome of asymmetric proximal and distal pain and loss of sensation to small fiber modalities (pain and temperature). In this case, nerve conduction studies are normal, but diagnosis can be confirmed with skin biopsies from proximal and distal sites stained with protein gene product 9.5 (PGP 9.5).

Multifocal sensory loss may also be related to rare inflammatory diseases such as a chronic immune sensory polyradiculoneuropathy (CISP); chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies (CANOMAD); and chronic ataxic neuropathy with anti–disialosyl IgM antibodies (CANDA).[38]

Distal Symmetric

As discussed above, distal symmetric polyneuropathy is often sensory predominant with no motor involvement until later in the course of the illness. Small fiber polyneuropathy is a subset of distal symmetric polyneuropathy in which only the small unmyelinated nerve fibers are impaired. These fibers carry pain and temperature sensation as well as the autonomic fibers destined for the sweat glands and viscera, so, by definition, patients have no somatic motor involvement. The most distal nerves tend to be affected most, so symptoms usually begin in the toes or balls of the feet and gradually spread proximally up the legs and eventually into the hands. Patients may report a general sense of numbness in these areas or specifically note an inability to distinguish temperatures or recognize painful stimuli. Painless injuries may occur. Most patients report paresthesia and neuropathic pain. On examination, patients will have decreased pain and thermal sensation, with preserved position sense. Strength and deep tendon reflexes are generally spared. Autonomic nerve dysfunction may cause decreased sweating in the affected areas. Loss of autonomic vasomotor control may result in skin color changes, leaving the

TABLE 1-9 **Neuromuscular Disorders That Present Acutely or Subacutely**

Localization	Examples of Disorders
Motor neuron	Acute flaccid paralysis, paraneoplastic
Spinal root	Disk herniation, varicella-zoster virus
Sensory neuron	Paraneoplastic, Sjögren syndrome, pyridoxine toxicity
Plexus	Idiopathic neuralgic amyotrophy, diabetic lumbosacral radiculoplexus neuropathy
Nerve	Direct nerve trauma, toxic (eg, chemotherapy or heavy metal-induced), vasculitic mononeuritis multiplex, acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and variants
Neuromuscular junction	Botulism
Muscle	Inflammatory myopathies, rhabdomyolysis due to a metabolic myopathy, toxic myopathies

skin looking shiny, dry, and atrophic. Other autonomic symptoms, such as gastroparesis, erectile dysfunction, or constipation, may occur.[39]

The differential diagnosis for small fiber or sensory predominant polyneuropathy is broad. Some of the more common etiologies include diabetes mellitus, chronic alcohol use disorder, drug toxicity, and associated with paraproteinemia.

KEY POINT

● The most useful screening laboratory tests for the workup of distal symmetric polyneuropathy are tests for diabetes or prediabetes, serum lipids and cholesterol, a vitamin B_{12} level, and serum protein electrophoresis and immunofixation.

ACUTE OR SUBACUTE ONSET

Although the distribution of signs and symptoms is of paramount importance in categorizing peripheral nervous system disorders, the time course can narrow the differential diagnosis even further, especially if symptoms develop rapidly. The only truly acute neuromuscular disorders are those related to trauma, such as a peripheral nerve injury. Infectious, inflammatory, and toxic processes may present subacutely, developing over hours to days. TABLE 1-9 provides examples of subacute disorders organized by neuroanatomic localization.

DIAGNOSTIC TESTING

Blood tests, CSF analysis, electrodiagnostic studies, imaging, and tissue biopsy all serve a situational role in the workup for sensory and motor symptoms. The history and physical examination are paramount in the diagnosis of neuromuscular disorders and inform the yield of specific diagnostic tests.

Blood Testing

The purpose of blood testing is to identify evidence of a systemic disorder that may cause or put the patient at risk for a neuromuscular syndrome. Mononeuropathy and radiculopathy are usually caused by local trauma; therefore, blood testing is generally not indicated.

Distal symmetric polyneuropathy, on the other hand, is presumed to be the result of a systemic process, although it is not always possible to identify the culprit. Dozens of tests could, in theory, suggest an underlying cause, but only a select few have a high enough yield to merit testing in all patients with a distal symmetric polyneuropathy phenotype.[40] The most useful test is a measure of serum glucose. This may include a hemoglobin A_{1c}, fasting glucose, or 2-hour oral glucose tolerance test. It is controversial whether hemoglobin A_{1c} values in the range suggestive of prediabetes, impaired fasting glucose, and impaired glucose tolerance should be considered abnormal in the workup of neuropathy.[41] Patients with distal symmetric polyneuropathy have a very high risk of having metabolic syndrome, so a fasting cholesterol panel and serum triglycerides should also be checked. Serum protein electrophoresis and serum immunofixation should be obtained to screen for paraproteinemia, also known as monoclonal gammopathy. The immunofixation is important because it may help identify low-level paraproteins that may be overlooked on serum protein electrophoresis alone. The level of the paraprotein correlates with risk of malignancy, but even low-level paraproteinemia may be associated with neuropathy. A serum vitamin B_{12} level should be obtained; if the value is borderline (above the lower limit of normal but lower than 500 pg/mL), a serum methylmalonic acid level should be checked as well. Elevated levels may suggest a functional vitamin B_{12} deficiency, even when the vitamin B_{12} level is borderline. Up to 50% or more of patients with distal symmetric polyneuropathy have prediabetes or diabetes, and even more have metabolic syndrome.[42] The serum protein electrophoresis and immunofixation are abnormal in 9%, and vitamin B_{12} is abnormal in 3.6%.[40] Little evidence is available to support the

routine testing of thyroid-stimulating hormone (TSH), erythrocyte sedimentation rate, folate, antinuclear antibodies, Venereal Disease Research Laboratory (VDRL), or other commonly employed blood tests. However, if patients have systemic symptoms, rapid onset of neuropathy, motor predominance, or a non–length-dependent pattern, a more thorough evaluation may be indicated.

If hereditary neuropathy is suspected, the clinical phenotype and electrodiagnostic features can help the physician estimate the likelihood of specific genetic abnormalities. However, the widespread availability of next-generation sequencing panels that include both common (*PMP22*, *MPZ*, *GJB1*, and *MFN2*) and uncommon mutations may obviate the need to choose individual genes to sequence.[18] X-linked Fabry disease is a treatable cause of small fiber neuropathy, cardiovascular dysfunction, renal failure, and skin lesions. Men with Fabry disease will have deficient α-galactosidase A in plasma and leukocytes. Female carriers can identified by confirming elevated plasma lyso-Gb3 levels.[43] In the absence of clinical features other than small fiber neuropathy, the yield of molecular testing is low.[44] Hereditary transthyretin (TTR) amyloidosis is an autosomal dominant multisystem disease that can present with sensorimotor polyneuropathy. Since it is treatable, some authors advocate for genetic testing early in the workup of neuropathy, especially when patients have a family history, evidence of cardiovascular disease, carpal tunnel syndrome, and prominent dysautonomia.[45] Routine genetic testing of patients with uncomplicated distal symmetric polyneuropathy is not recommended.

Mononeuritis multiplex and nontraumatic plexopathies are often associated with systemic disease, but little consensus exists on which blood tests have the highest yield. Studies may include a complete blood cell count, basic metabolic panel, hemoglobin A_{1c}, HIV, hepatitis panel, and autoimmune testing, including antinuclear antibodies, erythrocyte sedimentation rate, C-reactive protein, antineutrophil cytoplasmic antibodies (ANCA), rheumatoid factor, complement levels, and cryoglobulins.

If the history and examination suggest MMN, it is worthwhile to check for GM1 ganglioside antibodies. Anti-GM1 ganglioside antibodies are detected in at least 50% of patients with MMN, and their presence is reasonably specific for this condition.[34]

Blood testing is usually nondiagnostic in demyelinating neuropathies. If the time course and phenotype are suggestive of CIDP or DADS neuropathy, serum protein electrophoresis and immunofixation should be obtained. If an IgM paraprotein is identified, antibodies against MAG may verify the diagnosis of DADS neuropathy. If an IgA or IgG paraprotein is identified, further workup may be indicated to screen for POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes) syndrome.

In patients with a phenotype suggestive of a sensory neuronopathy, the workup should include paraneoplastic autoantibodies (especially anti-Hu antibodies), anti–Sjögren syndrome A (SSA) and anti–Sjögren syndrome B (SSB) antibodies to screen for Sjögren syndrome, and HIV testing. Pyridoxine levels should be obtained if a clinical suspicion for toxicity exists. Serum protein electrophoresis, immunofixation electrophoresis, and Gd1b antibody testing may be helpful in this population to screen for the rare disorders CANOMAD and CANDA.[46]

Blood tests are generally low yield in the workup of motor neuron diseases, with a few exceptions. Genetic testing may be considered in patients with ALS and affected family members. In cases in which the diagnosis is uncertain or the patient has signs of frontotemporal dementia, obtaining *C9orf72* hexanucleotide repeat testing may be helpful, even in patients without a clear-cut family history.

Spinal bulbar muscular atrophy should be considered in a male patient with bulbar-predominant pure lower motor neuron weakness and signs of androgen insensitivity. The diagnosis can be verified by identifying a CAG repeat expansion on the androgen receptor gene.

CSF Testing

CSF albuminocytologic dissociation is defined as a CSF protein concentration of greater than 45 mg/dL with white blood cell count of less than 50 cells/mm^3. In the correct clinical context, this finding is supportive of the diagnosis of AIDP. A 2019 study found the sensitivity of this finding to be 73.2% when CSF was obtained an average of 13 days after symptom onset.[47] During the course of the disease, early protein levels may correlate with disease severity. Normal CSF results must be interpreted with caution. Some studies suggest that more than 50% of patients will have normal CSF levels within 1 to 2 weeks of symptom onset, and 12% of patients never show abnormalities.[48] A significant pleocytosis in a patient with AIDP suggests associated HIV. The primary use of CSF analysis in a patient suspected of AIDP is to exclude infectious diseases and malignancies.

The role of CSF albuminocytologic dissociation in the diagnosis of CIDP is even less clear. One of the most common reasons for the overdiagnosis of CIDP is putting too much stock in mildly to moderately elevated CSF protein levels.[49] Rather than using the standard upper limit of normal of 45 mg/dL, evidence indicates that higher age-matched upper limits of normal should be implemented (50 mg/dL for patients younger than 50 years of age and 60 mg/dL for patients older than 50 years of age).[50] In the absence of both clinical and electrodiagnostic criteria that support the diagnosis of CIDP, an elevated CSF protein should not be used to justify immunomodulatory treatment.[51]

Electrodiagnostic Testing

Electrodiagnostic testing is used to identify a wide range of neuromuscular disorders. A complete electrodiagnostic evaluation includes two complementary tests, nerve conduction studies and needle EMG. Nerve conduction studies are most commonly performed by placing surface electrodes approximating the location of the nerves beneath the skin. The nerve is stimulated in one location, and a recording electrode detects a remote response over the surface of the nerve or an associated muscle. Needle EMG involves inserting a thin needle into skeletal muscles and recording the electrical activity within the muscle.

Using a combination of these techniques, the electrodiagnostic consultant can identify and localize neuromuscular lesions to any level of the peripheral nervous system, including the motor neuron, spinal root, plexus, sensory and motor peripheral nerves, neuromuscular junction, and the muscle itself. Electrodiagnostic studies can provide information about whether a process is focal or generalized, whether a neuropathy is primarily axonal or demyelinating, and whether nerve dysfunction is subacute or chronic.

Practically speaking, electrodiagnostic testing is more useful for some diagnoses than others. It should be considered foundational for the diagnosis of mononeuropathies, mononeuritis multiplex, demyelinating neuropathies, sensory neuronopathy, plexopathies, disorders of neuromuscular junction transmission, and motor neuron disorders.

Electrodiagnostic testing has some value in the diagnosis of radiculopathy. It can determine the function of nerve roots and the chronicity of lesions and rule

KEY POINTS

- **Paraproteinemia may be associated with chronic inflammatory demyelinating polyradiculoneuropathy, is common in patients with distal acquired demyelinating symmetric neuropathy, and is present in most patients with POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes) syndrome.**
- **The overreliance on modest CSF protein elevations is a common reason for the overdiagnosis of chronic inflammatory demyelinating polyradiculoneuropathy.**

out mimics such as mononeuropathy or plexopathy. However, conventional electrodiagnostic tests can only examine the function of the motor roots. They are less sensitive in patients with isolated pain and sensory symptoms, a common clinical scenario.

Electrodiagnostic testing is probably overused in the workup of distal symmetric polyneuropathy. Nerve conduction studies can identify and determine the severity of large fiber axonal polyneuropathy but should be normal in pure small fiber neuropathy.[52] Knowing whether large fibers are involved in a distal symmetric polyneuropathy often has no meaningful impact on patient management. Thus, the role of electrodiagnostic testing in patients with isolated distal symmetric numbness is unclear. For more information on the role of electrodiagnostic testing in the evaluation of peripheral neuropathies, refer to the article "Test Utilization and Value in the Evaluation of Peripheral Neuropathies" by Brian C. Callaghan, MD, MS, FAAN,[53] in this issue of *Continuum.*

Imaging

MRI of the cervical, thoracic, or lumbar spine is the preferred imaging modality for visualizing the soft tissues and bony structures that comprise the neuraxis. It can identify the most common space-occupying lesions that compress the exiting nerve roots and abnormalities within the roots themselves. MRI may also show hypertrophic or enhancing nerve roots in patients with demyelinating polyradiculoneuropathies such as AIDP, CIDP, and CISP. Dynamic MRI of the cervical spine can be diagnostic of Hirayama disease. The major limitation of MRI of the spine is that potentially pathogenic changes, such as intervertebral disk bulges and neuroforaminal stenosis, are found in a high proportion of asymptomatic individuals.

Focused MRI of the brachial or lumbosacral plexus may have a role in identifying neoplastic or infectious infiltration or structural lesions such as neurogenic thoracic outlet syndrome. The clinical utility of MRI in the diagnosis of motor neuron disease is unclear. Hyperintense signal along the corticospinal tracts has been noted in patients with upper motor neuron–predominant disease.[54]

Ultrasound is not a new technology, but its role in the diagnosis of neuromuscular disorders has been expanding with the application of high-frequency transducers and improved image processing. Ultrasound imaging enables real-time morphologic evaluation of nerves and muscles. In the correct clinical context, the finding of an enlarged cross-sectional nerve diameter is sensitive, but not specific, for the nerve swelling associated with compression mononeuropathy.[55] Other sonographic features can be used to identify traumatic peripheral nerve injury and demyelinating neuropathies.[56] Ultrasound has been used as an adjunct to EMG to identify fasciculations, decreased muscle thickness, and increased muscle echo intensity and echo variance in patients with motor neuron disease.[57] Ultrasound is painless and thus is better tolerated than EMG. Ultrasound is operator dependent and is limited by inadequate penetration, which is problematic with patients who are obese or when assessing deeper structures.[58]

Tissue Biopsy

In the correct clinical context, a nerve or skin biopsy may aid in the diagnosis of polyneuropathy.

NERVE BIOPSY. Nerve biopsy is most useful in the evaluation of mononeuritis multiplex. Systemic vasculitides that involve small to medium-sized arteries may affect epineurial vessels, resulting in asymmetric painful neuropathy. Serologic testing, urinalysis, and body imaging may identify the underlying condition, obviating the need for biopsy to support the initiation of immunomodulatory treatment.

If a patient with mononeuritis multiplex has no systemic symptoms or all the tests for systemic vasculitis or inflammatory disorders are negative, a nerve biopsy may be necessary to diagnose nonsystemic vasculitic neuropathy. Pathologic findings include inflammation around and necrosis of the vessel walls. Biopsy of a nearby muscle increases diagnostic sensitivity for vasculitis.

Nerve biopsy has limited utility in the diagnosis of CIDP. Pathologic changes are often more extensive in proximal portions of peripheral nerves and may affect motor nerves more than sensory nerves. At the time of biopsy, disease-specific features may have already disappeared. However, signs of demyelination are still considered a supportive feature in the European Federation of Neurological Societies/Peripheral Nerve Society criteria for CIDP.[59]

Electrodiagnostic testing can be used to identify a functionally impaired cutaneous nerve for biopsy. The most commonly biopsied nerves are the sural, radial, or superficial fibular (peroneal) nerves. Complications of nerve biopsy include sensory loss, chronic pain, and wound infection. These are usually mild, but, nonetheless, nerve biopsy should be avoided if the diagnosis can be made with noninvasive testing.

SKIN BIOPSY. Skin biopsy to directly measure epidermal fiber density has become increasingly used to diagnose small fiber polyneuropathy and determine if it is length dependent or diffuse. A biopsy is taken from a distal and a proximal site in a lower extremity and the tissue is stained with an antibody to PGP 9.5, a panaxonal marker (FIGURE 1-3). The primary usefulness of this test is when the diagnosis of neuropathy is uncertain or if a non–length-dependent small fiber neuropathy is suspected. The test may be overused in patients whose clinical manifestations are consistent with distal symmetric small fiber polyneuropathy because the results only rarely lead to a change in management.

Immunoglobulin light chain amyloidosis is a rare but serious cause of small fiber–predominant polyneuropathy, often with

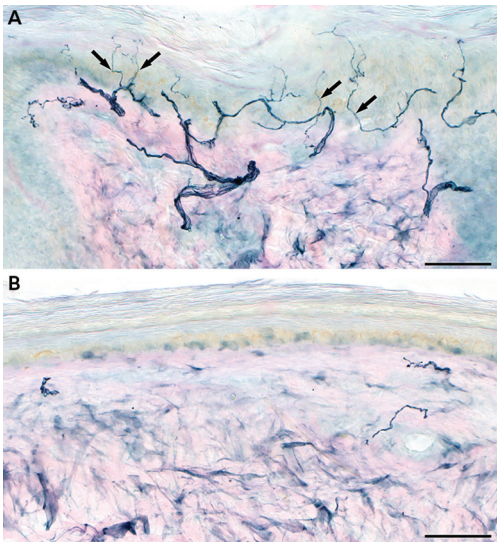

FIGURE 1-3
Skin biopsies from the distal leg stained with protein gene product 9.5 (PGP 9.5), a panaxonal marker, demonstrate normal intraepidermal nerve fiber density (*A*) in an asymptomatic patient and reduced density (*B*) in a patient with distal symmetric polyneuropathy. *Arrows* designate normal epidermal axons. The bar represents 50 microns.
Figure courtesy of A. Gordon Smith, MD, FAAN.

KEY POINTS

- **Electrodiagnostic testing is an important part of the workup for mononeuropathies, mononeuritis multiplex, demyelinating neuropathy, sensory neuropathy, and motor neuron disease, but it is not sensitive for small fiber polyneuropathy or pure sensory radiculopathy.**
- **MRI of the spine can identify common causes of radiculopathy and aid in the diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy and Hirayama disease but may show degenerative changes of questionable significance in both symptomatic and asymptomatic individuals.**
- **Ultrasound imaging is useful in the workup of entrapment neuropathies and has emerging indications in the workup of other neuromuscular disorders.**
- **A nerve biopsy is the diagnostic test of choice for suspected nonsystemic vasculitic neuropathy. In the setting of known systemic vasculitis, nerve biopsy should only be performed if demonstrating peripheral nerve involvement will lead to a change in immunomodulatory treatment.**

dramatic dysautonomia. Although nerve and skin biopsy with Congo red staining may demonstrate amyloid deposits, these deposits can be found in bone marrow, salivary gland, or subcutaneous fat in 85% of affected patients.[60]

CONCLUSION

Focal lesions of the peripheral nervous system cause deficits that may be unique to the involved neuroanatomic structure. Multifocal or generalized peripheral nervous system disorders can be identified by the characteristic patterns of sensory and motor involvement. Clinicians should use the history and physical examination to inform the judicious use of diagnostic testing. Electrodiagnostic studies, CSF analysis, and tissue biopsy are particularly useful in many clinical settings but may be overused in other settings. The focus of testing should be to confirm or refute suspected diagnoses when doing so is likely to impact patient management.

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