

Evaluating the Patient with Peripheral Nervous System Complaints

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Patients commonly seek care from their family physicians for symptoms that are suggestive of peripheral nervous system (PNS) dysfunction. At some point in active practice, virtually all family physicians will be required to conduct at least an initial evaluation of a patient with PNS. The authors outline and describe common themes found in the symptoms and diagnoses of PNS dysfunctions. These themes may be useful to physicians when performing initial evaluations of patients with PNS dysfunctions. The authors also discuss diagnostic methods and effective therapeutic interventions for this population.

The human nervous system is an incredibly complex network of pathways that allows us to interact successfully with our environment. The nervous system can be divided into two parts: the central nervous system (CNS), which includes the brain, brainstem, and spinal cord, and the peripheral nervous system (PNS) that consists of the individual cranial, motor, and sensory nerves.

Although the autonomic nervous system (ie, the sympathetic and parasympathetic nervous system) is often considered part of the PNS, this review will focus on disorders of the motor and sensory nerves within the PNS. This review will only briefly address cranial neuropathies and autonomic nervous system dysfunction.

Clinical Presentation

Disorders of the PNS present in myriad ways that can make clinical diagnosis challenging. The key to efficient diagnosis lies in being able to recognize certain patterns in patients' personal and family histories and in the results of physical and neurologic examinations. If PNS disorder is suspected, family physicians can request targeted diagnostic evaluations and consider giving their patients referrals to neurologists.

In general, patients with PNS dysfunction complain of sensory disturbance, motor weakness, or both. Peripheral nerve pain is often more active at night.

Typically, symptoms of sensory disturbance range along a continuum from "negative" phenomena (eg, numbness, loss of sensation) to "positive" phenomena (eg, tingling, burning, "pins and needles," bands of tightness, and stabbing or shooting pain or both). Sensory symptoms may be subtle and are not always present during physical examinations, particularly when it is early in the progression of PNS dysfunction.

Dysesthesia refers to unpleasant sensations perceived in response to normally nonnoxious stimuli. Alternatively, *paresthesia* is an unpleasant sensation that is perceived despite the absence of external stimuli. Finally, when normal stimuli are perceived as painful, *allodynia* is the descriptor used.¹

In most cases of injury to the PNS, patients' sensory symptoms are length-dependent, beginning in the distal portions of the lower extremities (toes) and progressing proximally.¹ Occasionally, sensory symptoms may begin in the distal portions of the upper extremities (fingers). This common anatomic distribution of symptoms is referred to as a *stocking-glove pattern* and is virtually pathognomic for a peripheral neuropathy.

Once sensory symptoms have progressed to the midshin, patients may report the involvement of the fingers.² Patients may also report difficulties with balance and coordination that may be secondary to a loss of distal sensation.

Radiculopathy

Radiculopathies are not length-dependent, but there is, once again, a continuum of sensory symptoms that patients may describe. Along this continuum, physicians may receive patient reports of pain levels that range from an "ache" to a "shooting electric-shock-like pain" that radiates toward the periphery of the limb. Patients may also have spasms of the paraspinal muscles, which are often sore and tender to the touch.

Radiculopathies are often exacerbated by certain activities that increase intra-abdominal pressure, such as coughing or sneezing.¹ When stationary, patients may naturally favor certain positions (eg, standing versus sitting) to accommodate and minimize their pain.

Motor symptoms may include motor weakness or muscle fatigue or atrophy. Patients typically complain about impaired motor abilities after the onset of sensory symptoms, but exceptions are not uncommon.

As with sensory symptoms, motor weakness often involves the distal musculature initially, though it may have begun with weakness when the toes were in flexion or exten-

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sion. Motor weakness is usually more prominent in extensor muscles than in the flexor muscles (ie, walking on one's heels is affected earlier than walking on one's toes). Motor weakness may progress proximally.

A loss of muscle mass (atrophy), abnormally frequent and painful cramps, or fasciculations are strongly suggestive of lower motor neuron involvement. Patients with these symptoms may have difficulty in ambulating, problems with manual dexterity, or both.²

When taking notes on personal and family medical history, it is important to document the age of symptom onset, the progression of symptoms over time, any similarities to other family members, comorbidities, and the anatomic pattern of symptom involvement.

Identification of exacerbating and alleviating factors can help physicians localize patient complaints. Symptoms involving a specific dermatome suggest a nerve root problem. Conversely, sensory involvement limited to one limb, in a territory not conforming to a particular dermatome, may suggest the involvement of a particular peripheral nerve.

Polyneuropathy

Polyneuropathies usually present with a symmetric stocking-glove pattern of symptoms that do not respect individual peripheral nerve or dermatomic areas.

Symptoms in children and young adults—particularly if there is a family history suggestive of this dysfunction—may indicate a hereditary neuropathy.

A chronic or slowly progressive course may also suggest a hereditary, metabolic, or pathologic cause. Acute onset of symptoms—particularly involving the territory of a specific peripheral nerve or root—may suggest spinal compression or trauma, or an ischemic injury.

Physical Examination

All patients presenting with the complaints detailed in the previous section should receive a complete physical examination to identify comorbid conditions that may be causative of sensory or motor symptoms.

In particular, findings that suggest the source of dysfunction might be an underlying metabolic disease (eg, thyroid condition, diabetes mellitus), nutritional deficiency (alcoholism), malignant disease, or inflammatory disorder (eg, lupus, sarcoidosis, Sjögren's syndrome) can quickly narrow the focus of the differential diagnosis.

Early in the course of certain PNS disorders, sensory symptoms are prominent and signs of peripheral neuropathy may be subtle. However, most patients with sensory neuropathies will have some degree of neurologic dysfunction when diagnostic testing is performed. When noting personal and family medical history, the goal of the physician should be to define anatomically and chronologically the areas of the body that have been affected.

Peripheral neuropathies have a characteristic pattern of findings on physical examination. In mononeuropathy, sensation should be decreased only in that nerve's distribution. Sensory findings owing to a median neuropathy with compression at the wrist (ie, carpal tunnel syndrome), for example, classically involve nocturnal paresthesias with decreased sensation over the palmar surface of the first three fingers—but sparing the thenar eminence.³

With mononeuritis multiplex (MNM) or multifocal mononeuropathy, sensory deficits localized to multiple individual peripheral nerves will be found simultaneously. In cases of mononeuropathy or MNM, typically all sensory modalities are affected (ie, pinprick, temperature, vibration, and touch).

Polyneuropathies can imply systemic illness. Sensation usually is decreased in a stocking-glove pattern, but sometimes there is a disproportionate loss of certain sensory modalities. Patients with small-fiber sensory (unmyelinated) neuropathy (SFSN) may have decreased sensitivity to pinprick and temperature sensory modalities, but their response to vibration remains relatively normal. Conversely, patients with large-fiber neuropathies may first have vibration or proprioception preferentially affected.¹

Deep-tendon reflexes (DTRs) are often decreased or absent in PNS dysfunction. Hyporeflexia implies dysfunction of large myelinated fibers representing the afferent limb of muscle spindle-initiated reflexes. If the pathologic process is limited strictly to small sensory fibers, DTRs may not be affected.² As with the sensory examination, documenting DTR abnormalities can help physicians localize the site of PNS dysfunction.

Orthopedic findings such as pes cavus (talipes), "hammer toe," and high arches are seen in many cases of neuropathy that are known to be of hereditary origin.

Motor findings on examination imply motor weakness. Affected muscles may be within the myotome of an individual nerve (eg, "foot drop" with a peroneal nerve injury) or they may involve distal muscles in a symmetric fashion. Thus, motor findings suggest a more diffuse dysfunctional progression. Classically, disease of the PNS causes motor weakness, muscle atrophy, and fasciculations to varying degrees of severity.

Motor symptoms are usually found in combination with sensory deficits. Isolated motor findings do occur, however, and suggest that the disease process may be limited to the ventral horn or roots. Such findings may represent acute inflammatory demyelinating polyradiculoneuropathy (AIDP), amyotrophic lateral sclerosis (ALS), or polio, among other disease entities.⁴

In summary, on physical and sensory examination, patients with mononeuropathies usually demonstrate impaired sensation, motor weakness, muscle atrophy, and decreased DTRs in some combination. The site of dysfunction is localized strictly to the area innervated by the dysfunctional peripheral nerve. Alternatively, patients with radiculopathies will usually

have paresthesias, sensory and motor findings, and decreased DTRs in a dermatomal or myotomal pattern. Patients with polyneuropathies usually demonstrate a symmetric stocking-glove pattern of sensory deficits, decreased distal DTRs, and sometimes motor weakness.

Types of Neuropathy

Neuropathies can be defined using any number of classification schemes. The following scheme may be helpful.

Anatomic Neuropathies

Anatomic neuropathies can be classified based on the location of the causative lesion within the neuroaxis and divided into one of three groups: mononeuropathy, radiculopathy, or polyneuropathy. The differences among these classifications follow.

■ **Mononeuropathy**—This classification of anatomic neuropathy implies dysfunction of a single peripheral nerve (eg, median neuropathy). Any peripheral nerve can be affected, but most often those with superficial courses (eg, median, ulnar, radial, and peroneal) are involved.

Anatomic mononeuropathies can lead to paresthesias, sensory loss, and motor weakness—with or without atrophy and fasciculations—but they all involve areas specifically innervated by the dysfunctional peripheral nerve.

As noted, one special form of mononeuropathy is MNM, in which multiple mononeuropathies occur simultaneously.

■ **Radiculopathy**—This classification of anatomic neuropathy implies that a lesion involves the ventral and/or dorsal peripheral nerve roots proximal to their union, which forms the individual spinal nerves.

Radicular lesions cause motor weakness, sensory loss, paresthesias, and decreased DTRs in any combination. The characteristic finding with radicular lesions is loss of sensation or physical strength and/or DTRs in a dermatomal and myotomal pattern.

Radicular lesions are often painful because of impingement on the dorsal roots as the PNS enters the spinal cord. Certain positions (sitting) and activities (sneezing, straining) often exacerbate symptoms in patients with radiculopathy. As previously noted, radiculopathies are not length-dependent.¹

■ **Polyneuropathy**—This classification of anatomic neuropathy describes the simultaneous dysfunctional involvement of multiple peripheral nerves. Polyneuropathies are usually bilateral and symmetric, demonstrating the classic distal-to-proximal pattern of sensory loss and/or motor weakness.

Polyneuropathies are almost always length-dependent and commonly involve the distal portions of the lower extremities first. At the ankles, DTRs may be decreased, a symptom that can also indicate underlying systemic disease.

As noted, one special form of polyneuropathy is known as *small-fiber sensory neuropathy (SFSN)*. This unmyelinated form of polyneuropathy is the most common type of painful neu-

ropathy in patients over the age of 50,¹ and patients typically present with painful, “burning” feet. Although no cause is found for SFSN in a large percentage of patients, known causes include diabetes mellitus, amyloidosis, toxic exposure, and inherited sensory and autonomic neuropathies.¹ Diagnosis of SFSN is made on the basis of the clinical history and neurologic examination, electromyography that includes normal nerve conduction studies (EMG/NCS), and abnormal specialized studies of small-fiber function such as quantitative sensory testing (QST), sudomotor index testing, and autonomic testing.^{1,5}

Pathologic Neuropathies

Neuropathies can also be classified by the primary pathologic process affecting the nerves. Pathologic neuropathies can be further divided into two broad classes: demyelinating and axonal pathologic neuropathies. The differences between these two classifications and a description of each class’ subcategories and specific clinical-diagnostic manifestations follow.

■ **Demyelinating**—The classification of demyelinating pathologic neuropathies encompasses those PNS disorders where there is loss of the myelin sheath surrounding nerve axons. Demyelination occurs in a segmental or “patchy” fashion. If the loss of myelin is severe, nerves may be unable to conduct an action potential known as *conduction block*.

There are two subcategories of demyelinating pathologic neuropathies, hereditary and acquired. The differences between these two subcategories follow.

□ **Hereditary**—Demyelinating neuropathies can be categorized as hereditary, as in instances of Charcot-Marie-Tooth disease type 1 (CMT 1). In general, the number of inherited disorders described in the literature continues to increase as new genetic mutations are identified and defined. Although a discussion of every disorder of this category of demyelinating pathologic neuropathy is beyond the scope of this review, some general principles may be helpful to the primary care physician who is seeing a patient that is presenting for the first time with symptoms of this type of PNS disorder.

As noted, family history of similar motor symptoms is an obvious clue and the first place to begin looking for useful information. Hereditary neuropathies can progress very slowly, but symptom onset usually dates to childhood or young adulthood.

Hereditary neuropathies most commonly occur in an autosomal or X-linked fashion, although sporadic cases are not uncommon. Hereditary demyelinating neuropathies result from perturbations in the genetic code for certain neural proteins.

Patients may present with atrophy of distal muscles of the calves and feet (peroneal atrophy). These patients may also have a history of orthopedic changes (eg, talipes, “hammer toe,” and high arches).²

Additionally, because of repeated episodes of demyelination and remyelination, results from nerve biopsies will show “onion bulbs.” In such cases, clinicians may also note palpably enlarged nerves.

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Diagnosis is made after a consideration of family and personal history, physical examination of the patient and other affected family members, electrodiagnostic (EDX) testing, and genetic testing.

Results from EDX testing that are positive for hereditary neuropathy will show diffuse slowing of conduction velocities, prolonged distal latencies, and increased duration of nerve conduction potentials without conduction block. Nerve action potentials typically have normal or slightly decreased amplitudes in the demyelinating range.³

Treatment for patients with hereditary neuropathy is mainly supportive. Genetic testing and family counseling may be useful options for certain patients.

□ *Acquired*—Demyelinating neuropathies classified as acquired include acute idiopathic polyneuritis (ie, Guillian-Barré syndrome),^{2,6} chronic inflammatory demyelinating polyneuropathy (CIDP),⁷ and multifocal motor neuropathy (MMN) with conduction block.⁸ These PNS disorders result from immune-mediated destruction of the myelin sheaths.

Four acquired demyelinating neuropathies are detailed in the following paragraphs: AIDP, CIDP, MMN, and demyelinating neuropathies that are the result of monoclonal gammopathy.

Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is usually monophasic. Its classic presentation is as an acute ascending paralysis with a loss of reflexes.⁶ This PNS dysfunction most often occurs 1 to 3 weeks following a nonspecific viral upper respiratory infection or gastroenteritis, at the time of human immunodeficiency virus (HIV) seroconversion,⁹ or after vaccinations or surgery.

This acquired form of demyelinating neuropathy can be painful because of the involvement of the peripheral nerve's dorsal roots. Additionally, this PNS disorder can be life threatening, as it is accompanied in some patients by severe bulbar, autonomic, and respiratory dysfunction.

In patients with AIDP, close monitoring of respiratory function, blood pressure, and heart rate are recommended, as is the need for aggressive pain management. In fact, pain control often requires intensive care unit (ICU)-level observation.

Results of EDX testing for patients with AIDP show diffuse slowing of action potential conduction velocities, prolonged distal latencies, and delayed or absent F waves. Conduction blocks are typically noted, however. Treatment with intravenous immunoglobulin (IVIg) or plasma exchange speeds patient recovery, and studies find that, over several months, most patients recover well.¹⁰

Although steroids are considered an effective treatment option for patients with CIDP, that treatment modality is not recommended for patients with AIDP because steroids have not been proven efficacious for that clinical application.^{10,11}

Chronic inflammatory demyelinating polyneuropathy (CIDP) can be progressive or polyphasic.⁶ Diagnosis can be difficult

because of CIDP's varied clinical phenotypes, multifocality, and predilection for proximal nerve segments.^{7,12} Patients' bulbar and respiratory functions are typically spared.

Similar to findings in AIDP, some patients with CIDP usually have progressive—usually distal-to-proximal—motor weakness, loss of DTRs, and sensory loss in stocking-glove pattern. The disease process is considered chronic, and is accordingly diagnosed as CIDP, if symptoms continue for at least 2 months.

Results of EDX testing for patients with CIDP indicate diffuse slowing of action potential conduction velocities, prolonged distal latencies, prolongation of F waves, and/or the presence of conduction block or temporal dispersion.⁷

An effective treatment option for CIDP is immunosuppressive steroidal agents (eg, prednisone),¹³ For maintenance therapy, IVIg or plasma exchange is recommended, though some clinicians may reserve these modalities to treat any exacerbation of symptoms.^{10,11}

Multifocal motor neuropathy (MMN) is characterized by severe multifocal demyelination of PNS motor nerves. This PNS disorder most often presents as a progressive, mostly distal, asymmetric limb weakness preferentially involving the upper extremities. In fact, MMN differs from CIDP in that it is often asymmetric and affects the upper extremities first. Patients with MMN may have IgM anti-GM1 antibodies in their sera.⁸

The results of EDX testing should also show multifocal conduction block.

Treatment with IVIg is recommended.^{10,13} There is no evidence indicating that patients with MMN respond well to treatment with either steroids or plasma exchange.⁸

The last demyelinating neuropathies reviewed in this article are those that are the result of a *monoclonal gammopathy*. Researchers have found that gammopathies may be the result of elevated production of IgM, IgG, or IgA by plasma cell clones.^{14,15}

Approximately two-thirds of cases of gammopathies are initially diagnosed as monoclonal gammopathy of uncertain significance.¹⁶ The remaining one-third of cases are associated with multiple myeloma, lymphoma, amyloidosis, or other malignant disease.¹⁶

Patients with gammopathies require lifelong care because of the high risk of developing a primary malignancy. Neuropathies secondary to IgM-associated gammopathy are considered to be more severe and typically do not respond well to immunosuppressive therapy, IVIg, or plasma exchange.

IgG and IgA gammopathies are not as well studied, but they are thought to be more responsive to therapy than are IgM-associated gammopathies.¹⁴

■ **Axonal**—Although axonal neuropathies may also be inherited, as in CMT type 2 (ie, hereditary motor sensory neuropathy type 2), PNS disorders in this class of demyelinating pathologic neuropathies are characterized by a progressive

loss of nerve function because of injury to the neuron cell body or axon. Therefore, this type of PNS dysfunction is classified separately.

Most commonly, axonal neuropathies are acquired illnesses that appear as symmetric polyneuropathies secondary to underlying systemic disease.

□ *Critical illness polyneuropathy (CIP)*—An example of an acquired axonal neuropathy that practitioners may see in the ICU setting is CIP. Sepsis is the main cause of CIP in this clinical setting as it is the result of sepsis-mediated damage to the peripheral nerves and muscles.

Critical illness polyneuropathy is characterized by motor weakness, muscle atrophy, and difficulty weaning from ventilatory support. However, CIP is monophasic and self-limited once the underlying condition is adequately treated.^{17,18}

Etiologic Neuropathies

Neuropathy can also be defined on an etiologic basis as any of the following types: compressive, traumatic, hereditary, metabolic, nutritional, infectious, autoimmune or inflammatory, and toxin or medication induced.

■ **Compressive**—Nerve injury that is the result of compression most often involves nerves that have a superficial course. Virtually any peripheral nerve can be involved.

The most common entities likely to be seen include: median neuropathy at the wrist (ie, carpal tunnel syndrome [CTS]), ulnar neuropathy at the elbow, radial neuropathy at the spiral groove or wrist, peroneal neuropathy at the fibular head, and compression of the lateral femoral cutaneous nerve in the inguinal area.

Compressive etiologic neuropathy in patients may also be accompanied by paresthesias, sensory loss, motor weakness, and muscle atrophy in the distributions of the affected peripheral nerves.

□ *Carpal tunnel syndrome (CTS)*—A condition that has received wide media coverage in recent years. This syndrome results from compression of the median nerve as it courses through the carpal tunnel of the wrist. Patients may have CTS as a result of metabolic disease (eg, diabetes, hypothyroidism) or because of structural dysfunction (eg, ganglion cyst).

Maintaining the wrist in prominent flexion or extension (eg, when driving, sleeping, or typing) exacerbates symptoms, which include some combination of paresthesias and pain (particularly at night), numbness of the fingers, and weakness in grip strength.

Results from physical examinations may be normal or show sensory loss involving the palmar surface of the first three fingers *but sparing the thenar eminence*.³ This is an important point. Sensory loss over the thenar eminence implies that the lesion is proximal to the wrist. Weakness of grip, with atrophy of the thenar eminence, is seen later in the progression of this syndrome.

Symptoms of CTS may be reproducible by one or both of the following methods: Tinel's sign, with percussion of the median nerve at the carpal tunnel, or Phalen's maneuver, with flexion of the wrists to 90 degrees for more than 1 minute.

Sensory fibers of the PNS are often preferentially affected by CTS. Results of EDX testing for patients with CTS will initially show slowing of median nerve conduction velocities across the carpal tunnel with prolonged distal latencies. Axon loss, resulting in decreased amplitudes with subsequent denervation changes, are seen later in the progression of this dysfunction.³

Conservative treatment includes rest, splinting to maintain the wrist in neutral position, and additional therapeutic modalities under the direction of an experienced occupational therapist that specializes in hand therapy. More aggressive treatment methods include steroid injections and surgical release for the carpal tunnel.

□ *Ulnar*—Compressive neuropathy of the ulnar at the elbow is the second most common compressive lesion of the PNS. The most frequent cause of ulnar neuropathy is cumulative compressive injury caused by leaning or resting on the elbows.¹⁹

The ulnar nerve passes through the ulnar groove formed by the olecranon process laterally, the medial epicondyle of the humerus medially, and a band of fibrous tissue superficially. Inflammation of the fibrous tissue can lead to compression injuries in this area.

Ulnar neuropathy at the elbow manifests with paresthesias, numbness, and/or sensory loss of the fourth and fifth fingers of the hand. Motor weakness in finger adduction and wasting of intrinsic muscles of the hand occur later in the progression of this PNS dysfunction.³

As with CTS, evaluation of ulnar neuropathy requires EDX testing to assist in localizing the lesion. Also, physicians will find EDX testing useful for ruling out ulnar neuropathy at the wrist, polyneuropathy, brachial plexopathy, or cervical radiculopathy.

Recommended therapy for ulnar neuropathy at the elbow includes conservative measures such as active avoidance of leaning and resting on the elbows. More aggressive treatment methods include steroid injections into the cubital tunnel and surgical release for the ulnar tunnel.¹⁹

□ *Radial*—The effects of radial neuropathies can be dramatic depending on the site of compression. Relatively minor sensory symptoms involving the dorsal aspect of the lateral hand can be seen with compression of the superficial radial sensory nerve caused by tight-fitting watches, bracelets, or handcuffs.

Complete paralysis of wrist and finger extension appears with more proximal radial nerve lesions. "Saturday night palsy" can result from prolonged compression of the proximal radial nerve at the spiral groove caused by resting the forearm on a hard surface such as the edge of a bathtub or back of a chair. Patients may demonstrate "wrist drop" owing to paralysis of wrist and finger extensors innervated by the peripheral radial nerve.

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Lesions at, or distal to, the proximal radial nerve's spiral groove will spare elbow extension and the triceps reflex. In contrast, fractures of the humerus or other lesions of the radial nerve proximal to the spiral groove may result in paralysis of the triceps as well.³

Identification of a Tinel's sign may locate the site of compression injury to the peripheral nerve.²⁰ The results of EDX testing can be a helpful addition to the findings of physical examinations in confirming the localization of the lesion.

Treatment is usually conservative unless a humeral fracture is involved. Splinting of the wrist and the services of an experienced occupational therapist that specializes in hand therapy are often helpful.²⁰

□ *Peroneal*—The peroneal nerve is superficial as it courses around the fibular neck. Because of its location, it is highly susceptible to injury. Compression of the peroneal nerve at the fibular head usually manifests as "foot drop."

Weakness of dorsiflexion and eversion may result in patient complaints of falling because they have caught their toes while climbing stairs or walking on thick rugs. Inversion of the foot is preserved. Patients with foot drop have a characteristic gait that requires the proximal leg to be lifted high while the foot slaps onto the ground.²

Personal medical history is important in diagnosing these patients, as similar findings may be seen with an L5 disk lesion.⁵ Electrodiagnostic evaluation, therefore, can be helpful in diagnosis, particularly if the patient has concurrent complaints of back pain.

Common causes of compressive peroneal neuropathy include sitting with the legs crossed, improper positioning or cushioning of the legs during surgical procedures, poor-fitting casts, significant weight loss in obese patients, and insufficient padding for patients seated in wheelchairs.

In most cases, therapy consists of supportive measures. Properly fitted orthotics can significantly improve patients' ability to ambulate.

□ *Femoral*—The lateral femoral cutaneous nerve is part of the lumbar plexus formed by peripheral nerves with roots in the inguinal area (ie, L2 and L3). This nerve provides sensation to the anterior and lateral aspect of the proximal thigh.

Patients with compressive femoral neuropathy may complain of numbness or paresthesias (meralgia paresthetica) in the inguinal distribution. As the nerve affected is purely sensory, no motor weakness is seen.

This type of neuropathy is most frequently seen in patients who are obese or pregnant. Also affected are those who wear tight-fitting pants that can lead to compression of the femoral nerve as it passes over the inguinal ligament.

Electrodiagnostic testing is not necessary in the evaluation of these patients unless physicians note motor weakness or changes in DTRs, both of which suggest the involvement of the lumbar plexus or a radiculopathy.

Treatment is mainly supportive as eliminating the offending agent is usually curative.²

■ **Trauma**—Traumatic nerve injury is usually obvious and can be diagnosed by history alone.

Trauma may lead to complete nerve transection or partial peripheral nerve injury. Evaluation with EDX testing is essential for gauging the extent of PNS injury and patients' prognosis for recovery. Because wallerian degeneration can last 4 to 7 days, however, the results of EDX testing performed in the acute phase of traumatic peripheral nerve injury may show only decreased PNS recruitment with otherwise normal findings. Ten to 14 days after the acute phase of traumatic injury, the results of EDX testing are likely to be more revealing and can provide valuable prognostic information.

■ **Hereditary**—Hereditary neuropathies are suspected in cases where a family history of similar symptoms is present. In fact, studies suggest that many patients referred to tertiary centers for evaluation of "unclassified neuropathy" are ultimately diagnosed with a hereditary disorder.³ However, the appearance of hereditary neuropathy can be sporadic and not easily diagnosed. Features of the most common hereditary neuropathies (eg, CMT 1) were discussed previously.

Personal and family medical history, neurologic examination, and EDX testing in combination with genetic testing or nerve biopsy evaluation may be required before a suspected diagnosis of hereditary neuropathy can be given.

■ **Metabolic or Nutritional**—Metabolic and nutritional derangements can lead to neurologic disease. Diabetes mellitus is the most common cause of metabolic neuropathy in the United States.²¹

A slow progressive, usually symmetric, polyneuropathy is often found on neurologic examination when the cause of neuropathy is metabolic or nutritional. The results of neurologic examination usually demonstrate the stocking-glove pattern of sensory changes, distal weakness, and loss of ankle reflexes.

■ **Infectious**—Although an in-depth discussion of neuropathies caused by infectious agents is well beyond the scope of this review, we will outline the following infectious causes of neuropathy briefly: Lyme disease, syphilis, HIV, varicella zoster virus (VZV), leprosy, tuberculosis, diphtheria, and botulism. Also, as previously noted, CIP secondary to sepsis can lead to diffuse PNS dysfunction.¹⁷

□ *Lyme disease (borreliosis)*—Lyme disease is caused by the organism *Borrelia burgdorferi* and is transmitted by tick bite (*Ixodes scapularis* and *I pacificus*).

Classically, Lyme disease begins with the appearance of a skin lesion (ie, erythema chronicum migrans) at the site of the tick bite. This lesion may be followed by a systemic flu-like illness. The involvement of the CNS is manifested in meningoencephalitis or transverse myelitis.

Diagnosis of neuropathy from Lyme disease can be challenging, as many patients do not recall having been exposed.

In addition, Lyme disease can manifest as virtually any type of PNS lesion. Lyme disease is one of the more common causes of unilateral facial nerve paralysis (ie, Bell's palsy). A painful polyradiculopathy can result from involvement of multiple peripheral nerve roots. Lyme disease should be considered in the differential diagnosis of MNM.

Diagnosis is made by demonstrating Lyme antibodies in the serum and cerebrospinal fluid, or by locating Lyme DNA through polymerase chain reaction testing.

Preferred treatment options for neuropathies caused by Lyme disease include administering a third-generation cephalosporin, amoxicillin, or doxycycline monohydrate.²²

□ *Syphilis*—A sexually transmitted disease caused by infection with *Treponema pallidum*. Again, virtually any part of the CNS can be involved. Once considered a neurologic curiosity, the threat of syphilis has reemerged owing to the emergence of the HIV epidemic.^{22,23}

□ *HIV infection*—The neurologic complications of HIV infection are protean and include opportunistic infections, lymphomas, and peripheral neuropathy.²⁴ Meningoencephalitis may occur at the time of seroconversion. Acquired immunodeficiency syndrome (AIDS) dementia complex is a known CNS complication of that syndrome.^{24,25}

An inflammatory, demyelinating neuropathy may be the first neurologic complication of HIV in cases where CD4 cell counts remain relatively high.⁹ A distal, symmetric, sensorimotor polyneuropathy that is often painful becomes more prevalent as the disease progresses.⁹

Since many of the available antiretroviral medications used to treat AIDS cause similar symptoms as are found with this type of neuropathy, however, defining the actual causative process of the neuropathy can be complicated.²⁶ In fact, owing to the widespread use of highly active antiretroviral therapy (HAART) in the treatment of patients with AIDS, the incidence of HIV-associated sensory polyneuropathy is decreasing. In contrast, the incidence of antiretroviral drug-induced neuropathy has increased. Overall, because HIV-infected patients are living longer, the prevalence of HIV peripheral neuropathy is increasing.^{24,25}

□ *Varicella zoster virus (VZV)*—Thought to reside in the dorsal root ganglia, VZV usually manifests as herpes zoster in elderly or immunocompromised patients. Herpes zoster represents the reactivation of latent peripheral nerve infection.

Initially, patients with neuropathy caused by VZV complain of painful, erythematous rashes that are usually confined to a thoracic dermatome or trigeminal nerve distribution. After 3 to 5 days, a vesicular eruption occurs in the same areas.

The recommended pharmacologic treatment is acyclovir sodium, though prednisone therapy is also often added to patients' treatment plans, particularly for elderly patients, as it is thought to reduce the risk of developing postherpetic neuralgia.²²

□ *Leprosy*—Also known as *Hansen's disease*, leprosy is caused by

the etiologic agent *Mycobacterium leprae* and results in the infection of individual Schwann's cells, leading to demyelination.

In patients with neuropathy as a result of leprosy, pain fibers are particularly affected and result in the loss of sensation and tissue injury.

□ *Tuberculosis*—Caused by *Mycobacterium tuberculosis*, tuberculosis leads to granulomatous inflammation with injury to cutaneous sensory nerves, often in a patchy distribution. Mycobacterial infection can result in MNM.²²

□ *Diphtheria*—Neuropathy caused by diphtheria results in neurologic damage from exposure to the exotoxin of *Corynebacterium diphtheriae*. Patients experience a painful, symmetric sensorimotor polyneuropathy.²²

□ *Botulism*—Caused by *Clostridium botulinum*, botulism affects the presynaptic neuromuscular junction, inhibiting the release of acetylcholine, which leads to a flaccid paralysis with a loss of reflexes.

We note botulism, in particular for this section, because it can mimic a severe polyneuropathy.

Botulism in infants (aged ≤ 12 months old) occurs after the ingestion of certain foods such as honey. Because the intestinal flora in infants is not fully developed, *C botulinum* germinates and produces a toxin that results in a host of symptoms that, when combined, are described as "floppy baby." Other symptoms include poor sucking, swallowing, and respiratory difficulty.

Among other age groups, botulism occurs after the ingestion of the same toxin when it is already present in foods that are improperly prepared or refrigerated. Classically, botulism results in a descending flaccid paralysis, with involvement of papillary responses and prominent bulbar and respiratory dysfunction.

Treatment for both populations consists of supportive therapy. Patients may need ICU management, in some cases, however.²²

■ **Autoimmune or Inflammatory**—Patients can have any number of neurologic complications as a result of an underlying autoimmune disorder. In addition to AIDP, CIDP, and MMN, other connective tissue processes (eg, systemic lupus erythematosus, Sjögren's syndrome, and rheumatoid arthritis) can cause a mononeuropathy, radiculopathy, or polyneuropathy.

Rheumatologic disease is thought to damage nerves by inducing a vasculitic process. Vasculitis results in patchy areas of ischemic injury through its inflammatory effects on microscopic vessels of the vasa nervorum.²⁷

Rheumatologic evaluation and referral to a neurologist is warranted in most cases where autoimmune or inflammatory causes of PNS dysfunction are suspected.

■ **Toxin or Medication Induced**—Prolonged exposure to certain industrial chemicals, radiation, and medications can result in injury to the peripheral nerves. The causes of PNS disorder usually present as a symmetric polyneuropathy.

□ *Medication induced*—The medications used to treat life-threat-

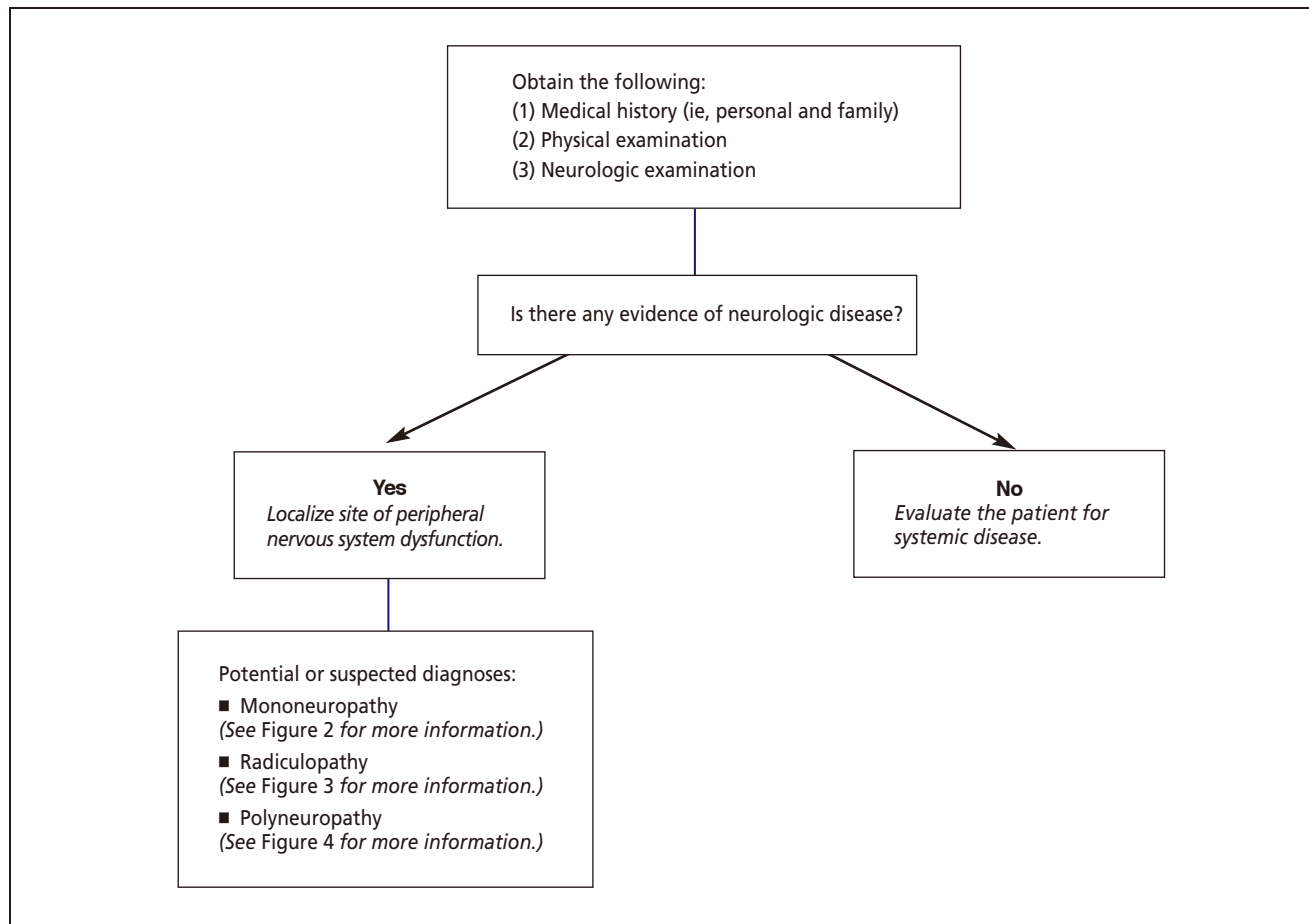


Figure 1. Proposed algorithm for evaluation of peripheral neuropathy.

ening conditions such as HIV/AIDS and cancer are common offenders. Specifically, HAART, which is used in the treatment of HIV infection, adversely affects mitochondrial function and inhibits DNA polymerase activity, inducing neuropathy in some patients.

Chemotherapeutic agents such as cisplatin, oxaliplatin, and carboplatin can induce dose-, length-, and time-dependent axonal polyneuropathies that may have purely sensory symptoms and are often painful.^{28,29}

Administration of tacrolimus can lead to demyelination and can mimic AIDP or CIDP.²⁸ Vincristine, paclitaxel (Taxol), and suramin hexasodium more commonly cause mixed sensorimotor neuropathies, with or without concomitant autonomic nervous system involvement.

Patients with premorbid diabetes or inherited neuropathies probably carry an increased predisposition to chemotherapy-induced neurologic dysfunction.²⁹

□ *Toxin induced*—Unfortunately, alcohol abuse is likely the most common cause of toxic PNS dysfunction. Long-term

alcohol abuse can produce cognitive difficulties, unstable gait, poor coordination, cramps, and myalgia. Gait and coordination difficulties can result from cerebellar disease alone, though, in many cases, there is a superimposed axonal sensorimotor polyneuropathy, an alcoholic myopathy, or both.

Alcohol is a potent inhibitor of protein synthesis and is toxic to nerves and muscles, independent of the common comorbidities of malnutrition and liver disease found in these patients.³⁰

Patient Evaluation

Most patients with neurologic complaints initially consult with their family physicians. Evaluation of suspected neuropathy begins with a complete personal and family medical history and a physical examination. A thorough interview and examination may reveal stigmata of systemic diseases, exposure to toxic agents, or genetic predisposition.

Neurologic examination should focus on defining the pattern of motor weakness, sensory loss, and/or changes in DTRs. This information should assist the evaluating physi-

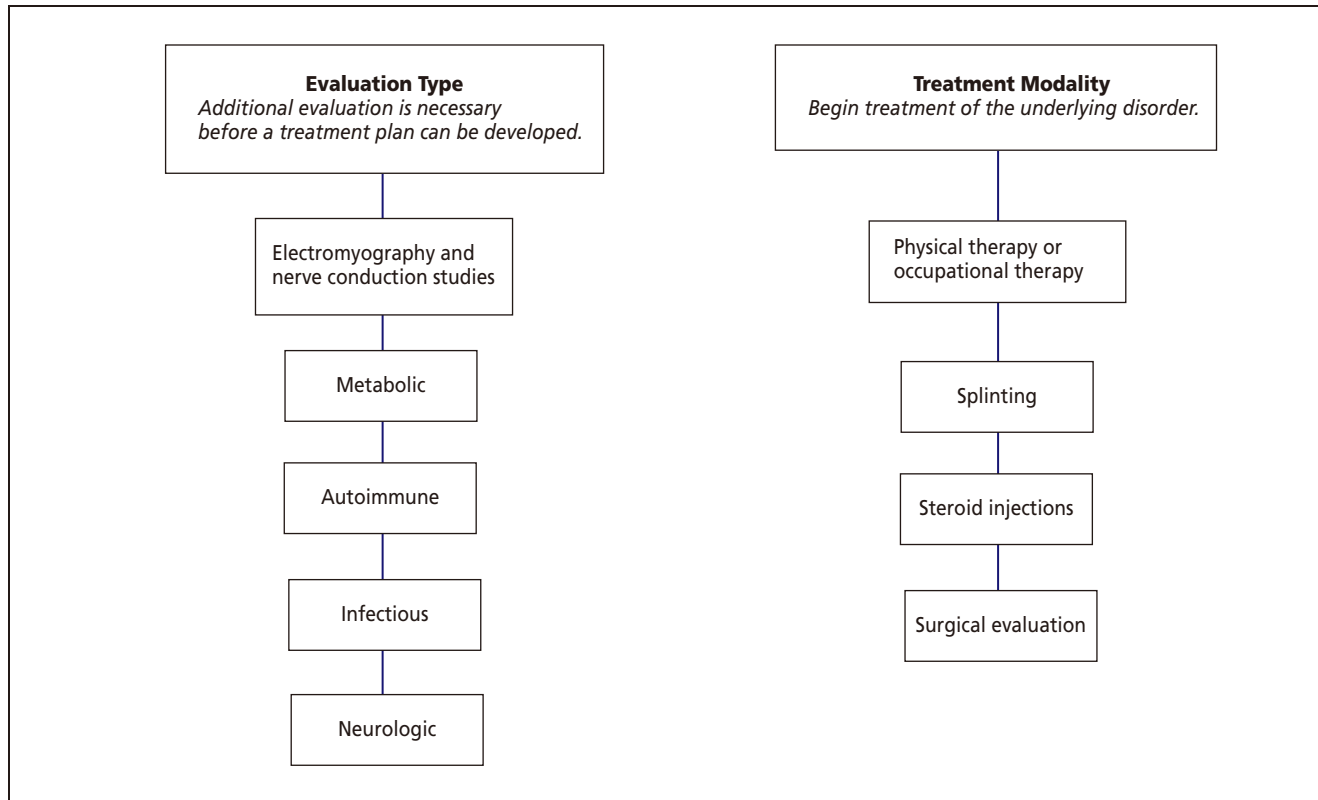


Figure 2. Evaluation and treatment of suspected mononeuropathy (eg, carpal tunnel syndrome, ulnar neuropathy at the elbow).

cian in determining the type of neuropathy present (ie, mononeuropathy, radiculopathy, or polyneuropathy). By better defining the general type of neuropathy in this way, physicians can better tailor additional diagnostic evaluations to pinpoint possible causes and appropriate treatment options (Figure 1).

In most cases, patients should undergo basic laboratory testing, including complete blood cell count with platelets, electrolyte and glucose levels, renal function tests, liver function tests, erythrocyte sedimentation rate, antinuclear antibody analysis, urinalysis, thyroid function tests, B₁₂ and B₆ levels, Lyme antibodies, and rapid plasma reagin. A chest radiograph should also be performed for patients with risk factors for malignancy, infection, or granulomatous disease.

Results from these laboratory studies will provide a general screening for underlying metabolic, inflammatory, and autoimmune disorders as well as potential malignant or infectious processes. Abnormalities should be pursued appropriately with additional laboratory studies (eg, hemoglobin A_{1c} levels, oral glucose tolerance testing, serum protein electrophoresis) or referral to a specialist. Early detection of underlying derangements is important, as treatment methods are probably most effective early in the course of neuropathy.²¹

In patients with evidence of mononeuropathy or radiculopathy, imaging the appropriate level of the neuroaxis is warranted. In general, magnetic resonance imaging (MRI) is the preferred diagnostic method as it provides better anatomic resolution. For patients who cannot undergo MRI testing (eg, those with pacemakers or claustrophobia), computed tomographic scanning is a logical alternative. Structural abnormalities identified through imaging necessitate referral to an orthopedist or neurosurgeon.

Other useful diagnostic tools in the assessment of PNS dysfunction include those performed in EDX testing, such as electromyography and nerve conduction studies (EMG/NCS) and/or quantitative sensory testing (QST). Of these methods, EMG/NCS is currently the most useful. When performed by experienced and trained neuromuscular specialists, EMG/NCS can define the underlying disease process (ie, axon loss versus demyelination) and can provide helpful data for localizing the site of PNS dysfunction and prognostic purposes.

Quantitative sensory testing is usually done in combination with EMG/NCS for patients whose symptoms are consistent with SFSN.¹ Evoked potential testing is usually of little help in the evaluation of peripheral neuropathies.

Nerve biopsies may be useful in the evaluation of demyeli-

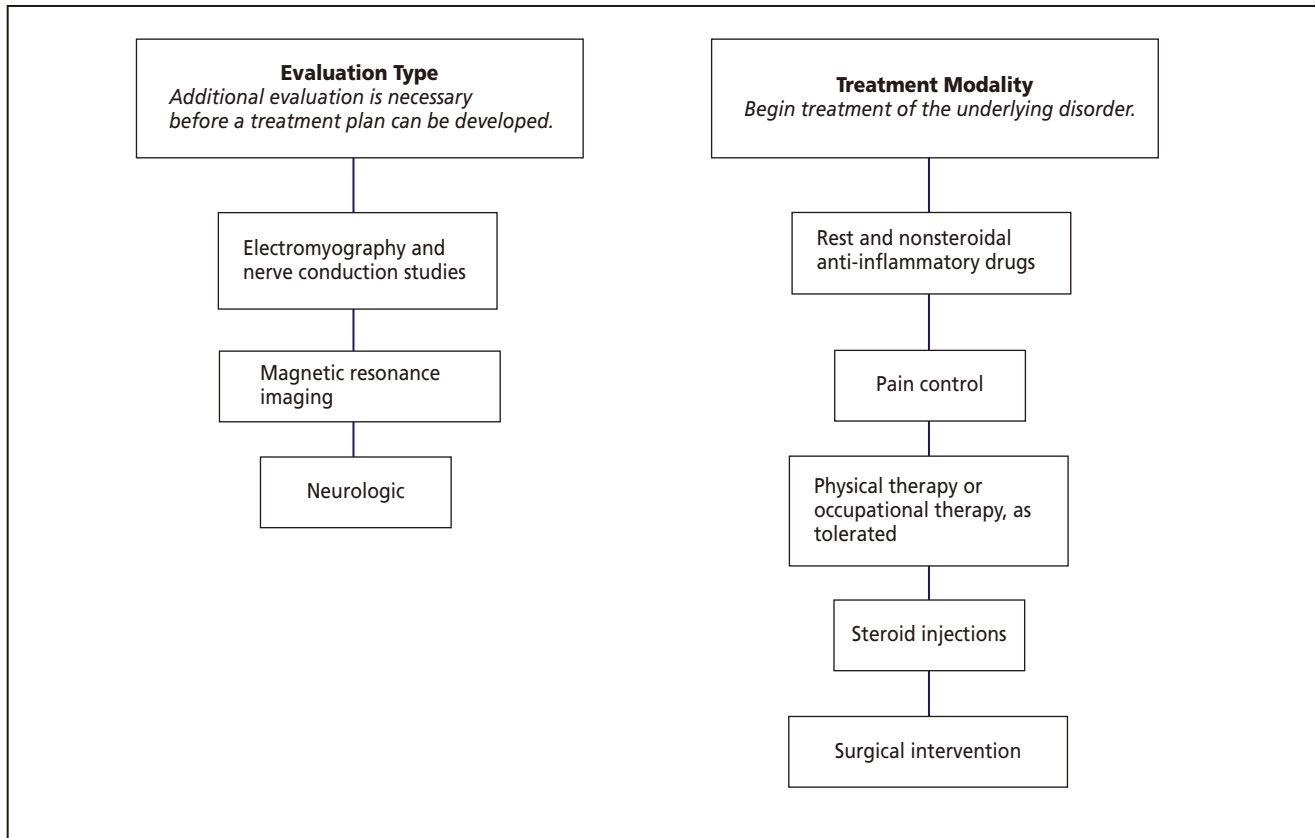


Figure 3. Evaluation and treatment of suspected radiculopathy.

nating or vasculitic processes. Superficial pure sensory nerves such as the sural nerve or superficial radial sensory nerves routinely undergo biopsy evaluation. Nerve biopsy is a diagnostic method that should be reserved until after a specialist’s evaluation in most cases.

Treatment

Treatment plans should be tailored to the patient and the type of neuropathy discovered. In general, identification and treatment of any underlying systemic disorder is the initial interventional goal. In some cases (eg, neuropathies associated with diabetes mellitus or renal disease), there may be chronic disorders that require long-term care and may respond incompletely to therapy.¹

Mononeuropathies are most commonly the result of compression or trauma. Compressive neuropathies are typically treated initially with conservative therapy. Carpal tunnel syndrome and ulnar neuropathy at the elbow are the two compressive entities most commonly seen. Other compressive neuropathies such as superficial peroneal neuropathy resulting in foot drop and wrist drop owing to radial nerve compression (ie, Saturday night palsy) can be dramatic but are less common. For

those with atypical presentations or less than satisfactory improvement, further evaluation by a neurologist may be warranted.

Carpal tunnel syndrome may improve with rest and refraining from exacerbating activities. Maintaining the wrist in a neutral position with soft wrist supports is often helpful. For more severe cases of CTS, steroid injections into the carpal tunnel may be considered. Occupational therapy by a therapist specializing in hand therapy is also beneficial. For patients with CTS who do not respond to these therapies or who have significant muscle wasting, evaluation by a neurologist or an orthopedist for surgical release of the carpal tunnel is warranted.³

Treatment of ulnar neuropathy at the elbow begins with avoidance of prolonged periods of resting on the elbows or maintaining the elbows in a flexed position. Padding of the elbows may be beneficial. Patients who fail to respond to conservative therapy may require surgical evaluation for ulnar tunnel release.¹⁹

Traumatic mononeuropathies should be evaluated by a neurologist with the assistance of EMG/NCS testing for better localization and prognosis. Again, the results of EDX testing are the most informative as long as the test is performed at least

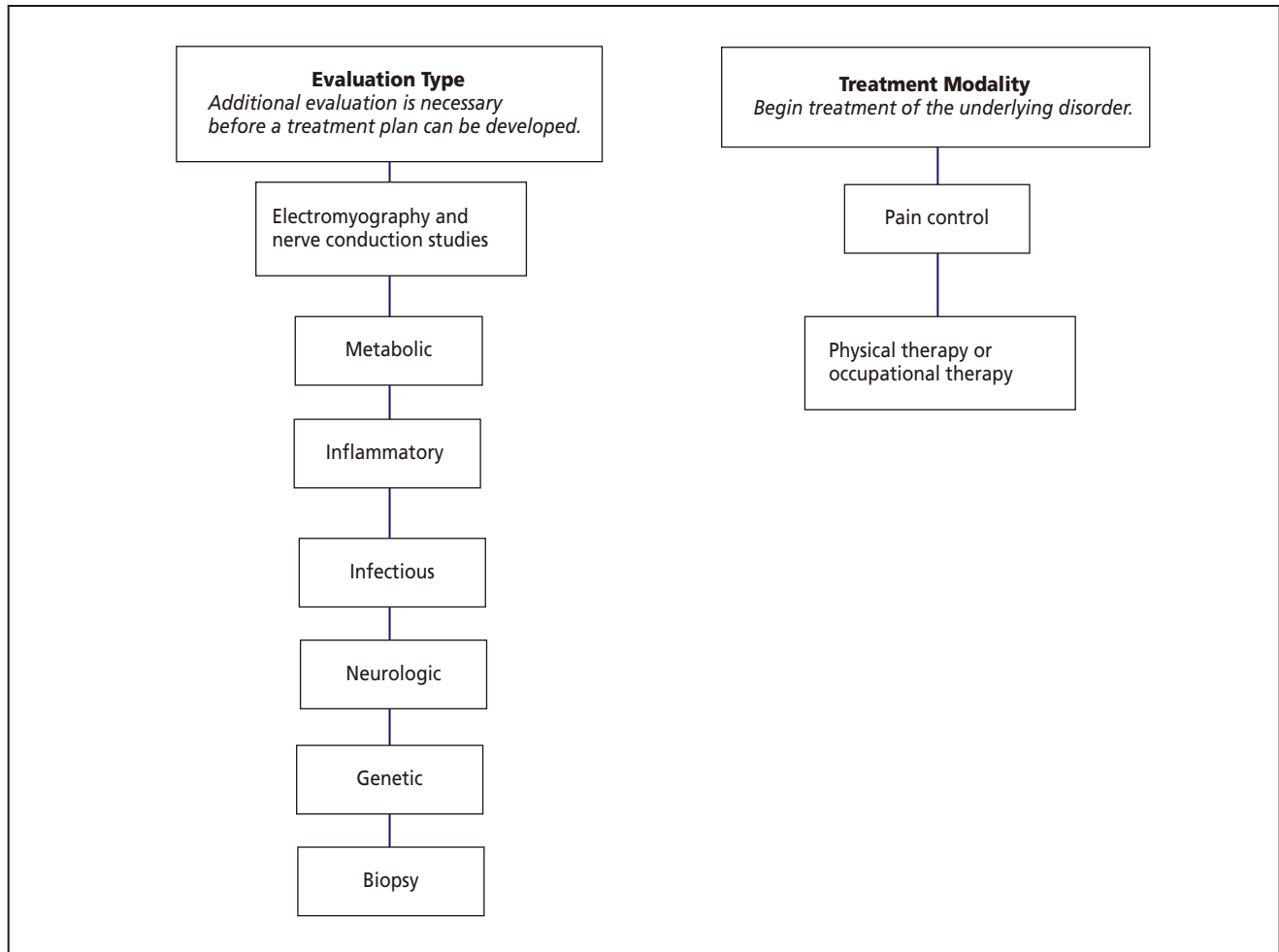


Figure 4. Evaluation and treatment of suspected polyneuropathy (eg, multifocal mononeuropathy).

14 days after the injury. Some patients with traumatic mononeuropathies may benefit from surgical intervention.

Radiculopathies are initially treated with bed rest and pain control (Figure 3). As patients' symptoms improve, activity levels can be increased as tolerated. Physical therapy for traction (in cases of cervical radiculopathy), stretching, and other treatment modalities may be beneficial. Patients with severe pain and/or compromised neurologic function should be referred to a neurologist and orthopedist for surgical evaluation.

Polyneuropathies, including SFSN, are likely to be the most commonly encountered form of neuropathy for physicians practicing in the family care setting (Figure 4).

Polyneuropathies are often secondary to underlying metabolic derangements, with diabetes mellitus being far and away the most common cause. Early detection of abnormal glucose metabolism is critical, as strict glycemic control may slow disease progression.³¹

Polyneuropathies present with symmetric stocking-glove pattern sensory deficits, decreased DTRs, and/or motor weakness. Identification and treatment of the underlying condition offers the only potential cure.

Treatment of acquired immune-mediated neuropathies can speed recovery. As noted, AIDP is not responsive to steroid therapy¹⁰ and should be treated with IVIg or plasma exchange.³² Patients with AIDP may have significant bulbar, respiratory, or autonomic insufficiency requiring ICU-level management. Data is insufficient to support the use of immunosuppressive agents in the management of MMN,³² and IVIg remains the only proven treatment.^{13,32}

Chronic inflammatory demyelinating polyneuropathy is best managed with long-term immunosuppression using steroids or other agents.³² As noted, IVIg may be used for maintenance therapy or reserved for exacerbations.^{10,32} Although paraproteinemic demyelinating neuropathies have

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been little studied, small trials have shown some benefit for patients who receive plasma exchange and IVIg.³²

Neuropathies caused by infectious agents require identification of the inciting organism and institution of an appropriate antibiotic or antiviral therapy. Use of recombinant human nerve growth factor and reduction of viral load may improve nerve function in patients with HIV.²⁶

Control of neuropathic pain can be difficult and, unfortunately, often incomplete. Most patients require long-range treatment and may benefit from evaluation by a pain management specialist. Tricyclic antidepressants (TCAs) are the most thoroughly studied pharmacologic treatment modality and have been the first-line therapy for neuropathic pain for many years.^{1,33,34} Selective serotonin reuptake inhibitors (SSRIs), while better tolerated, have been found to be less efficacious than TCAs for most patients.^{1,35-37}

Many anticonvulsant medications are currently being used in combination with TCAs for the treatment of neuropathic pain. Carbamazepine has been studied the longest; however, its benefit has primarily been limited to trigeminal neuralgia.³⁸ Administering gabapentin starting at 100 mg to 300 mg twice daily with titration to effect is a reasonable starting regimen, particularly in painful diabetic and postherpetic neuralgia.³⁹⁻⁴¹ Daily doses in excess of 1600 mg are usually necessary.¹ Lamotrigine and bupropion hydrochloride⁴² represent other treatments that may be useful in neuropathic pain.^{21,43} Lamotrigine has proven efficacy for the treatment of refractory trigeminal neuralgia, HIV neuropathy, and central post-stroke pain.^{39,43} A common mistake physicians make in prescribing anticonvulsant medications for pain control is in not treating patients long enough and in insufficiently high doses.

Other alternatives for pain management include topical agents such as over-the-counter creams, lidocaine patches, and capsaicin cream. Lidocaine patches are usually cut to the appropriate size and applied to the skin over particularly painful areas. Applied topically, capsaicin depletes sensory nerves of substance P. Symptoms may worsen upon initiation of topical capsaicin treatment, however, and the time investment required from the patient to achieve effective treatment can make this a less attractive therapeutic option.¹

In general, narcotics are often ineffective and typically are not first-line agents for neuropathic pain. Narcotic medications have many complicating adverse effects, such as dependence, tolerance, constipation, sedation, and confusion. One exception is oxycodone hydrochloride, which has proven effectiveness in postherpetic neuralgia.⁴⁴ Additionally, tramadol hydrochloride is well tolerated and has shown efficacy similar to that of TCAs. Tramadol demonstrates low-affinity binding to opioid receptors and is considered less likely to induce dependence.¹

Alternative therapies, including acupuncture and transcutaneous nerve stimulation, have shown mixed results.¹

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