Clinical Approach to Peripheral Neuropathy: Anatomic Localization and Diagnostic Testing

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ABSTRACT

Purpose of Review: This article provides a clinical approach to peripheral neuropathy based on anatomic localization and diagnostic testing.

Recent Findings: Advances have been made in the evaluation of small fiber neuropathy and in the known genetic causes of neuropathy.

Summary: History and physical examination remain the most useful tools for evaluating peripheral neuropathy. Characterization of a neuropathy aids in limiting the differential diagnosis and includes consideration of temporal profile (tempo of onset and duration), heredity, and anatomic classification. Anatomic classification involves (1) fiber type (motor versus sensory, large versus small, somatic versus autonomic), (2) portion of fiber affected (axon versus myelin), and (3) gross distribution of nerves affected (eg, length-dependent, length-independent, multifocal). Diagnostic testing may include serologic and CSF evaluation, electrodiagnosis, skin biopsy, quantitative sensory testing, autonomic testing, nerve biopsy, confocal corneal microscopy, and laser Doppler imager flare.

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INTRODUCTION

The prevalence of peripheral neuropathy is estimated to be between 2% and 8%.[1] Given the numerous causes of polyneuropathy, determining the etiology can be challenging.[2] This article provides a framework for the clinician to approach the diagnosis and testing of a patient with suspected polyneuropathy. The terms neuropathy, polyneuropathy, and peripheral neuropathy will be used synonymously in this article.

ANATOMY

Neuropathic disorders encompass diseases of the neuron cell body (neuronopathy) and their peripheral processes (peripheral neuropathy). Neuronopathies include anterior horn cell disorders, which are termed motor neuron disease, and dorsal root ganglion disorders, which are termed sensory neuronopathy or ganglionopathy. Peripheral neuropathies can be subdivided into two major categories: primary axonopathies and primary myelinopathies.

Neuropathies can be further subdivided on the basis of the diameter of the impaired axon. Large myelinated axons include motor axons and sensory axons responsible for proprioception, vibration, and light touch. Thinly myelinated axons include sensory fibers responsible for light touch, pain, temperature, and preganglionic autonomic functions. Small unmyelinated fibers convey pain, temperature, and postganglionic autonomic functions.

KEY POINTS

- The peripheral nervous system consists of large myelinated motor axons and sensory axons that convey proprioception, vibration, and light touch; small myelinated axons that convey light touch, pain, temperature, and preganglionic autonomic function; and small unmyelinated axons that convey pain, temperature, and postganglionic autonomic functions.
- Neuropathy symptoms can be motor, sensory, or autonomic. Questions regarding impairment in activities of daily living are informative.

Peripheral nerve damage can comprise a focal lesion of a single nerve (mononeuropathy) or multiple nerves (polyneuropathy). This article focuses on polyneuropathy. Because ''sick nerves are liable to compression,'' a mononeuropathy may be superimposed on a polyneuropathy (eg, carpal tunnel syndrome superimposed on a diabetic polyneuropathy).

HISTORY

Neuropathy may present with a variety of signs and symptoms that allow the clinician to narrow the list of diagnostic possibilities. Symptoms may be classified as either negative or positive. Positive symptoms reflect inappropriate spontaneous nerve activity, whereas negative symptoms reflect reduced nerve activity. Negative motor symptoms include weakness, fatigue, and wasting, and positive symptoms include cramps, twitching, and myokymia. Weakness may not be appreciated until 50% to 80% of nerve fibers are lost; positive symptoms may present earlier in the disease process. Negative sensory symptoms include hypesthesia and gait abnormalities such as ataxia. Other common symptoms include difficulty differentiating hot from cold and worsening balance, especially in the dark when visual input is less able to compensate for proprioceptive loss. Positive sensory symptoms include burning or lancinating pain, buzzing, and tingling/paresthesia. Other symptoms include discomfort to sensory stimuli that are normally not painful (allodynia) and an increased sensitivity to painful stimuli (hyperalgesia). Patients with hyperalgesia may describe a sensation of walking on hot coals. Symptoms suggesting autonomic nerve involvement include early satiety, bloating, constipation, diarrhea, impotence, urinary incontinence, abnormalities of sweating (hyperhidrosis, anhidrosis), and lightheadedness associated with orthostasis. Patients with vasomotor instability may report cold extremities associated with skin color and trophic changes.

It is helpful to ask about impairment in activities of daily living, such as a change in handwriting, problems fastening jewelry or buttons or inserting and turning keys, tripping on a carpet or a curb, falling, and having difficulty arising from a commode. Details regarding disease onset, duration, and progression are quite important for further characterization. The patient should be queried regarding asymmetry at onset, location at first onset, involvement of the trunk or cranial nerve region, and the specific tempo of progression (monophasic, steadily progressive, fluctuating, or stepwise). Other important questions regarding the history are similar to those that would be asked of any other patient with a suspected neurologic disorder. These include questions concerning impairment of consciousness, visual disturbances (eg, diplopia), dysphagia, dysarthria, focal motor weakness, sensory disturbances, radicular pain, autonomic dysfunction, and bowel and bladder dysfunction. Bowel and bladder dysfunction is uncommon in polyneuropathy (apart from cauda equina syndrome) and should prompt a search for an alternative diagnosis.

The standard history and physical examination serve as a general framework for the approach to neuropathy. Social history can include questions regarding occupation (possibility of toxic exposures to solvents, glues, fertilizers, oils, and lubricants), sexual history (HIV, hepatitis C), recreational drug use (vasculitis secondary to cocaine), excessive alcohol intake, dietary habits (eg, strict vegan diet), and smoking (paraneoplastic disease). Drugs of abuse confer a severalfold risk: the toxic effects of the agent drug or impurities plus the behavior-related consequences,

including HIV, hepatitis C, and nutritional deficiency. A childhood history of ''clumsiness'' or poor athletic performance suggests a hereditary cause.

Medical and family history should focus on illnesses associated with neuropathy, such as endocrinopathy (diabetes mellitus, hypothyroidism), renal insufficiency, hepatic dysfunction, connective tissue disorders, and cancer. Patients with cancer may develop neuropathy related to nutritional deficiency, chemotherapy side effects, or a paraneoplastic syndrome. Surgical history should address bariatric surgery, multiple orthopedic procedures, and multiple surgeries for ''entrapped nerves.''

The medication list should be reviewed to determine a possible temporal association between agent use and neuropathy onset. The ''coasting effect'' of toxic neuropathy describes symptom progression for months to a year despite agent discontinuation. HIV-related treatment and chemotherapeutic agents are the most common causes of toxic neuropathy. Antibiotics such as quinolones may induce a neuropathy. Nonprescription medications should also be assessed. Vitamin B_6 (pyridoxine) dosing exceeding 50 mg to 100 mg daily (and possibly even lower doses) may induce neuropathy.

Review of systems should include dermatologic changes, arthralgias, dry eyes and mucous membranes, orthostasis, gastrointestinal symptoms, and constitutional symptoms (fever, weight loss, night sweats).

PHYSICAL EXAMINATION

Orthostatic vital signs may identify evidence of dysautonomia. Skin and mucous membranes may demonstrate vasculitic rashes (purpura, livedo reticularis), hyperpigmentation (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes [POEMS]), oral ulcers (Behçet disease, HIV), salivary gland swelling, dry eyes or mouth (sarcoidosis, Sjögren syndrome), extremity hair loss (hair follicle denervation), and gum ''lead lines'' (lead exposure). Integumentary changes may suggest a specific diagnosis. For example, Mees lines in the nails may suggest arsenic or thallium poisoning; alopecia may suggest hypothyroidism, systemic lupus erythematosus (SLE), amyloidosis, or thallium poisoning; curly hair may suggest giant axonal neuropathy; and distal calf hair loss may suggest distal symmetric axonal polyneuropathy. Skeletal deformities such as hammer toes, pes cavus, and kyphoscoliosis are suggestive of an inherited polyneuropathy. The feet should be specifically examined for signs of trauma in an insensate foot that could be an early indicator of an impending Charcot foot deformity. Nerve enlargement can suggest demyelinating neuropathy, neoplasia in neurofibromatosis, or possible leprosy. Easy locations to palpate nerves are the ulnar nerve in the ulnar groove and the superficial radial nerve with a rolling palpation against the radius just proximal to the wrist.

Cranial nerve assessment should include assessment for anosmia (Refsum disease, vitamin B_{12} deficiency), optic atrophy (inherited neuropathies with central and peripheral demyelination), anisocoria or impaired pupillary light reflexes (parasympathetic dysautonomia), impaired ocular motility (botulism, Miller Fisher syndrome), facial weakness (Guillain-Barré syndrome [GBS]), and trigeminal sensory loss (Sjögren syndrome). A comprehensive motor examination should assess muscle bulk, including observation for intrinsic hand and foot muscle atrophy, hyperexcitability, tone, and strength using the Medical Research Council scale. Many neuropathies present with a relative symmetry of weakness. Dynamometry can be used for

KEY POINT

- History should include timeline of disease progression, social history, family history, medical history (including underlying conditions associated with neuropathy), surgical history, and review of neurotoxic medications.

KEY POINTS

- Weakness of flexion and extension of the small toes and weakness of great toe extension may be an early sign of motor dysfunction.
- The sensory examination should be approached with knowledge of peripheral nerve anatomy and types of disease patterns.

more precise strength measurement. Because most neuropathies cause distal weakness, the intrinsic foot muscles may be affected first, resulting in clawed feet and hammer toes. Weakness of flexion and extension of the small toes and weakness of great toe extension may occur early in the disease. The angle between the shin and the unsupported foot should be approximately 130 degrees. A larger angle suggests ankle dorsiflexion weakness. In the hands, the second and fifth digit abductors are often affected first.

The sensory examination should be approached with peripheral nerve anatomy and types of disease patterns in mind. It can be divided into small and large fiber evaluation. Assessment of large fiber function includes vibration, joint position, and light touch, and small fiber assessment includes pinprick and temperature. Romberg testing also evaluates large fiber function.

Light touch evaluates low threshold mechanoreception and is mediated by both small and large fibers. Monofilament probes can grade severity of loss. Detection of lightest touch or stroking represents a measure of low-threshold sensory perception. Impairment of perception to 10-g microfilaments is associated with increased risk of unappreciated trauma.

Small fiber evaluation may be performed by examining pain and temperature using a pin or broken cotton applicator stick. The goal is to apply sharp stimuli without applying significant pressure. Difficulty distinguishing between sharp and dull stimuli indicates loss of nociceptive fibers relative to low-threshold mechanoreceptor fibers.

While performing the sensory examination, think anatomically to discern different patterns of numbness, including the following:

- Mononeuropathy
- Polyneuropathy—distal symmetric
- Polyneuropathy—symmetric but length-independent
- Polyneuropathy—multifocal
- Radiculopathy (including suspended sensory level, saddle anesthesia)
- Plexopathy
- Central causes (syrinx, heminumbness, thoracoabdominal sensory level)

During light touch and pin testing, ask the patient whether the tested areas feel the same or different from other areas. Attempt to establish an area of relatively normal sensation for comparison. Compare proximal and distal locations; the face, arm, and leg; and the right and left sides. Most major dermatomes and nerves should be covered. A suggested initial screen involves testing bilaterally at the forehead, cheek, chin, lateral upper arm, palmar surfaces of digits two and five, lateral thigh, calf (anteromedial, anterolateral), distal dorsum of great toe, and lateral sole toward the plantar aspect. Temperature sensation can be assessed with ice water, but a tuning fork may be sufficiently cold and is readily available.

Vibratory perception is best assessed with a 128-Hz tuning fork. The malleolus, tibial tuberosity, finger, and wrist can be assessed. The time interval until perception of vibration is lost is measured. A young adult should appreciate vibration at the great toe for a minimum of 15 seconds; this value may decline by 1 second per decade. Vibratory perception of less than 10 seconds at the great toe is abnormal at any age. A quantitative tuning fork can be more precise. To minimize the time needed to perform the vibratory examination, we suggest an alternative testing method. Initial testing uses only a very light percussion of the tuning fork. If vibration is detected, then vibratory perception is considered normal in that location. If vibratory perception is not detected, then a moderate or a strong percussion

can be used. This leads to a rapid and relatively reproducible vibratory perception assessment with four possible grades.

Joint position testing is less sensitive than vibratory testing for large fiber function and may only be impaired in severe cases. Joint position is tested in the large toe and second finger at the distal interphalangeal joint. The digit should be held at the lateral borders and the movement excursion should be minimal. Proximal joints are tested if distal impairment is present.

Reflex impairment aids in determination of a lower motor neuron localization. Reinforcement can augment hypoactive reflexes. Ankle hyporeflexia or areflexia is common in large fiber neuropathy, but ankle reflexes are typically preserved with small fiber neuropathy (SFN). Reflexes may be preserved in a mild to moderate large fiber neuropathy. Reflexes diminish with age; an absent ankle jerk at age 80 may be normal.

Gait examination can reveal subtle weakness not noted on manual muscle testing, especially with toe, heel, and tandem walking; squatting; and hopping. Footdrop may result in a steppage gait that is sometimes audible. In length-dependent neuropathy, patients have more difficulty heel walking than toe walking. A wide-based gait or difficulty with tandem walking may highlight subtle sensory ataxia.

CONFIRMATION OF A NEUROPATHY

On the basis of the history and physical examination, the physician should assess whether the signs and symptoms correlate with a neuropathy. The first step is to confirm that the signs and symptoms correspond to a neurologic disease rather than a primarily psychiatric disorder.[3] Next, diseases of the brain (multiple sclerosis, cerebrovascular disease) and the spine (cervical spondylotic myelopathy, multiple sclerosis, poliomyelitis related to West Nile virus) that may masquerade as neuropathy should be excluded. Some neuropathies may coexist with CNS disease. Alternative neuromuscular disorders should also be considered, including polyradiculopathy (multiple compressive radiculopathies related to spondylosis, subarachnoid space infection, or malignancy), ALS, neuromuscular junction disease, and myopathy. MRI may aid in localization.

CHARACTERIZATION OF A NEUROPATHY

The history and physical examination are often able to confirm a polyneuropathy. However, electrodiagnostic studies, skin biopsy, quantitative sensory testing, and other testing may be needed. These tests are described in the next section. In addition to confirming a polyneuropathy, these tests may help with the next step of evaluation, characterization of the neuropathy. Characterization of a neuropathy includes consideration of the temporal profile (tempo of onset and duration), heredity, and anatomic classification. Anatomic classification involves (1) fiber type (motor versus sensory, large versus small, somatic versus autonomic), (2) portion of fiber affected (axon versus myelin), and (3) gross distribution of nerves affected (eg, length-dependent, length-independent, multifocal).

Characterization of the neuropathy helps the clinician minimize the testing needed to determine the etiology of the neuropathy. Diabetic neuropathy is the most common cause of neuropathy in the United States and has several phenotypes, which are discussed in detail in the article ''Diabetic Neuropathy'' in this issue of CONTINUUM.

KEY POINTS

- Ankle jerk hyporeflexia or areflexia is common with length-dependent neuropathy, but ankle reflexes are normal with small fiber neuropathy.
- Gait examination can reveal weakness not identified on manual muscle testing. The patient may be asked to heel, toe, and tandem walk; squat; and hop.
- Characterization of a neuropathy includes consideration of the temporal profile (tempo of onset and duration), heredity, and anatomic classification. Anatomic classification includes (1) fiber type (motor versus sensory, large versus small, somatic versus autonomic), (2) portion of fiber affected (axon versus myelin), and (3) gross distribution of nerves affected (eg, length-dependent, length-independent, multifocal).
- Characterization of a neuropathy helps the clinician minimize the testing needed to distinguish among the numerous toxic, hereditary, and acquired disorders.

KEY POINTS

- Most neuropathies are chronic and progressive with an insidious onset; an acute onset over 1 month or less suggests Guillain-Barré syndrome, vasculitis, porphyria, an infectious etiology (eg, diphtheria, Lyme disease), or toxic/drug exposure (eg, arsenic, thallium, chemotherapeutic agents, dapsone).
- A genetic cause of neuropathy should be considered in patients with a family history of neuropathy, lack of positive sensory symptoms, early age at onset, symmetry, associated skeletal abnormalities, or very slowly progressive course.

Onset and Duration of Clinical Course

Most neuropathies are chronic and progressive with an insidious onset. Thus, a neuropathy that has an alternate onset or course may direct the clinician to a limited differential diagnosis. A known precise date of onset is suggestive of an infectious neuropathy. Hyperacute lesions presenting over 24 to 72 hours are rare and may reflect vasculitic lesions causing mononeuropathy multiplex.

An acute onset with presentation and progression over 1 month or less suggests GBS, vasculitis, porphyria, an infectious etiology (eg, diphtheria, Lyme disease), or toxic/drug exposure (eg, arsenic, thallium, chemotherapeutic agents, dapsone). In a critical illness setting, development of weakness over days is most likely related to critical illness myopathy with thick filament (myosin) loss, but may be caused by critical illness neuropathy.

Subacute onset of neuropathy over 6 months or less can suggest toxic neuropathy, nutritional deficiency, malignancy, paraneoplastic syndromes (sensory neuronopathy), and some metabolic abnormalities. A neuropathy with a relapsing and remitting course suggests demyelination and subsequent remyelination. Possible etiologies include chronic inflammatory demyelinating polyneuropathy (CIDP), porphyria, and hereditary neuropathy with liability to pressure palsies (HNPP). Repeated toxic exposures should also be considered. Vasculitis may also have this temporal profile.

Heredity

A genetic etiology should be considered in a generalized polyneuropathy. Family history, lack of positive sensory symptoms, early age at onset, symmetry, associated skeletal abnormalities, and very slowly progressive course may alert the clinician. HNPP is an exception, as it often presents with a relapsing and remitting course.

Patients with inherited neuropathies tend to have a relative paucity of symptoms in comparison to their physical examination signs. Genetic neuropathies are covered in more detail in the article ''Charcot-Marie-Tooth Disease and Related Genetic Neuropathies'' in this issue of CONTINUUM.

Anatomic Classification

There are several different ways to classify a neuropathy anatomically. The types of classification fall into three main groups: nerve fiber type, portion of fiber affected, and distribution of nerves affected in the body.

Fiber type. Classification by fiber type includes motor versus sensory, somatic versus autonomic, and small versus large fiber size. Many neuropathies involve a combination of fiber subtypes.

Motor versus sensory. It is rare for neuropathy syndromes to be purely motor or sensory. Although most neuropathies are mixed, they may predominantly reflect dysfunction of one fiber type. It is relatively common for patients to notice only motor or sensory symptoms but to have the examination or diagnostic testing confirm that both fiber types are involved. During history taking, sensory symptoms often overshadow motor symptoms. Motor nerve symptoms are infrequently the sole presentation. This is related to many factors, including the exquisite sensitivity of the sensory system, the earlier involvement of the sensory system, and the redundancy and reserve built into the motor system. Intrinsic foot muscle weakness often goes unnoticed by the patient.

Neuropathies with predominant motor involvement include GBS, CIDP, multifocal motor neuropathy (MMN), porphyria, diphtheria, lead intoxication,

botulism, hereditary neuropathies, and toxic exposure related to dapsone, amiodarone, and vincristine. Pure sensory neuropathy is rare and can result from diabetes mellitus, vitamin B_{12} deficiency, HIV, amyloidosis, leprosy, Sjögren syndrome, sarcoidosis, uremia, paraneoplastic syndromes, pyridoxine (vitamin B_6) intoxication, and hereditary neuropathies.

Somatic versus autonomic. Autonomic dysfunction may be seen as a component of a generalized polyneuropathy or a distal small fiber sensory neuropathy or may occur as a result of a predominantly autonomic neuropathy. Although autonomic nerves outnumber somatic nerves, autonomic neuropathy symptoms are less common than somatic nerve symptoms. When autonomic symptoms predominate, the most common causes are diabetes mellitus, amyloidosis, and GBS. If the onset is acute or subacute, the main considerations are autoimmune autonomic ganglionopathy, paraneoplastic syndromes, GBS, botulism, toxic neuropathies, and acute porphyria. In chronic predominantly autonomic neuropathies, considerations include diabetes, amyloidosis (primary and familial), inherited diseases (eg, hereditary sensory and autonomic neuropathy [HSAN]), Fabry disease, Sjögren syndrome, and toxic and infectious neuropathy, including HIV.

Fiber size. In many polyneuropathies, small fibers are predominantly affected, causing patients to report pain as their main symptom. Common causes of SFN include diabetes, glucose intolerance, toxins (especially alcohol), Fabry disease, Tangier disease, HIV, amyloidosis, connective tissue disease (Sjögren syndrome, SLE), sarcoidosis, HSANs, idiopathy, and drugs (eg, antiretrovirals). A more detailed list of less common causes can be found in a textbook by Herskovitz and colleagues.[4] This topic is also discussed in detail in the article "Painful Small Fiber Neuropathies" in this issue of CONTINUUM. Amyloid neuropathy may cause severe pain. Isolated SFN may evolve to include large fibers.

Axonopathy versus myelinopathy. A neuropathy may be classified as predominantly or initially involving the Schwann cell, causing demyelination, or involving the axon itself. This classification can be made electrodiagnostically or pathologically. Features suggestive of a demyelinating neuropathy include weakness without atrophy, a length-independent distribution with a proximal predominant or asymmetric/patchy distribution either clinically or electrodiagnostically, early involvement of proximal reflexes, and myokymia. On the other hand, distal reflex loss (ankle jerk) with preserved proximal reflexes is common in length-dependent neuropathy. The etiology of demyelinating neuropathy includes genetic neuropathy (Charcot-Marie-Tooth disease [CMT] type 1, HNPP, Refsum disease, metachromatic leukodystrophy), CIDP, GBS, MMN, paraproteinemia-related neuropathy, diphtheria, infectious neuropathy (HIV, Lyme disease, leprosy, hepatitis C, diphtheria), and, less commonly, toxin-related neuropathy (eg, *n*-hexane, amiodarone). CIDP may be associated with systemic disease, including infections, inflammatory bowel disease, metabolic conditions, and connective tissue disorders.

Distribution. A final way to anatomically classify neuropathy is based on the global distribution of the neuropathy throughout the body and the location along the nerve pathway. The initial question is whether a neuropathy is symmetric. The next question is length dependency. Most neuropathies are symmetric and length-dependent. They are most commonly attributed to metabolic, idiopathic, inherited, or toxic conditions.[5] Distal dying-back

KEY POINTS

- Prominent autonomic neuropathy symptoms suggest diabetes mellitus, amyloidosis, or Guillain-Barré syndrome.
- Features suggesting demyelinating neuropathy include weakness without atrophy, a length-independent distribution with a proximal predominant or asymmetric/patchy distribution either clinically or electrodiagnostically, early involvement of proximal reflexes, and myokymia.

KEY POINTS

- Most neuropathies are symmetric and length-dependent and are commonly attributed to metabolic, idiopathic, inherited, or toxic conditions. Hand symptoms begin once leg symptoms have ascended toward the knees.
- A neuropathy with significant early proximal involvement, especially hip flexor weakness, raises the possibility of a demyelinating neuropathy. Combined proximal and distal weakness is the hallmark of chronic inflammatory demyelinating polyradiculoneuropathy.

axonopathies have a classic symmetric length-dependent pattern of symptom evolution. Sensory symptoms start in the feet, which are supplied by the longest axons. After dysesthesia and numbness ascend to the calves, the fingertips become affected. The legs, forearms, and eventually the anterior chest may be affected. Motor symptomatology first affects the intrinsic foot muscles, causing toe flexor weakness and clawed toes. Anterior tibial compartment muscle weakness then causes ankle dorsiflexion weakness. Plantar flexion is relatively preserved, possibly related to the functional redundancy of the large bulk of posterior compartment musculature. The intrinsic hand muscles become involved only after the calf muscles are involved. Motor weakness is usually greater in extensor groups than in corresponding flexor groups. Unfortunately, despite adequate and thorough evaluation, many chronic sensorimotor axonopathies remain idiopathic.[6]

In contrast, length-independent neuropathies or asymmetric neuropathies may begin proximally or have a patchy distribution. They are commonly immune mediated or infectious and associated with demyelination. Although demyelinating neuropathy may affect any nerve segment, the segments traversing the subarachnoid space and the most distal segments may be more susceptible to metabolic and immunologic changes because of a weaker blood-nerve barrier. Length-independent neuropathies run a spectrum from a clear mononeuropathy multiplex to a neuropathy with mild patchiness or asymmetry noted on clinical or electrodiagnostic examination. The term mononeuropathy multiplex traditionally refers to individual nerve involvement in a stepwise temporal progression. With severe disease, this may result in a confluent pattern similar to asymmetric polyneuropathy. Vasculitis and multiple nerve involvement with infectious, metabolic, and toxic neuropathies or with HNPP cause this pattern. The differential diagnosis of length-independent neuropathy includes CIDP (demyelinating neuropathy—especially multifocal acquired demyelinating sensory and motor neuropathy [MADSAM] variant), MMN, Lyme disease, HIV, sarcoidosis, carcinoma, amyloidosis, lymphoma, porphyria, leprosy, and Tangier disease.

A neuropathy with significant early proximal involvement raises the possibility of a demyelinating neuropathy. Combined proximal and distal weakness is the hallmark of CIDP. In particular, hip flexor weakness is suggestive of CIDP, as it is frequently involved and cannot be attributed to L4-S1 compressive polyradiculopathy. However, demyelinating neuropathy may mimic a length-dependent pattern, as the longer fibers have a higher probability of being affected.

In a predominantly sensory neuropathy, asymmetric, proximal, or patchy distribution of dysfunction suggests a sensory neuronopathy directly affecting the dorsal root ganglia initially. Sensory involvement of lips and mouth suggest a length-independent process. The differential diagnosis of dorsal root ganglionopathy is limited and includes heavy metals, paraneoplastic syndromes, Sjögren syndrome, HIV, pyridoxine toxicity, cisplatinum, and idiopathic. A limited number of neuropathies involve the cranial nerves. Celiac neuropathy may include facial sensory symptoms (**Case 1-1**). Acute facial diplegia suggests GBS. CIDP and the gelsolin variety of amyloidosis also cause facial diplegia. The facial palsies associated with Lyme disease and sarcoidosis may occur either simultaneously or separated in time. In Melkersson-Rosenthal syndrome recurrent facial paralysis, lip and facial swelling, and fissured tongue occur.

Case 1-1

A 45-year-old teacher presented with a 6-month history of progressive bilateral foot, right thigh, and left face paresthesia. She denied loss of vision, diplopia, dysarthria, dysphagia, incontinence, limb weakness, or balance difficulty. She was recently diagnosed with hypertension and started on atenolol. She was married with three children. She drank socially and smoked one pack of cigarettes per day. She had a family history of diabetes and ovarian cancer. Physical examination was remarkable for reduced sensation to pinprick in the V2 distribution of the left face and reduced sensation to pinprick in the right thigh and foot. The remainder of the neurologic examination was normal. MRI of the brain was normal. Electrodiagnostic testing of the legs, including bilateral sural and superficial peroneal responses, was normal. Blink reflex responses were normal. Skin biopsy revealed normal right distal leg intraepidermal nerve fiber density and reduced right thigh intraepidermal nerve fiber density. Serum gliadin IgG and transglutaminase antibody levels were elevated. Laboratory testing for the following was normal: complete blood count, metabolic profile, 2-hour glucose tolerance test, hemoglobin A_{1c}, Lyme disease, angiotensin-converting enzyme, anti-Hu antibodies, HIV, antinuclear antibodies, erythrocyte sedimentation rate, C-reactive protein, double-stranded DNA, SS-A, SS-B, and gliadin IgA. Duodenal biopsy revealed severe villous flattening, crypt hyperplasia, and intraepithelial lymphocytosis.

Comment. This patient has a length-independent small fiber sensory polyneuropathy, which is confirmed by a decreased intraepidermal nerve fiber density. A diagnosis of celiac disease (gluten-sensitive enteropathy) is suspected based upon the elevated gliadin IgG and transglutaminase antibodies and is confirmed by the duodenal biopsy findings. Celiac neuropathy may occur in patients without gastrointestinal complaints.

Multifocal neuropathy affecting the arms more than the legs also raises the possibility of lead toxicity and porphyria. In leprosy, the nerves running closest to the surface of the body are most vulnerable because the cool tissue temperatures favor the mycobacterial growth.

KEY POINT

- Blood testing for the etiology of a neuropathy should include fasting blood glucose, electrolytes to assess renal and liver function, complete blood count and differential, vitamin B_{12}, erythrocyte sedimentation rate, thyroid-stimulating hormone or thyroid function tests, and serum immunofixation electrophoresis.

DIAGNOSTIC TESTING

Laboratory and Genetic Testing

Determining which laboratory tests to use to evaluate a neuropathy is challenging. Numerous tests are available, and they can be expensive. The AAN published practice parameters to guide laboratory and genetic testing in distal symmetric polyneuropathy.[1] The practice parameters recommend the following tests: fasting blood glucose, electrolytes to assess renal and liver function, complete blood count and differential, serum vitamin B_{12}, erythrocyte sedimentation rate, thyroid-stimulating hormone or thyroid function tests, and serum immunofixation electrophoresis (IFE).

The tests with the highest yield of abnormality are blood glucose, vitamin B_{12} with methylmalonic acid and homocysteine, and IFE. The 2-hour glucose tolerance test is more sensitive than hemoglobin A_{1c} and fasting plasma glucose and should be considered if the initial testing is normal. Vitamin B_{12} deficiency is a common treatable cause of neuropathy. Attention should be paid to the numeric value. When the vitamin B_{12} level is less than 400 pg/mL, the metabolites methylmalonic acid and homocysteine should be tested to

KEY POINT

- Genetic testing is most effective when tailored to the clinical presentation, inheritance pattern, and electrodiagnostic classification.

increase diagnostic yield.[7] Serum IFE is more sensitive than serum protein electrophoresis in detecting monoclonal gammopathy. When the laboratory results return, specifically check whether IFE was performed, because phlebotomy laboratories do not always perform IFE as an independent test in addition to the serum protein electrophoresis. A negative IFE report will typically include a statement that a monoclonal gammopathy was not detected. Quantitative Igs (IgG, IgA, IgM) may suggest an underlying lymphoproliferative disorder. If the initial tests are not revealing, serologic tests focusing on individual diseases should be considered.

Laboratory evaluation of suspected vasculitis and connective tissue disorders (eg, Sjögren syndrome, SLE, rheumatoid arthritis, mixed connective tissue disease, Wegener granulomatosis) may include C-reactive protein, antinuclear antibody, double-stranded DNA, rheumatoid factor, proteinase 3, myeloperoxidase, complement, angiotensin-converting enzyme, SS-A and SS-B, hepatitis B and C panels, and cryoglobulin. For infectious conditions, consider Lyme disease, rapid plasma reagin, and HIV. In a predominantly sensory neuropathy, especially in a patient who smokes, consider testing for anti-Hu antibodies, which are associated with paraneoplastic neuropathy. Celiac disease was seen in 2.5% of neuropathy patients at a referral center.[8] Testing for antigliadin IgG and IgA and transglutaminase should be considered if initial laboratory tests are nondiagnostic.

Serum and urine screening for heavy metal analysis is rarely useful unless heavy metal exposure is suspected. If increased urinary arsenic is detected, fractionation can distinguish between innocuous organic arsenic from food (eg, shellfish) and toxic inorganic arsenic. Copper deficiency neuropathy can be assessed with a serum copper level. This should be considered especially if a concomitant myelopathy is present or a predisposing factor such as bariatric surgery or excess zinc intake has occurred. A vitamin E level may also be considered, especially if the history suggests impaired fat absorption. Chronic neuropathy may be associated with IgM paraproteinemia such as myelin-associated glycoprotein (MAG), sulfatide, and GD1b antibodies. In demyelinating neuropathy with very prolonged distal latencies, consider anti-MAG. If MMN is suspected, consider anti-GM1. In patients with variants of GBS, consider testing for anti-GQ1b, anti-GM1, and anti-GD1a.

In neuropathy with significant autonomic involvement, consider evaluation for amyloidosis (fat pad aspirate, rectal biopsy, transthyretin/genetic testing), urinary porphyrins, paraneoplastic antibody panel (including ganglionic acetylcholine receptor antibody, anti-Hu), HSAN syndromes (genetic testing), and Fabry disease (α-galactosidase assay).

Genetic testing is most effective when it is tailored to the clinical presentation, inheritance pattern, and electrodiagnostic classification. Currently, CMT phenotypes have been linked to 44 loci with mutations in 50 genes. The efficiency of genetic testing can be improved with a stepwise evaluation. For example, hereditary demyelinating neuropathy is attributable to duplication of the peripheral myelin protein 22 gene, *PMP22*, in 70% of cases, so it is recommended for initial testing. The most common mutation associated with axonal CMT is the mitofusion 2 gene, *MFN2*. A detailed genetic testing algorithm is available in the AAN practice parameters.[1]

Additional testing may be warranted if a specific disease is suspected. This testing may include chest x-ray or CT for sarcoidosis; PET scan or CT of chest, abdomen, and pelvis for malignancy; skeletal survey and bone marrow biopsy

for lymphoproliferative disease; salivary gland biopsy for Sjögren syndrome; endoscopy and duodenal biopsy for celiac disease; and colonoscopy for inflammatory bowel disease.

If an infectious, immune-mediated, or neoplastic cause of a neuropathy is suspected, CSF can be evaluated. Malignancy and infection (eg, HIV, cytomegalovirus, Lyme disease, West Nile virus) cause a pleocytosis, whereas a dysimmune neuropathy is typically associated with elevated protein with normal cell counts (cytoalbuminologic dissociation). MRI may document nerve root enhancement in CIDP, show nerve root clumping in arachnoiditis, or reveal nerve enlargement in tumors.

For an extensive list of tests to consider in neuropathy see Herskovitz and colleagues.[4] Despite an extensive search for an etiology, the neuropathy remains idiopathic in a substantial number of patients, most commonly in elderly patients with mild disease.

Electrodiagnostic Testing

Electrodiagnostic testing refers to nerve conduction studies (NCSs) and needle EMG. These tests are the standard for large fiber polyneuropathy diagnosis and are normal in purely SFN. EMG may help exclude mimics of polyneuropathy, such as myopathy, neuronopathy, plexopathy, or polyradiculopathy. For example, sensory nerve action potentials (SNAPs) are preserved in preganglionic conditions, single myotomes are affected in radiculopathy, multiple nerves are affected in plexopathy, and paraspinal abnormalities suggest radiculopathy. As an extension of the clinical examination, electrodiagnosis augments the ability to assess the relative motor versus sensory involvement, the severity of the neuropathy, and the distribution of neuropathic dysfunction. Additionally, electrodiagnosis may determine the relative extent of axonopathy versus myelinopathy. Demyelination may be classified as uniform or patchy. Electrodiagnostic studies may be repeated to monitor disease progression. Although the examination may be uncomfortable, risk is minimal. Adequate sampling of nerves is necessary to assess for a mononeuropathy multiplex and for asymmetry. In neuropathy, electrodiagnostic evaluation should include a minimum of two limbs. Additional limbs should be evaluated if the initial testing is not sufficiently diagnostic, if there is any clinical or electrophysiologic suggestion of asymmetry or a length-independent process, or if there is a concern regarding multiple diagnoses.

NCSs involve electrical stimulation of a nerve and recording over a nerve or muscle, usually using surface electrodes. The size and shape (amplitude, duration, area, and phases) of the resultant action potential waveform are assessed. Recording from sensory nerves yields a SNAP, and recording from muscles yields a compound muscle action potential (CMAP). Reported parameters may include latency, amplitude, conduction velocity (CV), and duration. For a CMAP, a distal latency is reported for the terminal segment, as a pure nerve CV cannot be calculated given the included neuromuscular junction transmission time. Low-amplitude SNAPs may require averaging to increase the signal to noise ratio. F wave studies reflect conduction over the entire length of a motor nerve. The tibial H reflex is the electrophysiologic equivalent of the S1 reflex and assesses both sensory and motor nerve conduction. H reflex minimal latency prolongation is nonspecific and may be seen in early neuropathy. Erb point, axillary, and cervical or lumbosacral root stimulation may assess conduction block and slowing in proximal nerve segments.

In axonal neuropathy, reduced SNAP amplitudes typically develop first,

KEY POINT

- Electrodiagnostic studies are helpful in determining the location of peripheral nervous system involvement, the population of nerves affected (motor versus large fiber sensory), the severity and distribution of involvement, the portion of nerve affected (axon versus myelin), and the chronicity and regeneration status.

followed by reduced CMAP amplitudes. CVs are usually normal or only minimally affected until sufficient loss of large, fast-conducting fibers occurs. In length-dependent axonal polyneuropathy, initially SNAP amplitudes are reduced in distal nerves (sural and superficial peroneal). Thereafter, CMAP amplitudes of the peroneal nerves are reduced, followed by the tibial and then ulnar and median nerves.

In demyelinating neuropathy, distal latency prolongation and CV slowing may occur, with reduction of amplitude less likely early in the course. Additional findings may include conduction block (reduction in amplitude of proximal compared to the distal CMAP without a significant increase in duration); temporal dispersion[9] across a nerve segment (reduction in amplitude of proximal compared to the distal CMAP with a significant increase in duration [**Figure 1-1**]); temporal dispersion of the distal response (multiphasic waveform or prolonged [longer than 9 milliseconds] distal CMAP duration); markedly prolonged F wave minimal latency; and F wave impersistence, chronodispersion, or absence. These demyelinating findings are due to an increased range of nerve fiber conduction velocities caused by uneven involvement by demyelination or nerve inexcitability related to demyelination (**Case 1-2**). Severely prolonged motor distal latencies raise the possibility of anti-MAG neuropathy. Blink reflexes may show prolonged R1 latencies in demyelinating neuropathy. Unfortunately, the above demyelinating features may not be detectable in a

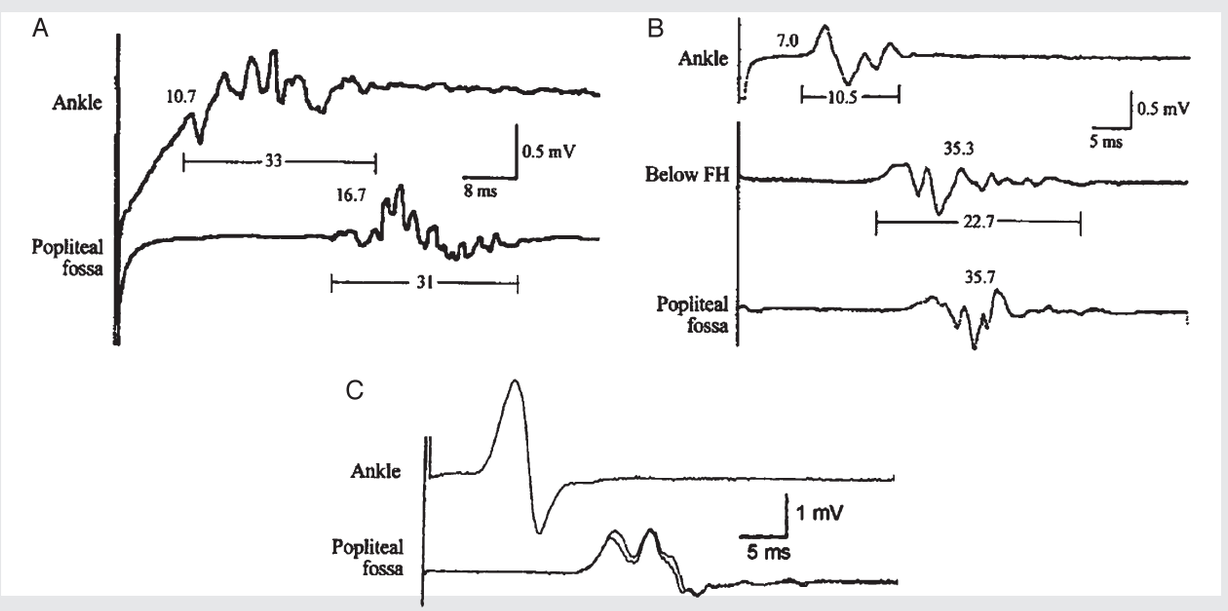

FIGURE 1-1 *A*, Temporal dispersion indicating demyelination. Tibial compound muscle action potentials (CMAPs). Note the multiphasic waveforms and the prolonged CMAP durations (33 and 31 milliseconds). A prolonged distal latency (10.7 milliseconds) and slowed conduction velocity (16.7 m/s) are also present. *B*, Peroneal CMAPs. Focal demyelination in the ankle-fibular head (FH) segment is indicated by the highly multiphasic waveform with below-FH stimulation along with a 116% increase in total duration (22.7 milliseconds) in comparison to ankle stimulation (10.5 milliseconds). The ankle and popliteal fossa CMAPs are also multiphasic. *C*, Tibial CMAPs with proximal temporal dispersion. The increased duration of the proximal response, along with relative preservation of the area, indicate the presence of temporal dispersion and not a conduction block.

Modified with permission from Sander HW, Oh SJ. Temporal dispersion terminology: multiphasic and multiturn CMAPs. J Clin Neuromuscul Dis 2006;7(3):173–174.

Case 1-2

A 69-year-old man with diabetes presented with a 4-year history of tingling and numbness affecting the feet and hands, difficulty with stair climbing, and imbalance in the shower when closing his eyes. The symptoms were progressive, although there were a few intervening months in which the symptoms seemed to have lessened. He was a retired used car salesman and lived with his wife. He denied alcohol or tobacco use. Diabetes was diagnosed 6 years ago and was controlled by diet and weight loss. His history was significant for hypothyroidism that was treated with levothyroxine and benign prostatic hypertrophy. Neurologic examination revealed 4/5 weakness of bilateral iliopsoas and extensor hallucis longus muscles and 4+/5 weakness of bilateral abductor digiti minimi and tibialis anterior muscles. Sensory examination revealed diminished light touch perception in a bilateral glove distribution to the wrist and in a stocking distribution to the midfoot. Vibratory perception was diminished in the toes. Ankle reflexes were absent. Romberg test was positive.

Hemoglobin A_{1C} and fasting blood sugar were mildly elevated. The antinuclear antibody was borderline positive. The serum thyroid peroxidase antibody level was markedly elevated. Laboratory testing for the following was normal: complete blood count, metabolic profile, thyroid-stimulating hormone, rheumatoid factor, Lyme disease, angiotensin-converting enzyme, HIV, C-reactive protein, double-stranded DNA, SS-A, SS-B, GM1, and anti–myelin-associated glycoprotein antibody. Motor nerve conduction studies revealed moderate conduction slowing and multiphasic responses in bilateral peroneal, right tibial, and right ulnar nerves, with normal to slightly low compound muscle action potential amplitudes. Bilateral peroneal distal compound muscle action potentials had increased duration. F wave responses were moderately prolonged. Bilateral tibial H reflexes were absent. Sensory nerve conduction studies revealed right median and ulnar mild conduction slowing with normal bilateral sural and superficial peroneal responses. Needle EMG revealed only a decreased interference pattern in bilateral tibialis anterior muscles.

Comment. This patient clinically has a length-independent sensorimotor large fiber polyneuropathy. Electrodiagnostic studies confirm a length-independent, demyelinating, motor-greater-than-sensory polyneuropathy. A diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) is established based on the clinical history, physical examination, and electrodiagnostic findings. CIDP responds to immunotherapy and may be treated with IVIg, plasmapheresis, or steroids. It is common for patients with CIDP to have concomitant autoimmune diseases or additional isolated laboratory markers suggesting autoimmunity. CIDP may also occur in association with diabetes.

KEY POINT

- Nerve conduction findings in axonal neuropathy include reduced sensory nerve action potential and compound muscle action potential (CMAP) amplitudes. Findings in demyelinating neuropathy include conduction velocity slowing, distal latency prolongation, conduction block, temporal dispersion, prolonged (greater than 9 milliseconds) distal CMAP duration, markedly prolonged F wave minimal latency, and F wave impersistence, chronodispersion, or absence. Asymmetry, sural sparing, and dissociation between motor and sensory function in the same nerve suggest possible acquired demyelinating neuropathy or a mononeuropathy multiplex.

demyelinating neuropathy because of either lack of sampling of affected nerves or secondary axonal loss with low amplitude or absent responses in severe disease. Asymmetry, sural sparing, and dissociation between motor and sensory function in the same nerve should raise the possibility of acquired demyelinating neuropathy or a mononeuropathy multiplex. Various electrodiagnostic criteria have been established for CIDP.[10,11] Recent criteria have been created for clinical rather than research use and have greater sensitivity. Uniform demyelinating

KEY POINTS

- Uniform demyelinating features are more commonly associated with hereditary neuropathies than acquired neuropathies. Conduction block and temporal dispersion are usually seen in acquired conditions.
- Magnetic stimulation and somatosensory-evoked potentials may assist in identifying root, plexus, and proximal nerve (eg, femoral) demyelination.

features are more commonly associated with hereditary neuropathies than with acquired neuropathies. Conduction block and temporal dispersion are usually seen in acquired conditions.

Needle EMG assesses electrical activity of voluntary muscles. At rest, the presence of fibrillation potentials and positive sharp waves indicates spontaneous discharge of individual muscle fibers. This finding suggests active denervation of muscle fibers, but it also occurs in some myopathies, likely due to muscle fiber splitting. Motor unit potential (MUP) morphology may suggest a neurogenic lesion with reinnervation (increased duration, amplitude, and polyphasia) or a myopathic lesion (brief duration, low amplitude, and polyphasia). A caveat is that MUPs in early reinnervation resemble MUPs of myopathy. With activation, the recruitment pattern may be divided into two components: interference pattern and firing rate. In neuropathy, there may be an increased firing frequency in association with a decreased interference pattern. In myopathy, there may be an early recruitment of MUPs with a low-amplitude envelope of the interference pattern. Needle EMG is useful to localize the distribution of dysfunction. It is also useful in defining the chronicity of an axonopathy based on the distribution and the amplitude of fibrillation and sharp waves as well as MUP morphology.

Neurophysiologic Testing

Magnetic stimulation may assess conduction in proximal segments such as the femoral nerve or cauda equina, but in general it has limited application in peripheral neuropathy. Documentation of cauda equina CV slowing can aid in diagnosis of a demyelinating neuropathy.[12]

Somatosensory-evoked potentials (SSEPs) may localize sensory symptoms to the nerve/plexus/root and evaluate proximal nerve segments that are inadequately assessed by NCSs. SSEPs may be absent or delayed because of root demyelination. SSEPs may be recordable even if SNAPs are absent because of central amplification and can document CV slowing. Yiannikas and Vucic highlighted the use of SSEPs to diagnose different phenotypes of CIDP.[13]

Quantitative Sensory Testing

Quantitative sensory testing (QST) involves administration of vibration, warm, cold, and heat pain stimuli to the great toe or index finger to determine the threshold to the sensation. Vibration sensory threshold measures large-diameter sensory fibers. Thermal and heat pain thresholds evaluate small unmyelinated fibers, which are not assessed with NCSs. QST is noninvasive and can be repeated to monitor progression.[14]

QST instruments use different algorithms to determine thresholds. Comparisons cannot easily be made between algorithms.[15] In the method of limits, stimulus intensity is gradually increased until the patient indicates perception. In the method of levels, individual stimuli are delivered and the patient indicates whether the stimulus was perceived. This method is reaction time-independent. Data can be reported in absolute units of stimulus intensity or in steps specified as ''just noticeable differences.'' See **Figure 1-2** for an example of QST.[16] Results are expressed as age- and sex-adjusted percentiles.

QST has been validated to detect and characterize sensory neuropathy. Studies of patients with diabetes with minimal or no symptoms have found thermal sensation testing to be more sensitive than vibratory testing or NCSs. However, other studies have found NCSs and vibratory testing to be more sensitive than thermal testing. This discrepancy is potentially explained by changes in the

predominant fiber type involved over the disease course. Thus, combined thermal and vibratory evaluation is beneficial and provides higher sensitivity. HIV neuropathy, Fabry neuropathy, toxic neuropathy, and demyelinating neuropathy have been evaluated using QST. Vibration and cooling thresholds appear most reliable and reproducible compared to warming and heat pain.

QST has limitations. It is time-consuming (takes at least 1 to 2 hours), requires special equipment, and is a psychophysiologic tool requiring patient cooperation. Inattention can lead to inaccuracy. Detecting malingering or other nonorganic abnormalities is challenging. Therefore, QST should not be used in resolving medicolegal matters. QST cannot differentiate between central and peripheral nervous system dysfunction. An AAN QST consensus report states: ''Its [QST's] role is only established when used as one of several tools in the evaluation of neurologic disorders,'' and ''QST is probably or possibly useful in identifying small and large fiber sensory abnormalities.''[15]

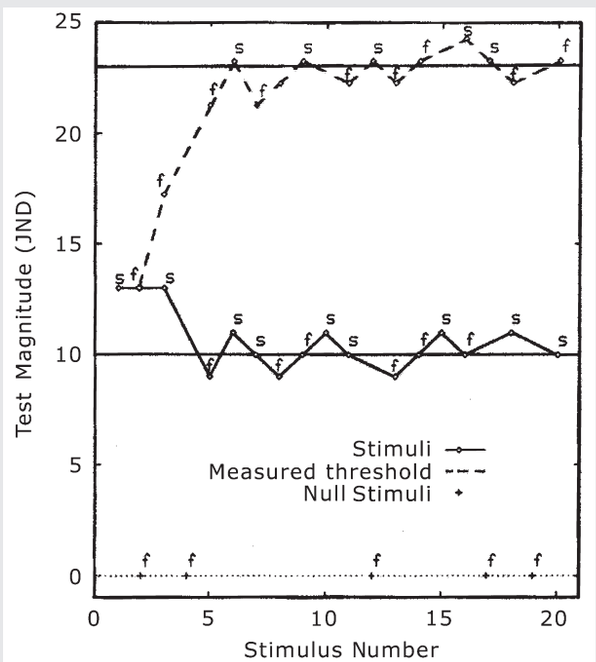

FIGURE 1-2 Examples of the 4-2-1 stepping algorithm for cooling thresholds. The *broken line* at the top is from a patient with painful diabetic neuropathy, and the *solid line* is from a normal control. Null stimuli are shown at the bottom (*dotted line*). Stimuli are started at level 13, and the control senses the first two stimuli. In the normal study, after the first turn point at stimulus 5, the patient fails (*f*) to note the stimulus, and the step is reduced to two just noticeable differences (JNDs). After the second turn point, the stimuli are refined to 1 JND, and a threshold of 10 JND (80th percentile) is determined. The patient with neuropathy fails to note the first three true stimuli at 13, 17, and 21 JND and two null stimuli (*not shown*). The intervals are refined until an abnormal threshold of 23 JND (98th percentile) is determined. This threshold corresponded to a physical change of −20°C (36°F) in skin temperature.

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Autonomic Testing

Autonomic testing may complement evaluation of polyneuropathy.[17,18] Sympathetic and parasympathetic function are assessed using cardiovagal, adrenergic, and sudomotor indices. Sympathetic sudomotor testing includes sympathetic skin response (SSR), quantitative sudomotor axon reflex testing (QSART), and thermoregulatory sweat testing (TST). Cardiovascular evaluation includes heart rate variability assessment during deep breathing (HRDB), Valsalva maneuver, and blood pressure response to standing and tilt. In SFN, sudomotor dysfunction is more likely to be identified than cardiovagal dysfunction. Many standard EMG machines can assess SSR and R-R interval. These tests are rapid and easily performed. Specialized laboratories are needed for the other studies mentioned.

The SSR measures changes in hand and foot skin resistance in response to an arousal stimulus, often electrical, that elicits a startle response. An absent response is considered abnormal. Quantitative criteria are not uniformly established. Some consider a side-to-side amplitude asymmetry of greater than 50% abnormal. This test is relatively insensitive for detection of mild dysfunction.

KEY POINT

- Although quantitative sensory testing is useful in identifying both small and large fiber neuropathy, it is time-consuming, dependent on patient cooperation, not truly objective, and unable to localize dysfunction.

KEY POINTS

- Sympathetic sudomotor testing includes sympathetic skin response, quantitative sudomotor axon reflex testing, and thermoregulatory sweat testing. Cardiovascular evaluation includes heart rate deep breathing, Valsalva maneuver, and blood pressure response to standing and tilt.
- In small fiber neuropathy, sudomotor testing is more sensitive than cardiovagal testing.

TST involves administering controlled heat stimulus and visualizing the sweat pattern response using indicator powders. Areas of reduced sweating are computed as a percentage of total anterior body surface. Patients with neuropathy have hypohidrosis or anhidrosis. TST sensitivity in SFN is high, especially for detection of distal loss of sweating; however, the test is not routinely available, as it requires a dedicated room and is messy and time-consuming. SSR and TST are nonlocalizing with regard to central versus peripheral sites of dysfunction.

QSART assesses postganglionic sudomotor nerve fibers with high sensitivity and specificity (**Figure 1-3**).[19] Axons in skin are activated via acetylcholine iontophoresis, resulting in an initial direct sweat response. Antidromic transmission to an axon branch point elicits an orthodromic response leading to a secondary sweat response of sweat glands adjacent to the site of primary stimulation. Sweat is measured with sweat cells, which are generally placed at four locations. In distal SFN, the most distal site may have a reduced or absent response. QSART is the most sensitive physiologic autonomic test in distal SFN, with a sensitivity of 75% to 90%.[20] Intraepidermal nerve fiber loss (somatic C fiber involvement) and QSART abnormality (autonomic C fiber involvement) are often correlated.

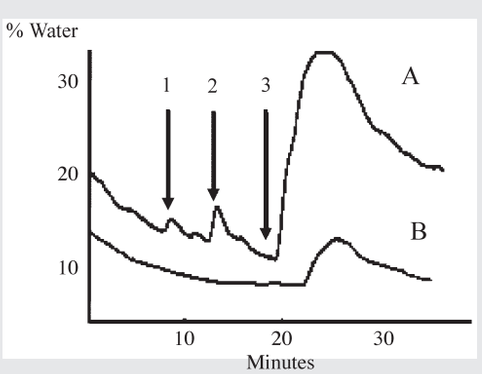

FIGURE 1-3 *A*, Normal quantitative sudomotor axon reflex testing (QSART) in a healthy control. *B*, Abnormal QSART in a patient with dysfunction of the postganglionic sympathetic sudomotor axon due to small fiber neuropathy. In contrast to the patient with small fiber neuropathy, sweating increases in the healthy control during mental arithmetic (*1*), during acoustic stimulation (*2*), and prior to acetylcholine iontophoresis (*3*).

Reprinted with permission from Hilz MJ, Dütsch M. Quantitative studies of autonomic function. Muscle Nerve 2006;33(1):6–20.

In normal physiology, the heart rate increases with inspiration and decreases with expiration. HRDB assesses variability in successive R-R intervals at six breaths/minute. The variation is largely related to parasympathetic/vagal nerve pathways and is reduced in autonomic dysfunction. HRDB has a sensitivity of approximately 80% in assessment of polyneuropathy.[20]

Valsalva maneuver assesses cardiovagal and sympathetic vasomotor function. It involves blowing against airway resistance at predetermined pressure, causing abrupt elevation of intrathoracic and intra-abdominal pressures. Technically, the maneuver consists of four phases, with phases II and IV playing the greatest diagnostic role (**Figure 1-4**).[21] Phase I, during the first 2 to 3 seconds of forced expiration, is associated with a brief decrease in heart rate and increase in blood pressure caused by aortic compression from increased intrathoracic and intra-abdominal pressure. During phase II (continued straining), the blood pressure first decreases (reflecting reduced venous return causing diminished stroke volume) and then increases. This is secondary to a baroreceptor-mediated increase in sympathetic activity with resultant increased heart rate and peripheral vasoconstriction. In phase III, the abrupt release of the strain causes passive blood pressure decline and a resultant increase in heart rate. In phase IV (continued relief), the blood pressure overshoots baseline because of

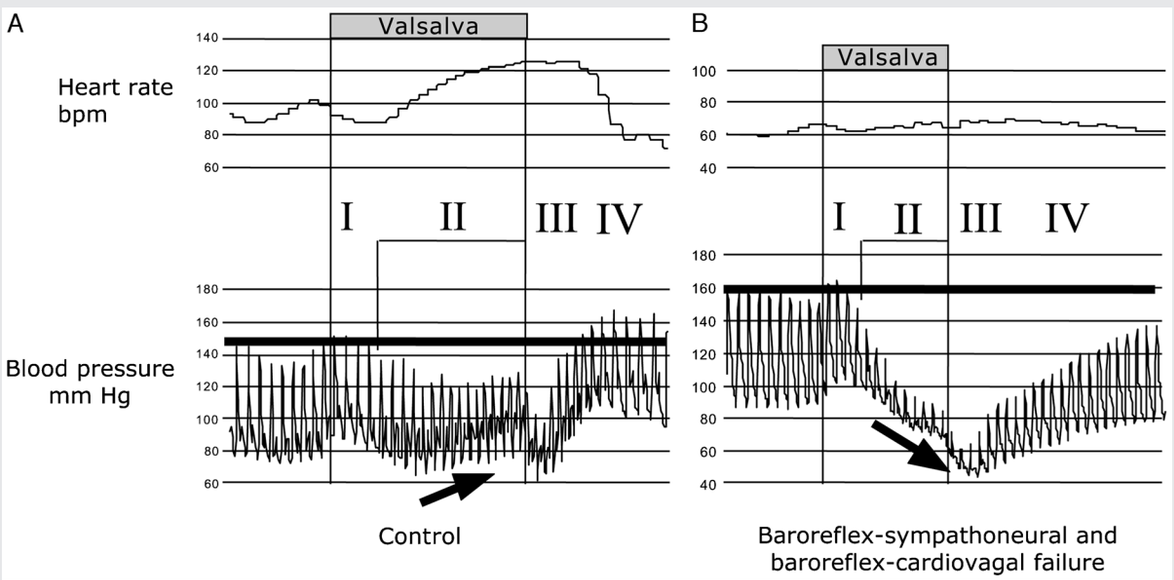

FIGURE 1-4 Blood pressure and heart rate response to Valsalva maneuver in a normal participant (*A*) and a patient with baroreflex-sympathoneural and baroreflex-cardiovagal failure (*B*). The patient has a progressive fall in blood pressure during the maneuver and slow blood pressure recovery after the maneuver, with absence of a pressure overshoot in phase IV. Concurrent heart rate changes are blunted for given changes in blood pressure.

persistent peripheral vasoconstriction in the setting of a normalized venous return and stroke volume. Baroreceptor-mediated vagal stimulation with reflex bradycardia and peripheral vasodilation then occurs. In patients with baroreflex failure, the blood pressure falls progressively in phase II and in phase IV blood pressure recovery time is prolonged with no pressure overshoot. The Valsalva ratio reflects parasympathetic function and is defined as the ratio of the fastest heart rate during or after phase II to the slowest heart rate in phase IV (after release of strain). A ratio below 1.10 is abnormal.

Orthostatic hypotension associated with neuropathy occurs when small myelinated and unmyelinated baroreflex fibers in splanchnic vasculature are damaged. Tilt-table testing can quantify and provide detail regarding orthostatic changes.

The composite autonomic scale is a 10-point scale that combines adrenergic, sudomotor, and cardiovagal testing and can be used to increase sensitivity and specificity for documenting autonomic dysfunction.

Nerve Biopsy

Historically, nerve biopsy (NB) was used to assess the etiology, pathologic localization, and severity of nerve damage. In the last two decades, NB has become less important because of progress in electrodiagnostic, laboratory, and genetic testing. Currently, the search for an etiology is the main indication for an NB. NB evaluation should not be performed before adequate clinical, electrophysiologic, and laboratory assessment. The yield of an NB depends on a number of factors, including patient selection, nerve sampled, laboratory experience, and techniques of evaluation.[22]

NB is helpful in only a small subset of patients. The yield is best in an acute/subacute, asymmetric, multifocal, severe

KEY POINT

- Nerve biopsy evaluation should not be performed before adequate clinical, electrophysiologic, and laboratory assessment.

KEY POINTS

- Nerve biopsy yield is best in an acute/subacute, asymmetric, multifocal, progressive neuropathy.
- The AAN practice parameters recommend nerve biopsy in the diagnosis of inflammatory diseases such as vasculitis, sarcoidosis, and chronic inflammatory demyelinating polyradiculoneuropathy; infectious diseases such as leprosy; or infiltrative disorders such as tumor or amyloidosis.
- Nerve biopsy is also recommended in diffuse cryptogenic neuropathy but is rarely informative in distal symmetric axonal neuropathy associated with toxic and metabolic conditions.

progressive neuropathy. It is most helpful in mononeuropathy multiplex or suspected vasculitis. AAN practice parameters support the usefulness of NB in the diagnosis of inflammatory diseases such as vasculitis, sarcoidosis, and CIDP; infectious diseases such as leprosy; or infiltrative disorders such as tumor or amyloidosis.[20] It is also recommended in progressive diffuse cryptogenic neuropathy. NB is rarely informative in distal symmetric axonal neuropathies associated with toxic and metabolic conditions. Hereditary neuropathies are better diagnosed with blood testing, although NB may help direct DNA analysis to a particular gene (**Table 1-1**).

The current role of NB in CIDP is controversial. Patients with CIDP may erroneously be classified as having an axonal neuropathy on electrodiagnostic studies because of sampling error in patchy disease. NB should be considered on a case-by-case basis for patients with cryptogenic neuropathy with atypical clinical or electrodiagnostic features or a rapidly deteriorating course.[23]

In axonopathy, NB findings include fiber loss, evidence of sprouting, and myelin breakdown material. In demyelinating neuropathy, the axons have inappropriately thin myelin sheaths relative to the diameter of the axons. When repetitive episodes of demyelination involve the same internode, Schwann cell proliferation creates concentrically oriented layers termed ''onion bulbs'' (**Figure 1-5**).[24] Tomacula are sausage-shaped myelin outfoldings observed on teased myelinated fibers and are most commonly observed in hereditary neuropathy, especially HNPP. The characteristic lesion of necrotizing vasculitis on nerve and muscle biopsy is fibrinoid necrosis of the endothelium and transmural inflammatory cell infiltration.

Sensory nerves are biopsied under local anesthesia. MRI and ultrasound may aid in nerve selection. The surgeon should be familiar with nerve identification and specimen handling. Total NB is more informative than fascicular biopsy. Favored nerves include the sural nerve above the lateral malleolus, the superficial peroneal nerve, or, less commonly, the superficial radial nerve at the wrist. When vasculitis, amyloidosis, or granulomatous disease is suspected, a biopsy of adjacent muscle may be performed. Following a sensory NB, sensory loss in the nerve distribution will occur. Dyck reported that 30% of patients experienced subjective and objective sensory abnormalities that resolved over time. Vallat and colleagues reported that approximately 60% of patients had no symptoms after sural NB.[25]

General pathologic evaluation uses frozen sections, conventional paraffin sections, epoxy (plastic) sections for light and electron microscopy, and teased myelinated fibers. Frozen tissue is usually not fixed before cutting sections. The tissue is fixed in formalin for paraffin sections and in glutaraldehyde for semithin plastic sections, electron microscopy, and teased fibers.[26]

Paraffin sections followed by routine hematoxylin and eosin staining is the most efficient method to screen for interstitial lesions such as inflammatory cells, neoplastic infiltration, and blood vessel changes. It is particularly helpful for detecting vasculitis, amyloidosis, and sarcoidosis.

Frozen sectioning allows for immunostaining. This may detect immunologically active cells in vasculitis and deposition of Igs (eg, IgM antibody to MAG) and complement components. Light microscopic analysis of resin-embedded material assesses for loss of myelinated fibers, onion bulb formation, and size of affected fibers. Quantifying the number of myelinated fibers per unit area of endoneurium may be necessary to determine significant loss.

TABLE 1-1 Summary of Clinical Situations When Nerve Biopsy May Be Very Useful or Indispensable for the Diagnosis

	Disease Groups	Condition	Comments on Nerve Biopsy
Acquired neuropathies	Immune-mediated neuropathies	Vasculitis	Diagnostic yield is variable and may be improved in combination with a muscle biopsy at the same site May be particularly useful when vasculitis is confined to peripheral nerves
		Chronic inflammatory demyelinating polyneuropathy (CIDP)	May be helpful in patients with clinically atypical presentations or when nerve conduction studies are not diagnostic
		Neuropathy associated with monoclonal gammopathy	May be extremely helpful to demonstrate: (1) presence of lymphomatous infiltrates (2) amyloidosis (3) endoneurial deposits (intramyelinic or interstitial) Exception: patients with IgM anti–myelin-associated glycoprotein neuropathy
	Toxic neuropathies	Various drug-induced neuropathies, particularly those causing demyelinating neuropathies	May help differentiate a toxic neuropathy from another type of neuropathy (eg, amiodarone-induced neuropathy with electrophysiologic features suggestive of CIDP)
Hereditary neuropathies	Charcot-Marie-Tooth disease (CMT)	CMT-like presentation in sporadic cases	May suggest a hereditary neuropathy in the absence of a family history May direct the search for specific gene mutations in some cases
	Storage disorders	Storage disorders with peripheral nervous system involvement	May reveal accumulation of abnormal material in Schwann cells or endothelial cells

Reprinted with permission from Vallat JM, Vital A, Magy L, et al. An update on nerve biopsy. J Neuropathol Exp Neurol 2009;68(8):833–844.

Electron microscopy is useful in examining unmyelinated nerve fibers; evaluating ultrastructural features, including cytoplasmic organelles and storage materials; and evaluating for demyelination. Diseases assessed by electron microscopy include CIDP; neuropathy due to a gammopathy (anti-MAG); hereditary neuropathies, including those that also affect the CNS; and toxic neuropathies.

Teased myelinated fiber examination usually involves grading 50 to 100 fibers for pathologic abnormalities. Quantitative studies in internodal length and myelinated fiber diameter are performed. Normally there is little variation

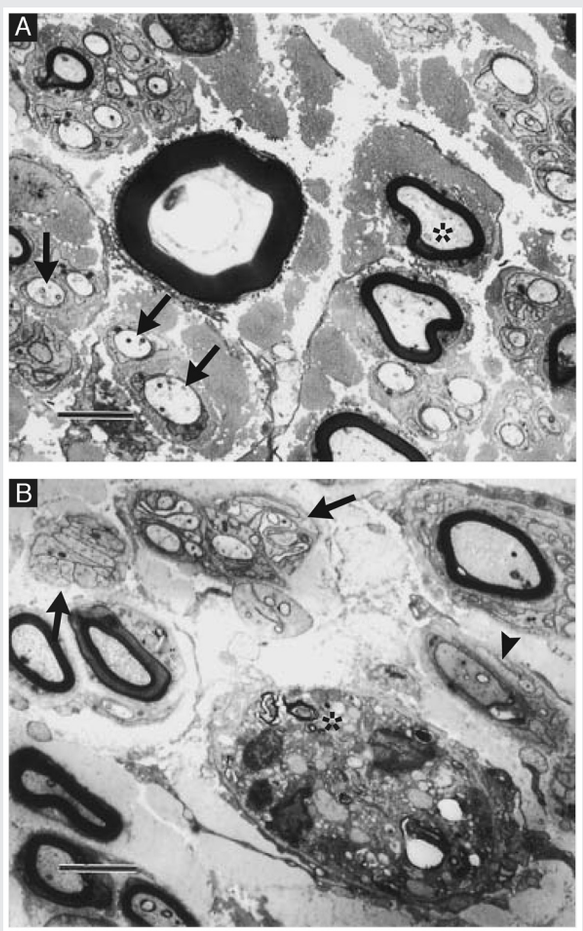

FIGURE 1-5 Electron micrographs of a sural nerve biopsy in chronic inflammatory demyelinating polyradiculoneuropathy specimen ([times]2870). *A*, shows that the axons have relatively thin myelin sheaths (*asterisk*), a finding suggesting remyelination. Some relatively large, unmyelinated axons indicative of demyelination (*arrows*) are also visible. *B*, shows a Schwann cell filled with myelin debris (*asterisk*). Stacks of cytoplasmic lamellae (*arrows*) indicate a loss of unmyelinated axons and myelinated axons. An ''onion bulb'' (*arrowhead*) surrounds an unmyelinated axon, a finding indicating demyelination. The bars represent 3.48 μm.

Reprinted from Sander HW, Hedley-Whyte ET. Case records of the Massachusetts General Hospital: weekly clinicopathological exercises. Case 6-2003: a nine-year-old girl with progressive weakness and areflexia. N Engl J Med 2003;348(8):735–743. Copyright © 2003, with permission from the Massachusetts Medical Society.

between internodal lengths in single fibers in early adulthood, but gradually increasing variation of internodal lengths occurs with age.

Teased fibers may demonstrate a demyelinating neuropathy with areas of segmental demyelination. In subacute or chronic neuropathies, thinly myelinated segments and short internodes can be evidence of remyelination but can also be caused by a chronic axonal disorder. Tomacula may be seen on teased fiber preparation. Myelin ovoids indicate active axonal degeneration, and uniformly shortened internodes are thought to be caused by axonal regeneration.

Skin Biopsy

Over the past two decades, understanding of cutaneous innervation has dramatically increased, leading to improved diagnostic and therapeutic techniques.[27] Skin biopsy is becoming the standard for assessment of unmyelinated cutaneous nerves. The intraepidermal small nerve fibers convey pain and temperature sensation from the skin and maintain autonomic function. The neurologic examination may miss subtle sensory abnormalities. Conventional electrodiagnostic studies assess only large nerve fibers.

Skin sampling is performed by skin punch or by the less common skin blister technique.[28] With a skin punch, a 3 mm diameter, 3 mm to 4 mm thick specimen is removed using local anesthetic without sutures and is fixed in paraformaldehyde. A small scar may occur. Although biopsy is a simple office procedure, pathologic analysis is complex. Intraepidermal nerve fiber density (IENFD) is quantified and morphologic features are assessed. Complications (infection, excessive bleeding, and prolonged healing) occur in fewer than 0.5% of patients.[29] Immunohistochemical staining is performed, most commonly with protein gene product 9.5, a cytoplasmic neuronal marker. Sections 50 μm thick are cut perpendicular to the epidermis. Using bright field light microscopy, the linear IENFD is calculated by counting the nerve fibers that cross the epidermal basement membrane. The isolated fragments of nerve

fibers in the epidermis can also be counted (**Figure 1-6A, B**). An alternative technique uses fluorescence labeling with or without confocal microscopy. Strict counting rules and intensive training have led to high interrater and intrarater reliability. The morphology of unmyelinated nerve fibers is assessed. Qualitative changes in neuropathy include attenuation of fibers, large globular and fusiform-shaped swelling, dystrophic change, and tortuous and increasing complex branching. Large axonal swelling is a predegenerative change predictive of nerve fiber degeneration (**Figure 1-6C**). In several studies, isolated morphologic abnormalities were noted in 20% to 29% of patients with normal IENFD.[30] Unfortunately, methods to reliably quantitate qualitative changes in morphology are lacking. In addition to IENFD, staining may also be performed for amyloidosis.

IENFD is compared to normative reference data, which are currently available for the bright field immunohistochemistry technique for the foot, proximal and distal thigh, distal leg, distal forearm, trunk, and heel. The procedure is most commonly performed in the distal leg calf and in the proximal lateral thigh. IENFD below the fifth percentile is generally considered abnormal. Mean IENFD gradually diminishes with age. Men have a slightly lower IENFD than women. There is no relationship between IENFD and race, height, or weight.

Quantitative nerve fiber analysis of the dermis has been limited. Several researchers have developed techniques to quantify the subepidermal nerve plexus. Other researchers are investigating abnormally short myelin internodes as a possible diagnostic technique for demyelinating disorders.

Sweat gland nerve fiber density (SGNFD) is assessed by skin biopsy with a manual or automated analysis. Sweat glands have sympathetic sudomotor

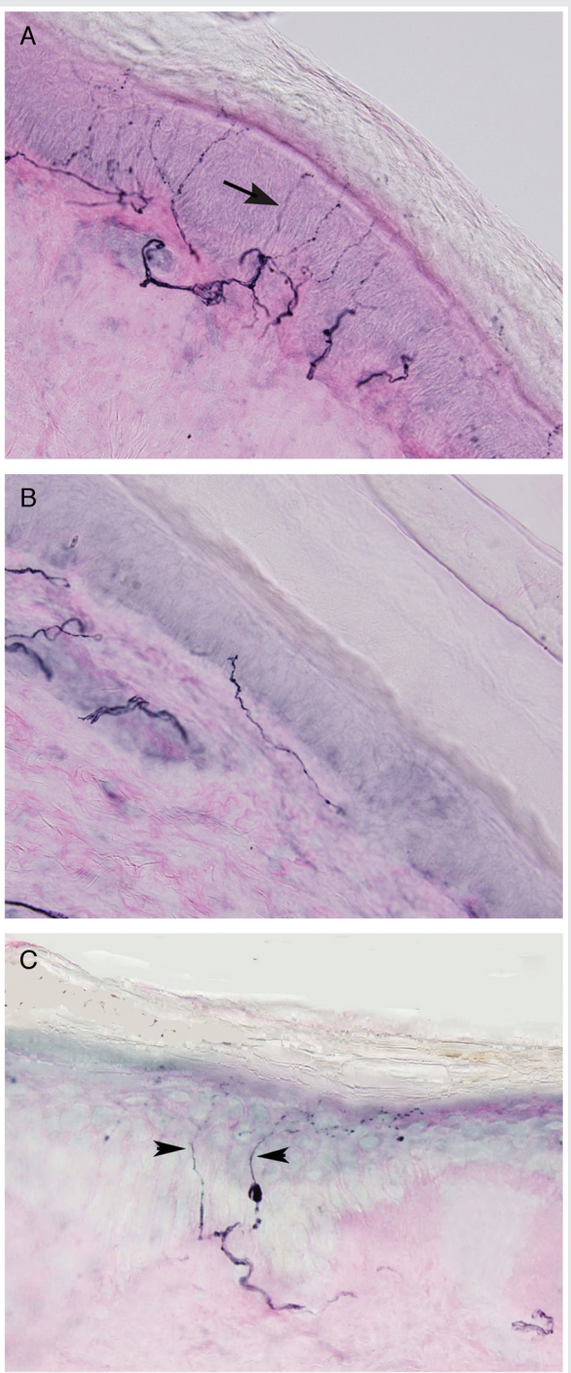

FIGURE 1-6 *A*, Normal intraepidermal nerve fiber density (IENFD). Small nerve fibers (*arrow*) in the epidermal layer of a skin biopsy with normal IENFD. *B*, Abnormal IENFD. Skin with abnormally low IENFD, consistent with a small fiber neuropathy. *C*, Axonal bulbing. Skin with abnormally low IENFD, consistent with a small fiber neuropathy. The *arrowheads* point to epidermal nerve fibers, and just below is an axonal swelling.

Figure courtesy of Therapath, New York, New York.

KEY POINT

- Skin biopsy is the best currently available test for small fiber neuropathy. Intraepidermal nerve fiber density and nerve fiber morphology are assessed. The most common biopsy sites are the distal calf and proximal lateral thigh.

innervation; therefore, SGNFD is complementary to IENFD, which measures somatic nerves (**Figure 1-7**).[31] The biopsy requires a thicker specimen (6 mm to 8 mm) than IENFD to allow for adequate sampling. Reduced SGNFD is concordant with symptoms of sudomotor dysfunction. In a recent study, 20% of skin biopsies found low SGNFD as the sole abnormality.[32]

Skin biopsies can distinguish neuropathy from radiculopathy because radiculopathy does not affect postganglionic fibers. Skin biopsy may help evaluate the length dependence of a neuropathy by comparing proximal and distal IENFDs. In length-independent neuropathy, reduced IENFD is equal or more prominent proximally. However, severe length-dependent neuropathy may cause IENFD reduction at all sites.

In the studies evaluated by the AAN practice parameter, IENFD diagnostic sensitivity ranged from 45% to 90% and specificity was 95% to 97%. In a study of 67 patients with SFN, 88% had reduced distal leg IENFD while sensory NCSs were normal.[33] The high specificity indicates that IENFD is a good tool to verify a neuropathy, but a normal IENFD does not exclude neuropathy.[20] In a large study, 11% of patients with SFN based on clinical examination and QST had normal IENFD.[33] IENFD is correlated with objective SFN signs. The rate of false-negative IENFD is higher in patients with symptoms but without signs.[29]

The literature on the agreement between QST and IENFD is conflicting. IENFD correlates with thermal and nociceptive detection thresholds; however, correlation with other measures is uncertain, possibly because biopsy and QST are performed in different areas. Most studies report that IENFD has a higher sensitivity than QST for SFN.[34] IENFD correlation with vibratory threshold is more likely with combined large and small fiber neuropathy.

Skin biopsies have proven useful longitudinally. IENFD may reliably predict risk of neuropathy in asymptomatic individuals. In SFN, progressive IENFD reduction correlates with neuropathy progression. Improved IENFD with regeneration is associated with reduced neuropathic pain and sensory symptoms. It is unknown what IENFD magnitude of change is meaningful, and IENFD improvement can serve as a reliable surrogate for evaluation of the long-term course of polyneuropathy either clinically or in research studies. Currently, IENFD is used as a secondary outcome in therapeutic trials.[30]

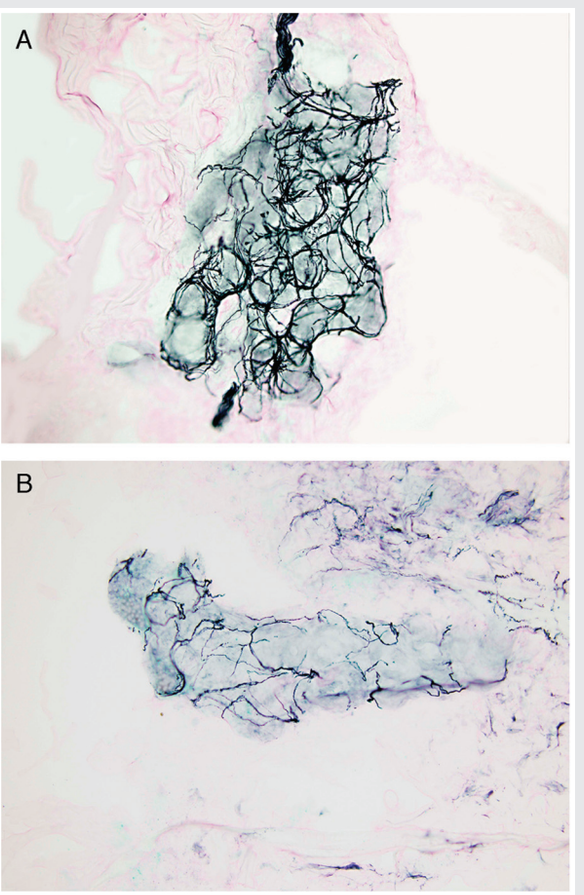

FIGURE 1-7 *A,* Normal skin sweat gland nerve fiber density. *B,* Abnormal skin sweat gland nerve fiber density.

Figure courtesy of Therapath, New York, New York.

Recent Advances

Two of the latest techniques used to investigate SFN are corneal confocal microscopy and laser Doppler imager flare (LDIF). Additionally, Meissner corpuscle (MC) density evaluation (using in vivo reflectance confocal microscopy) and skin wrinkling evaluation are in the early stages of development for clinical application.

Corneal confocal microscopy. In vivo laser corneal confocal microscopy (IVCCM) is used to image the sub-basal nerve plexus, which is composed of A delta and C fibers from the ophthalmic nerve that penetrate Bowman layers to become subjacent to the basal epithelial cells. Corneal nerve fiber density (CNFD), corneal nerve fiber length (CNFL), corneal nerve branching, and corneal nerve fiber tortuosity are assessed (**Figure 1-8**).[35] Reductions in CNFL and CNFD correspond to polyneuropathy severity. Serial examination has found early nerve regeneration (an increase in CNFD and CNFL) following pancreatic transplantation in diabetes. IVCCM has been evaluated in impaired glucose tolerance, diabetes,[36] Fabry disease, chemotherapy-induced neuropathy, anti-MAG neuropathy, and length-independent polyneuropathy/ganglionopathy (Sjögren disease and Crohn disease). This noninvasive and repeatable technique is particularly promising in length-independent SFN/ganglionopathy because of the proximal location.

The major limitation of IVCCM is limited availability of equipment and trained examiners. Some ophthalmologists have cautioned that the findings are nonspecific and may be seen in amiodarone-induced keratopathy and postphotorefractive keratectomy. Thus, more extensive normative data and larger confirmatory studies are needed before IVCCM can become a standard diagnostic procedure.

Laser Doppler imager flare. LDIF evaluates skin C fiber axon reflex response to heating (44°C [111.2°F]), with laser Doppler to measure the area of vasodilation in the neurogenic flare. The flare area is dependent on the receptive field size of the activated axons and is proportional to nerve fiber density. LDIF is reduced in neuropathy[37] and with local anesthetics (**Figure 1-9**).[38] Preliminary data[39] found LDIF to be more sensitive than quantitative thermal thresholds to detect SFN. Additionally, studies in patients with diabetes have shown

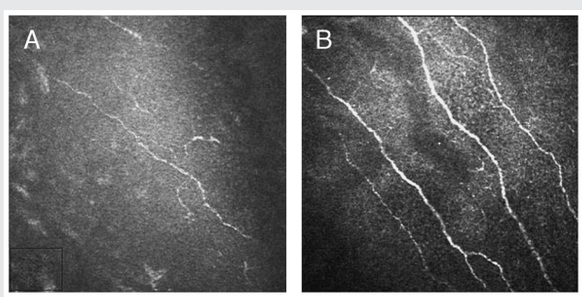

FIGURE 1-8 Frame from corneal confocal microscopy (original magnification × 3700). Decreased density of nerve fibers in Bowman layer in a patient with length-independent small fiber sensory neuropathy (as seen in **Case 1-1**) (*A*) compared with that in a normal control (*B*).

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KEY POINTS

- Analysis of sweat gland nerve fiber density is complementary to intraepidermal nerve fiber density in small fiber nerve evaluation, as they assess autonomic and somatic nerves, respectively.
- Skin biopsy may help differentiate between length-dependent and length-independent neuropathy. In length-dependent neuropathy, proximal intraepidermal nerve fiber density (IENFD) is relatively preserved, whereas in length-independent neuropathy, proximal IENFD may be equal or more affected than distal IENFD. In radiculopathy, IENFD is normal.
- Two of the latest techniques recommended to investigate small fiber neuropathy are corneal confocal microscopy and laser Doppler imager flare. Additionally, Meissner corpuscle density (using in vivo reflectance confocal microscopy) and skin wrinkling evaluation are in the early stages of development.

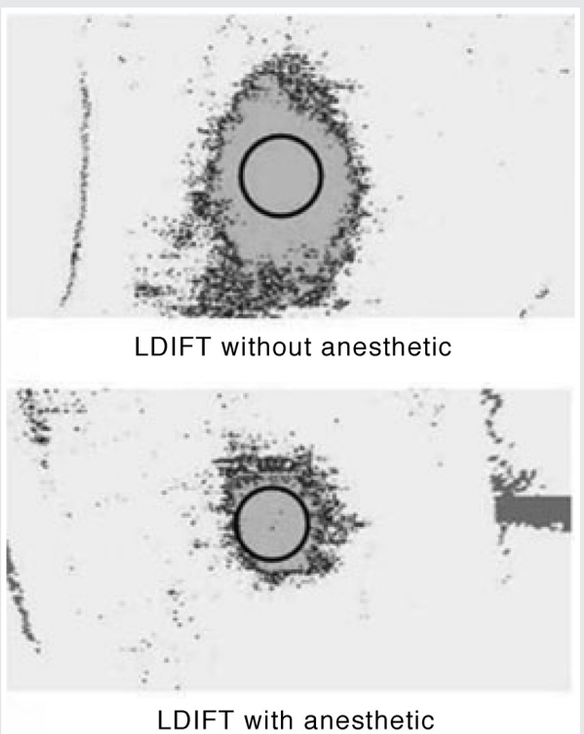

FIGURE 1-9 Laser Doppler imager flare technique. The *solid circle* represents the extent of the skin heater. The eutectic mixture of local anesthetics (lidocaine and prilocaine) blocks the axon reflex. The neurogenic (small fiber) component of the hyperemia is determined by the ratio of hyperemic area to stimulus area before and after anesthesia.

LDIFT = laser Doppler imager flare technique.

Reprinted with permission from Green AQ, Krishnan ST, Rayman G. C-fiber function assessed by the laser Doppler imager flare technique and acetylcholine iontophoresis. Muscle Nerve 2009;40(6):985–991.

LDIF abnormalities prior to neuropathy detection with currently available methods.

Meissner corpuscle density. MCs are skin mechanoreceptors that have one or more myelinated nerves at the base and contain a lobulated network of A beta and unmyelinated fibers. MCs can be assessed using in vivo reflectance confocal microscopy (**Figure 1-10**).[40] Fingertip MC density on skin biopsy paralleled reduction in IENFD in 25 patients with suspected neuropathy. More extensive experience, including normative data, is needed before this noninvasive method is widely used.

Stimulated skin wrinkling. A simple, noninvasive, bedside technique recently described is the use of stimulated skin wrinkling to assess small fiber function. Skin wrinkling is triggered by vasoconstriction that may be induced by immersion in water or by administration of a eutectic mixture of local anesthetics (EMLA). Water immersion–induced vasoconstriction is mediated by postganglionic sympathetic fibers. EMLA causes vasoconstriction possibly by acting on calcium channels in postganglionic neurons and smooth muscle cells. An abnormal result reliably predicts abnormal

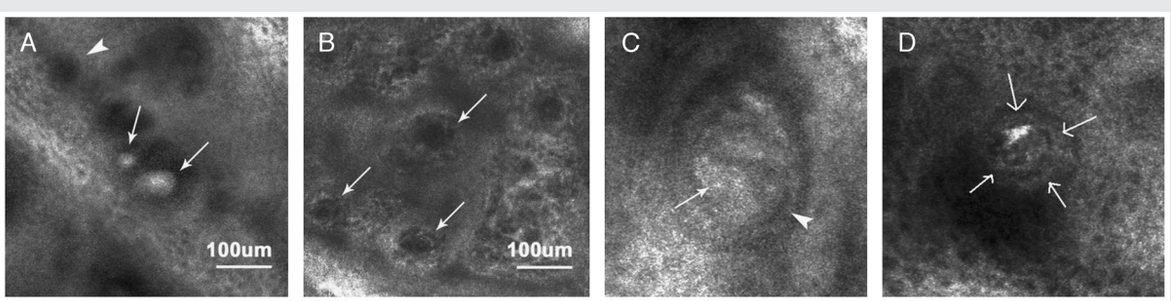

FIGURE 1-10 *A*, Identification of Meissner corpuscles (MCs) with in vivo reflectance confocal microscopy. Glabrous skin from the hand showing a dermal papilla with two MCs (*arrows*) and an empty papilla (*arrowhead*). *B*, Hairy skin of the forearm showing the expected absence of MCs in papillae (*arrows*). *C,* A higher magnification in vivo reflectance confocal microscopy image of an MC showing its capsule (*arrowhead*) and internal lobulated structure (*arrow*). *D,* An MC capsule (*arrows*) and heterogeneous bright signal on in vivo reflectance confocal microscopy of its internal axonal network.

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IENFD in sensory neuropathy, although a normal result did not correlate with normal IENFD.[41]

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