Sensory Polyneuropathies

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ABSTRACT

Purpose of Review: This article describes the methods of diagnosis and management of the sensory-predominant polyneuropathies. To simplify the approach to this category of patients, sensory-predominant polyneuropathies are divided broadly into either small fiber (or pain-predominant) neuropathies and large fiber (or ataxia-predominant) neuropathies, of which the sensory neuronopathies (dorsal root ganglionopathies) are highlighted.

Recent Findings: Physicians can now easily perform skin biopsies in their offices, allowing access to the gold standard pathologic diagnostic tool for small fiber neuropathies. Additional diagnostic techniques, such as corneal confocal microscopy, are emerging. Recently, small fiber neuropathies have been associated with a broader spectrum of diseases, including fibromyalgia, sodium channel mutations, and voltage-gated potassium channel antibody autoimmune disease.

Summary: Despite advances in diagnosing small fiber neuropathies and sensory neuronopathies, many of these neuropathies remain refractory to treatment. In select cases, early identification and treatment may result in better outcomes. ''Idiopathic'' should be a diagnosis of exclusion and a thorough investigation for treatable causes pursued.

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INTRODUCTION

This article reviews the various conditions that result in sensory polyneuropathies and guides the reader to the optimal way to evaluate and treat patients presenting with sensory symptoms. For the purpose of this article, the presentation, differential diagnosis, pathophysiology, and treatment are separated into small fiber (or pain-predominant) presentations and large fiber (or ataxia-predominant) presentations. Mixed small and large fiber sensory-predominant polyneuropathies (such as those caused by diabetes mellitus) are covered briefly at the end.

Nerves are classified by size, which correlates with their degree of myelination. Small fiber neuropathies are disorders that affect the small somatic fibers, including the small myelinated Aδ fibers and the small unmyelinated C fibers that transmit noxious and thermal signals.[1,2] In addition, the Aδ fibers mediate preganglionic sympathetic and parasympathetic function and the C fibers mediate postganglionic autonomic function.[2,3] Dysfunction of these small myelinated and unmyelinated fibers results in burning shooting pain as well as paresthesia and loss of small fiber function on examination.[2] In contrast, the large fiber neuropathies result from dysfunction of the Aβ fibers that mediate vibratory and touch sensation.[1] Patients who present with early-onset sensory ataxia may have pathology localized to the dorsal columns of the spinal cord, the dorsal root ganglia, or the Aβ nerve fibers, all of which carry large fiber–mediated proprioceptive information. Although the clinical

KEY POINTS

- Small fiber neuropathies result in burning pain and paresthesia, whereas patients who present with early-onset sensory ataxia typically have pathology that localizes to the dorsal columns, dorsal root ganglia, or large nerve fibers.
- Small fiber neuropathies commonly present in a length-dependent pattern. A patchy, non–length-dependent pattern suggests an autoimmune etiology.
- In patients with small fiber neuropathies, large fiber–mediated sensation, strength, reflexes, and gait should be normal.

hallmark of large fiber neuropathies is ataxia, damage to the small and medium-sized fibers may also occur, resulting in the positive sensory symptoms described above. The sensory neuronopathies (or dorsal root ganglionopathies) are caused by dysfunction of the dorsal root ganglia and are described in this article as they classically present with sensory ataxia.

The patient's clinical presentation, examination, and evaluation, including electrophysiologic testing and skin biopsy, will further support the localization of the polyneuropathy to either the small fibers or large fiber pathways (dorsal columns, dorsal root ganglia, or large nerve fibers). This, in turn, will allow the physician to arrive at a differential diagnosis to guide testing and management.

SMALL FIBER NEUROPATHY HISTORY AND EXAMINATION

Patients presenting with small fiber neuropathies may have negative neuropathic symptoms (loss of sensation) or positive neuropathic symptoms (burning, shooting, paresthesia) that typically follow a length-dependent or stocking-glove pattern. Rarely, patients will have a non–length-dependent pattern with prominent involvement of the face, trunk, and arms. This non–length-dependent pattern may be seen in patients with autoimmune diseases, such as Sjögren syndrome, celiac disease, sarcoidosis, and paraneoplastic syndromes, as well as in patients with diabetes mellitus, impaired glucose tolerance, vitamin B_{12} deficiency, and paraproteinemia.[4] Loss of thermal sensation leads to inability to sense hot versus cold, and loss of noxious sensation results in painless injuries and numbness. The pain caused by small nerve fiber dysfunction is often described as burning, shooting, electrical, or tingling paresthesia.[5] Patients may report that nonpainful stimuli are painful (allodynia) or that they perceive painful stimuli as even more painful (hyperalgesia). Neuropathic pain will often worsen at night and impair sleep. Autonomic nerve dysfunction may range from mildly decreased sweating in the affected areas to more generalized dysfunction, including dry eyes, dry mouth, orthostatic dizziness, erectile dysfunction, palpitations, urinary retention, gastroparesis, constipation, hypohidrosis, hyperhidrosis, and skin discoloration.[3,6,7] The time course varies depending on the etiology. For example, treatment-induced neuropathy of diabetes mellitus presents acutely, whereas idiopathic small fiber neuropathies are often indolent. **Table 10-1** [8–13] lists various causes of small fiber neuropathies along with their associated features and diagnostic evaluations.

On examination, patients may have dry, shiny, discolored, and atrophic skin in the affected areas due to loss of distal autonomic vasomotor control. Patients will have decreased pain (often tested with pinprick) and temperature sensation in either a length-dependent or non–length-dependent pattern. Muscle stretch reflexes, proprioception, and strength are preserved. As the dysfunction is localized only to the small nerve fibers, ambulation should be spared, although may be antalgic.

SENSORY NEURONOPATHY HISTORY AND EXAMINATION

The clinical hallmark of sensory neuronopathies is early-onset ataxia due to damage to the afferent fibers carrying proprioceptive information from the proximal arms and legs.[14] When severe, this results in writhing movements of the fingers and toes when the eyes are closed called *pseudoathetosis*.[14,15] When the small and medium-sized nerves are involved, the patient may also experience painful

TABLE 10-1 Disorders Associated With Small Fiber Neuropathy

Etiology	Associated Features	Diagnostic Evaluation
Metabolic		
Impaired glucose tolerance, impaired fasting glucose	Central obesity, sedentary lifestyle, risk of developing type 2 diabetes mellitus	2-hour glucose tolerance test, fasting blood sugar, glycosylated hemoglobin
Diabetes mellitus	Polyuria, polydipsia, retinopathy, nephropathy	Glycosylated hemoglobin, 2-hour glucose tolerance test, fasting blood sugar
Treatment-induced neuropathy of diabetes mellitus	Acute onset of pain within 8 weeks of correcting hyperglycemia	Clinical diagnosis
Hyperlipidemia (especially hypertriglyceridemia)	Increased risk of coronary artery disease and cerebrovascular disease	Lipid profile including triglycerides
Immune-mediated		
Sarcoidosis	Cough; dyspnea; chest pain due to diffuse interstitial lung disease; extrapulmonary involvement, including kidneys, skin, heart, joints, eyes, lymph nodes	Chest x-ray, serum angiotensin-converting enzyme, lymph node or other tissue biopsy
Sjögren syndrome	Sicca symptoms (xerophthalmia, xerostomia)	Anti-Ro (SSA)/anti-La (SSB) antibodies, rose bengal test, Schirmer test, lip/salivary gland biopsy
Systemic lupus erythematosus	Rash, Raynaud syndrome, arthralgia, renal impairment, cardiac disease, hematologic abnormalities	ANA, antiphospholipid antibodies, complement levels, ESR/CRP, anti-dsDNA and anti-Smith antibodies
Celiac disease	Diarrhea, flatulence, malabsorption	Antigliadin antibodies (serum IgA endomysial and tissue transglutaminase antibody), IgG-deamidated gliadin peptides, small bowel biopsy, testing for HLA DQ2/DQ8
Inflammatory bowel disease (Crohn disease and ulcerative colitis)	Abdominal pain, diarrhea, bloating, rectal bleeding	Routine laboratory studies, including inflammatory markers, endoscopy, barium studies
Paraneoplastic	Malignancy association likely with anti-Hu antibodies; with CASPR2 antibodies, subtype of voltage-gated potassium channel antibodies may have encephalitis and peripheral nerve hyperexcitability; with anti-Hu, often have large fiber involvement and may have associated limbic encephalitis, cerebellar dysfunction, autonomic dysfunction	Voltage-gated potassium channel antibodies, CASPR2 and anti-Hu antibodies

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TABLE 10-1 **Disorders Associated With Small Fiber Neuropathy** *Continued from page 1413*

Etiology	Associated Features	Diagnostic Evaluation
Infectious		
Leprosy	Affects cool regions; skin changes, enlarged nerves, anhidrosis	Serum antibodies to phenolic glycolipid-I, skin biopsy or nerve biopsy for acid-fast bacilli
HIV	Associated with lower CD4 counts and higher viral loads	HIV viral load and CD4 count
Hepatitis C	Hepatitis, cirrhosis, may occur without cryoglobulinemia	Hepatitis C virus antibody, hepatitis C PCR
Cryoglobulinemia	Typically occurs with hepatitis C virus and mixed cryoglobulinemia, purpuric cutaneous lesions, arthralgia; often with large fiber involvement	More often associated with mixed cryoglobulinemia; check cryoglobulins, hepatitis C virus antibody and PCR
Toxins		
Drugs	Many associations, including antiretrovirals, bortezomib, flecainide, metronidazole, nitrofurantoin, and others	Temporal relation to drug use and duration of use
Alcohol	Cirrhosis, platelet dysfunction, anemia, pancreatitis	Temporal relation to alcohol use and duration of alcohol use
Hereditary		
Hemochromatosis	Fatigue, cirrhosis, pancreatic involvement (diabetes mellitus), arthritis, cardiomyopathy, hyperpigmented skin, hypogonadotrophic hypogonadism	High serum ferritin
Fabry disease	Males (X-linked), episodic pain, strokes, hearing loss, angiokeratomas, corneal opacities; female carriers may have a milder phenotype	α-Galactosidase A mutation (enzyme assay to measure α-galactosidase A activity)
Familial amyloidosis	Sensory and autonomic neuropathy, carpal tunnel syndrome, cardiac and renal involvement	Genetic testing for transthyretin (*TTR*), apolipoprotein A1 (*APOA1*), and gelsolin (*GSN*) mutations
Ehlers-Danlos syndrome	More common in hypermobile type	Clinical diagnosis, includes hypermobile joints and hyperextensible skin
Other		
Fibromyalgia	Diffuse muscle pain and fatigue	Several published diagnostic criteria for fibromyalgia[8–13]
Sporadic amyloidosis	Cardiomyopathy, renal failure with nephrotic syndrome, hepatosplenomegaly, enlarged muscles, skin changes, increased bleeding, autonomic dysfunction	Serum protein electrophoresis, immunofixation, light chains, abdominal fat pad biopsy, rectal mucosa biopsy
Idiopathic		Diagnosis of exclusion

ANA = antinuclear antibody; CASPR2 = contactin-associated proteinlike 2; CRP = C-reactive protein; dsDNA = double-stranded deoxyribonucleic acid; ESR = erythrocyte sedimentation rate; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IgA = immunoglobulin A; IgG = immunoglobulin G; PCR = polymerase chain reaction; SSA = Sjögren syndrome A; SSB = Sjögren syndrome B.

positive sensory symptoms. These disorders often result in numbness and positive sensory symptoms in a non–length-dependent and multifocal pattern, which differentiates them from the typical length-dependent sensory and motor polyneuropathies. Nystagmus has been reported due to failure of proprioceptive input from the extraocular or vestibular system.[16,17] Strength is usually spared, although it is not uncommon for the motor fibers to be affected in paraneoplastic sensory neuronopathies. Patients may appear weak, however, as they have difficulty sustaining steady motor output because of lack of proprioceptive feedback. Muscle stretch reflexes are often unelicitable.[14] The time course for sensory neuronopathies is variable and can be subacute in paraneoplastic, immune-mediated, or postinfectious cases or indolent in the idiopathic forms.[14,16,18] **Table 10-2** lists ataxic neuropathies, their symptoms, clinical characteristics, and diagnostic evaluations.

DIAGNOSTIC STUDIES

The diagnosis of sensory polyneuropathies relies heavily on neurophysiologic testing and pathologic studies, including skin biopsy and corneal confocal microscopy. Imaging is typically only used in the context of sensory neuronopathies.

Nerve Conduction Studies and Electromyography

Routine nerve conduction studies and EMG should be normal in small fiber neuropathies, although many neuropathies that are clinically small fiber predominant will have electrophysiologic evidence of large fiber involvement. An electrodiagnostic study showing no evidence of polyneuropathy (including presence of sural and plantar responses) does not exclude a pure small fiber polyneuropathy.

Sensory neuronopathies are characterized by absent or reduced-amplitude sensory nerve action potentials (SNAPs) with normal or slightly reduced sensory conduction velocities.[19] Motor nerve conduction studies should be normal. Paraneoplastic sensory neuronopathies, such as anti-Hu syndromes, may have motor nerve involvement and conduction abnormalities in either an axon loss or demyelinating pattern.[19]

Blink reflexes have been demonstrated to be abnormal in patients with Sjögren syndrome–associated, idiopathic, and paraneoplastic sensory neuronopathies.[20] **Figure 10-1** shows a diagnostic algorithm for small fiber neuropathies, and **Figure 10-2** shows a diagnostic algorithm for sensory neuronopathies.

Autonomic Testing

A number of neurophysiologic tests other than nerve conduction studies and EMG have been studied and used in small fiber neuropathies, including autonomic testing, quantitative sensory testing for hot and cold sensation, sympathetic skin response, laser-evoked potentials recording, and electrochemical skin conductance.[21]

Autonomic testing is particularly helpful in the evaluation of small fiber neuropathies, especially in the presence of dysautonomia.[22] Standard tests of autonomic function include sympathetic adrenergic, parasympathetic cardiovagal, and sudomotor function testing. In small fiber neuropathies, the two most helpful tests are the quantitative sudomotor axon reflex test (QSART) and thermoregulatory sweat testing[7] neither of which is widely available. QSART measures local sudomotor function mediated by postganglionic unmyelinated sympathetic axons by detecting change in sweat production after acetylcholine is transported into the skin using a

KEY POINTS

- Sensory neuronopathies are characterized by early-onset sensory ataxia. The numbness is classically multifocal and non–length dependent.
- Nerve conduction studies and EMG are normal in small fiber neuropathies.
- The most helpful autonomic tests for small fiber neuropathies are the quantitative sudomotor axon reflex test and thermoregulatory sweat test; however, these tests are not widely available.

TABLE 10-2 Causes of Ataxic Neuropathies and Neuronopathies

Etiology	Associated Symptoms and Clinical Characteristics	Diagnostic Evaluations
Immune-mediated		
Connective tissue disease		
Sjögren syndrome	Sicca symptoms (xerophthalmia, xerostomia); usually presents as a sensory neuronopathy	Anti-Ro (SSA)/anti-La (SSB) antibodies, rose bengal test, Schirmer test, lip/salivary gland biopsy
Systemic lupus erythematosus	Rash, Raynaud syndrome, arthralgia, renal impairment, cardiac disease, hematologic abnormalities	ANA, antiphospholipid antibodies, complement levels, ESR, CRP, anti-dsDNA and anti-Smith antibodies
Demyelinating polyneuropathies		
Ataxic Guillain-Barré syndrome	Without ophthalmoplegia (differentiates from Miller Fisher syndrome), preceding infection, distal paresthesia, impaired sensation, prominent gait ataxia	Antibodies against anti-GD1b and GQ1b, CSF with albuminocytologic dissociation
Miller Fisher syndrome	Ophthalmoplegia, ataxia, areflexia, preceding infection	Anti-GQ1b antibodies
Distal acquired demyelinating symmetric (DADS) neuropathy or anti-MAG neuropathy	Sensory ataxia with minimal weakness, symmetric, distal sensory and motor deficit, slowly progressive, more common in older people	Anti-MAG antibodies, IgM monoclonal gammopathy, characteristic electrophysiologic studies with very prolonged distal motor latencies and lack of conduction block
Chronic ataxic neuropathy, ophthalmoplegia, M protein, agglutination with disialosyl antibodies (CANOMAD)[a]	Sensory loss, mild weakness, ophthalmoplegia, trigeminal neuropathy, bulbar dysfunction	Anti-GD1b antibodies, elevated ESR; CSF may demonstrate elevated protein
Chronic inflammatory sensory polyradiculopathy (CISP)	Gait ataxia, sensory symptoms, loss of large fiber–mediated sensation, frequent falls	Normal nerve conduction studies, abnormal SSEPs; enlarged nerve roots and elevated CSF protein
Gait ataxia, late-onset, polyneuropathy (GALOP)	Ataxia, sensory-predominant polyneuropathy	Monoclonal gammopathy (IgM), autoantibodies against central myelin antigen (CMA)

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TABLE 10-2 **Causes of Ataxic Neuropathies and Neuronopathies** *Continued from page 1416*

Etiology	Associated Symptoms and Clinical Characteristics	Diagnostic Evaluations
Other autoimmune		
Paraneoplastic sensory neuronopathy	Associated malignancy, often small cell lung cancer; may have prominent pain and some motor involvement; may have associated limbic encephalitis, cerebellar dysfunction, autonomic dysfunction	Anti-Hu and anti-CV2/CRMP-5 antibodies, malignancy workup
Celiac disease	Diarrhea, flatulence, malabsorption	Antigliadin antibodies (serum IgA endomysial and tissue transglutaminase antibody), IgG-deamidated gliadin peptide, small bowel biopsy, testing for HLA DQ2/DQ8
Autoimmune hepatitis	Hepatomegaly, jaundice, liver failure	Anti–smooth muscle antibodies, ANA, ALKM-1 and ALC-1 antibodies
Fibroblast growth factor-3 (FGFR3) antibody associated	Severe painful sensory neuronopathy with ataxia and frequent trigeminal involvement	FGFR3 antibodies
Nutritional deficiencies		
Vitamin B_{12} (subacute combined degeneration)	Distal weakness, spasticity and upper motor neuron findings, megaloblastic anemia, cognitive impairment	Vitamin B_{12}, MMA, homocysteine
Copper	Zinc toxicity predisposes (from zinc supplements, denture cream); associated with spasticity/hyperreflexia, sensory ataxia, large fiber involvement, progressive asymmetric weakness; may have associated hematologic features	Copper, CBC with differential, consider spine MRI (T2 signal increased in posterior columns)
Folic acid	Progressive leg numbness and ataxia	Red blood cell folate and serum homocysteine (high)
Vitamin E	Deficiency can be due to malabsorption/malnutrition; prominent large fiber dysfunction, sensory ataxia	Vitamin E
Thiamine (vitamin B_{12})	Polyneuropathy may be acute or chronic; sensory and motor symptoms, neuropathic pain If associated with Wernicke syndrome, will also have acute onset of confusion, ataxia, ophthalmoplegia	Do not wait for levels (eg, serum thiamine, erythrocyte transketolase activation assay) to come back before treating

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TABLE 10-2 **Causes of Ataxic Neuropathies and Neuronopathies** *Continued from page 1417*

Etiology	Associated Symptoms and Clinical Characteristics	Diagnostic Evaluations
Toxic		
Chemotherapy (platinum-based)	Sensory ataxia with paresthesia	Use of platinum drugs
Pyridoxine (vitamin B_6)	Sensory ataxia	Vitamin B_6
Nitrous oxide	Pansensory neuropathy and myelopathy, megaloblastic anemia	Clinical history of nitrous oxide abuse
Hereditary		
Friedreich ataxia	Cerebellar ataxia, gait instability, dysarthria, dysphagia, large fiber sensory loss, weakness, spasticity	Frataxin mutation, expansion of number of GAA repeats
Sensory ataxic neuropathy, dysarthria, and ophthalmoparesis (SANDO)	Large and small fiber neuropathy, sensory ataxia, variable strength, ptosis, ophthalmoplegia	*POLG* mutations, dominant or recessive
Neuropathy, ataxia, retinitis pigmentosa (NARP)	Sensory neuropathy, cerebellar ataxia, retinitis pigmentosa	Adenosine triphosphate (ATP) synthase 6 mutation, maternally inherited
Abetalipoproteinemia, vitamin E transporter deficiency	Prominent large fiber dysfunction, sensory ataxia	Vitamin E; microsomal triglyceride transfer protein mutations; low circulating β-lipoproteins, VLDL, LDL, chylomicrons
Infectious		
Syphilis (tabes dorsalis)	Impaired large fiber–mediated sensation, lightening pain, Argyll Robertson pupils, autonomic dysfunction, Charcot joints, aortitis	MHA-TP or FTA-ABS
Human T-cell lymphotropic virus type I (HTLV-I)/ human T-cell lymphotropic virus type II (HTLV-II)	Myelopathy, sensory ataxia, urinary and fecal incontinence	HTLV-I/II, MRI with increased T2 signal in the lateral columns and cord atrophy
Other		
Cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS)	Cerebellar ataxia, nystagmus, sensory polyneuropathy, autonomic	Brain MRI with cerebellar atrophy, abnormal vestibulo-ocular reflex, abnormal autonomic testing
Idiopathic		Diagnosis of exclusion

ALC-1 = anti-liver cytosol antigen; ALKM-1 = anti-liver/kidney microsome antibody; ANA = antinuclear antibody; CBC = complete blood count; CRMP-5 = collapsin response mediator protein-5; CRP = C-reactive protein; CSF = cerebrospinal fluid; dsDNA = double-stranded deoxyribonucleic acid; ESR = erythrocyte sedimentation rate; FTA-ABS = fluorescent treponemal antibody absorption; HLA = human leukocyte antigen; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; LDL = low-density lipoprotein; MAG = myelin-associated glycoprotein; MHA-TP = microhemagglutination assay for *Treponema pallidum* antibodies; MMA = methylmalonic acid; MRI = magnetic resonance imaging; POLG = polymerase DNA gamma; SSA = Sjögren syndrome A; SSB = Sjögren syndrome B; SSEP = somatosensory evoked potential; VLDL = very-low-density lipoprotein.

[a] The term *chronic ataxic neuropathy with disialosyl antibodies* (CANDA) has been adopted by some experts as a more inclusive (and less limiting) term.

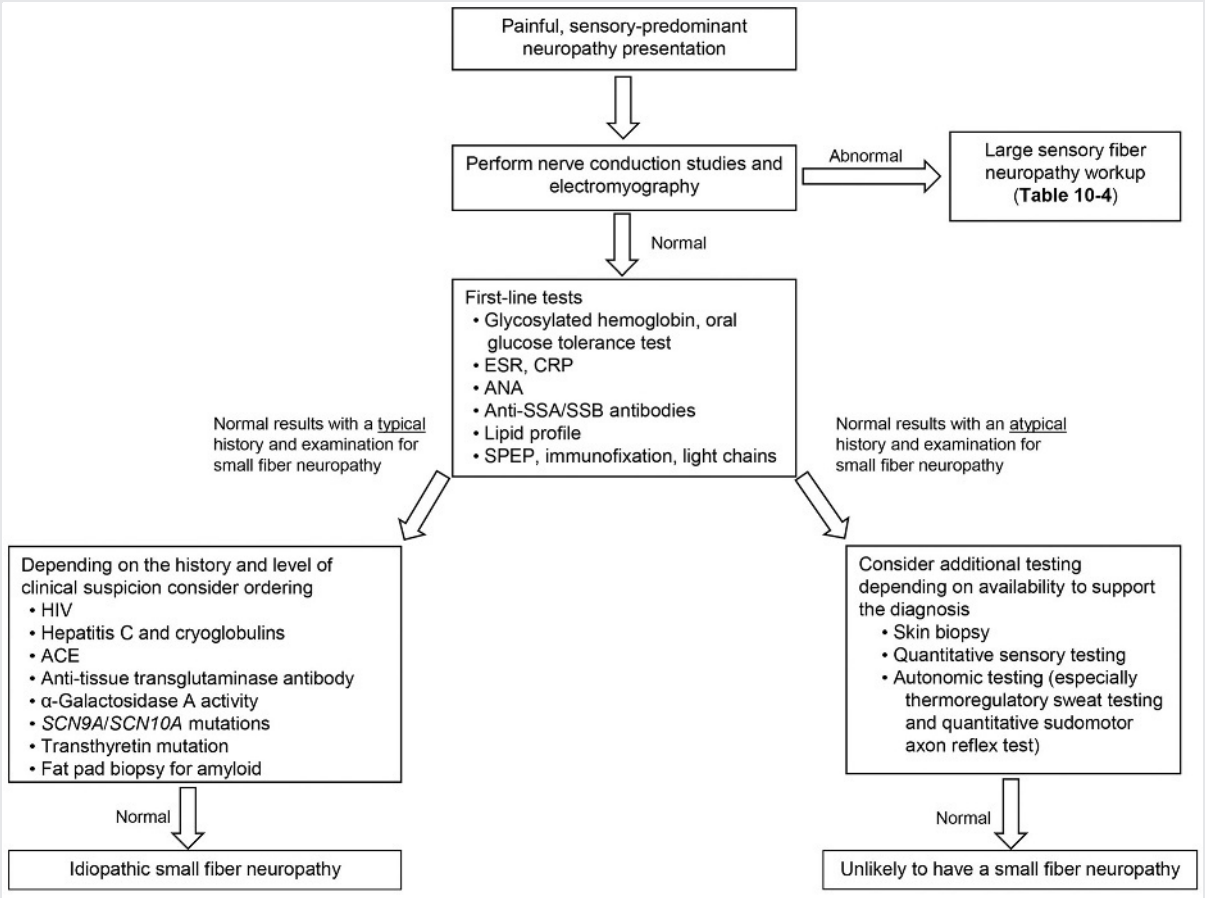

FIGURE 10-1 A diagnostic algorithm for small fiber neuropathies.

ACE = angiotensin-converting enzyme; ANA = antinuclear antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; HIV = human immunodeficiency virus; SPEP = serum protein electrophoresis; SSA = Sjögren syndrome A; SSB = Sjögren syndrome B.

small electrical current (iontophoresis). Four standard sites are used (proximal foot, distal leg, proximal leg, and forearm), and the sweat response is recorded from sweat chambers that are separated from the stimulus compartment.[7] The addition of QSART to the clinical examination, quantitative sensory testing, and skin biopsy increases the diagnostic yield in small fiber polyneuropathies.[23] A correlation exists between the severity of loss of intraepidermal nerve fibers (somatic C-fiber involvement) and QSART abnormalities testing autonomic C-fiber involvement.[24]

Thermoregulatory sweat testing demonstrates sweat production by raising the core body temperature in a hot and humid environment.[7] An indicator dye is applied to the body and measures maximal sweating. The percentage of anhidrosis is calculated from photographs of the sweat distribution on the anterior body. Thermoregulatory sweat testing has been reported to be abnormal in up to 91% of patients with small fiber neuropathy.[7] In a large series of patients with small fiber polyneuropathy, 98% had abnormal sudomotor testing, and a length-dependent pattern of sudomotor dysfunction was appreciated in most.[7]

Testing of cardiovagal function is assessed through the heart rate response

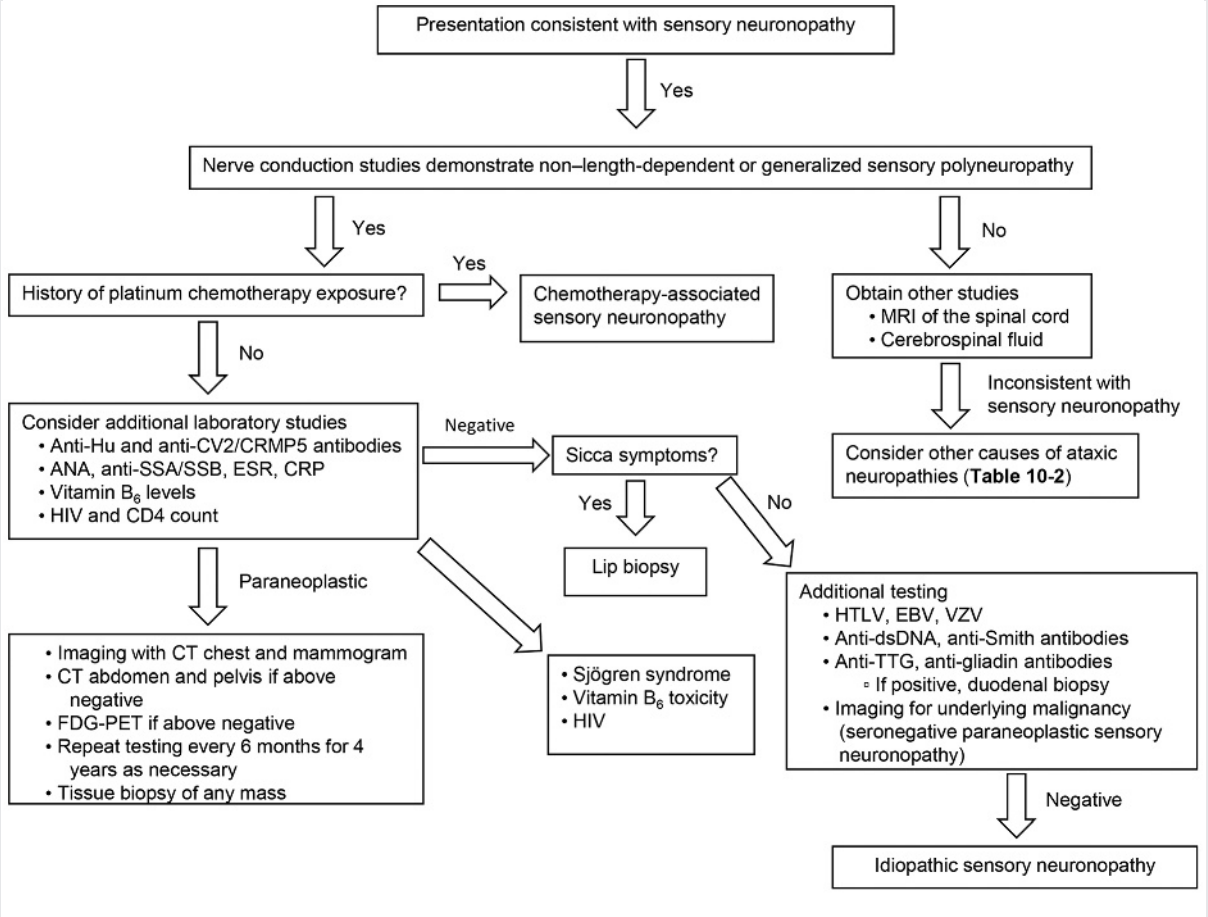

FIGURE 10-2 A diagnostic algorithm for sensory neuronopathies.

ANA = antinuclear antibody; CMRP-5 = collapsin response mediator protein-5; CRP = C-reactive protein; CT = computed tomography; dsDNA = double-stranded deoxyribonucleic acid; EBV = Epstein-Barr virus; ESR = erythrocyte sedimentation rate; FDG-PET = fludeoxyglucose positron emission tomography; HIV = human immunodeficiency virus; HTLV = human T-cell lymphotrophic virus; MRI = magnetic resonance imaging; SSA = Sjögren syndrome A; SSB = Sjögren syndrome B; TTG = tissue transglutaminase; VZV = varicella-zoster virus.

KEY POINT

■ Skin biopsy is the pathologic gold standard for diagnosing small fiber neuropathy.

to deep breathing and the Valsalva ratio. Sympathetic adrenergic testing is assessed by beat-to-beat blood pressure response during Valsalva maneuver and head-up tilt. Adrenergic function is measured by phase 2 and phase 4 of the blood pressure response to Valsalva maneuver. While these studies may demonstrate cardiovagal and sympathetic adrenergic dysfunction in small fiber polyneuropathies, the changes are typically mild.[7] Autonomic testing and somatic sensory testing (quantitative sensory testing and intraepidermal nerve fiber density) are considered independent and complementary measures of small fiber function.[25]

Skin Biopsy

The majority of patients with small fiber neuropathy do not need a skin biopsy to support the diagnosis; the history and examination findings are sufficient. However, skin biopsy is a validated efficient technique used to diagnose small fiber neuropathy and is

considered the pathologic gold standard.[22,26] The diagnostic sensitivity and specificity of skin biopsy have not been independently verified, so currently they have been defined through a clinical standard.[27] Sensitivities of skin biopsy have ranged from 45% to 90%[22] and specificities from 95% to 97%.[22,27] These procedures are easily performed in the outpatient setting. A 3-mm punch skin biopsy is taken typically at the distal leg 10 cm above the lateral malleolus.[2] Sites are added at the lateral distal thigh, lateral proximal thigh, and upper extremity to explore the presence of a non–length-dependent pattern.[2]

Intraepidermal nerve fiber density is the criterion most accepted to support a clinical diagnosis of small fiber neuropathy. Exposure of skin biopsy preparations to the antibody to protein gene product 9.5, a neuronal form of ubiquitin carboxyl-terminal hydrolase transported with the slow component of axonal transport, allows for visualization and quantification of the small fiber innervation of the epidermis.[28] In addition, the sudomotor fibers around the sweat glands and pilomotor fibers within the arrectores pilorum muscles can be quantified to support involvement of the autonomic nervous system.[2,5]

A study of small fiber neuropathy reported that patients lose epidermal nerve fibers at similar rates, whether the etiology is impaired glucose tolerance, diabetes mellitus, or idiopathic.[29] No difference was seen in loss of epidermal nerve fibers at proximal and distal biopsy sites, suggesting that these small fiber polyneuropathies are non–length-dependent terminal axonopathies. Skin biopsy in small fiber–predominant sensory neuronopathies may also demonstrate a non–length-dependent pattern of reduced intraepidermal nerve fiber density.[14]

Corneal Confocal Microscopy in Small Fiber Neuropathies

Corneal confocal microscopy is an emerging noninvasive diagnostic tool for assessment of corneal trigeminal small sensory fibers and immune cells that has been applied to the study of small fiber neuropathies.[30] At present, this technique is primarily used in the research realm and is not commonly used by clinical neurologists. Corneal nerve fiber density is decreased and tortuosity increased in patients with small fiber neuropathies.[30,31] Abnormalities have been described in patients with impaired glucose tolerance,[31] diabetes mellitus,[32] and idiopathic small fiber neuropathy.[33]

Imaging

Imaging has a role in the sensory neuronopathies. Most often, imaging is used to identify an underlying malignancy in those with a suspected paraneoplastic etiology. MRI may demonstrate increased T2-weighted signal in the dorsal columns as the result of degeneration of central sensory projections.[17] Recently, techniques such as multiple-echo data image combination (MEDIC) and turbo inversion recovery magnitude (TIRM) have shown characteristic changes in sensory neuronopathies.[34]

SPECIFIC SMALL FIBER NEUROPATHIES

Small fiber neuropathies are associated with a number of etiologies, ranging from metabolic diseases to drug toxicities, infections, autoimmune diseases, and inherited causes. Only a few specific small fiber neuropathies are discussed in detail here. Refer to **Table 10-1** for a more comprehensive list.

Small Fiber Neuropathy Due to Diabetes Mellitus, Impaired Glucose Tolerance, and Metabolic Syndrome

Diabetes mellitus is the most common cause of peripheral neuropathy

KEY POINTS

- Metabolic syndrome is associated with small fiber polyneuropathy. Lifestyle intervention may have a role in preventing the development of and treating established neuropathy in patients with impaired glucose tolerance.
- Treatment-induced neuropathy of diabetes mellitus is an acute small fiber neuropathy with severe neuropathic pain that occurs in the setting of rapid correction of hyperglycemia.

worldwide and may cause a small fiber neuropathy, large fiber sensory-predominant neuropathy, or sensorimotor neuropathy.[35] Diabetes mellitus is diagnosed with a glycosylated hemoglobin (hemoglobin A_{1c}) higher than 6.5%, a glucose of 200 mg/dL following a 2-hour oral glucose tolerance test, or a fasting glucose of greater than or equal to 126 mg/dL.[36] Individuals classified as prediabetic have a glycosylated hemoglobin between 5.7% and 6.4%, a 2-hour glucose tolerance test glucose of 140 mg/dL to 199 mg/dL, or a fasting blood glucose of 100 mg/dL to 125 mg/dL.[36] Diabetes mellitus and glucose intolerance are present in one-third of patients with a distal sensory polyneuropathy.[37] Nearly 50% of those who would otherwise be labeled as having idiopathic sensory neuropathy have evidence of impaired glucose tolerance, although whether this is an association or causative is unclear.[38–40]

Metabolic syndrome is diagnosed in the presence of a combination of dyslipidemia, elevated blood pressure, central obesity, and either diabetes mellitus or prediabetes and has a prevalence of 35% to 38% in the US population.[3,41] Metabolic syndrome has been reported to be an association or possible risk factor for distal sensory neuropathy.[42–44] A cross-sectional study of 548 patients with type 2 diabetes mellitus demonstrated that those with metabolic syndrome were twice as likely to have a distal sensory neuropathy as those without.[42] Independent of hyperglycemia, obesity and dyslipidemia are heavily associated with neuropathy.[43,44] Hypertriglyceridemia in particular may be associated with the development of small fiber neuropathy.[45]

Tight glucose control in type 1 diabetes mellitus is known to prevent the development of clinical neuropathy and likely prevents neuropathy in patients with type 2 diabetes mellitus.[46] The amount of benefit derived from glucose control is limited, as patients may progress to clinical neuropathy despite intensive glucose control.[41] Some patients stabilize without improvement.[47] Diet and exercise may delay the transition from impaired glucose tolerance to diabetes mellitus and may prevent the onset of neuropathy in patients with type 2 diabetes mellitus.[48] The Impaired Glucose Tolerance Neuropathy Study demonstrated improvement in small fiber neuropathy measures (intraepidermal nerve fiber density, QSART, and pain scores) and features of metabolic syndrome (body mass index, oral glucose tolerance test, cholesterol, and triglycerides) at 1 year with lifestyle interventions.[39] For most patients, management also includes treatment of neuropathic pain. Commonly used neuropathic pain medications are listed in **Table 10-3**.

Treatment-induced neuropathy of diabetes mellitus. Treatment-induced neuropathy of diabetes mellitus, previously also called *insulin neuritis*, is an acute small fiber neuropathy that occurs with rapid correction of hyperglycemia (**Case 10-1**). This entity has been described in patients treated with insulin, oral hypoglycemics, and weight loss who experience rapid glycemic control.[49] Severe neuropathic pain can develop acutely within 8 weeks, may be length dependent or diffuse, and usually has associated hyperalgesia and allodynia. Autonomic dysfunction may follow the onset of neuropathic pain.[49] The pathophysiology of this disorder is unclear. One study reported a strong correlation between the change in glycosylated hemoglobin and the severity of neuropathic pain.[49] The incidence of treatment-induced neuropathy of diabetes mellitus increases

TABLE 10-3 Common Neuropathic Pain Medications

Class/Drug	Mechanism of Action	Side Effects	Total Daily Dosing Range	Precautions
Serotonin norepinephrine reuptake inhibitor (SNRI)				
Venlafaxine	Inhibits reuptake of serotonin and norepinephrine	Nausea, blood pressure increase, headache, sleep disturbance	75–225 mg/d as a single dose (venlafaxine XR) or in 2 to 3 divided doses (venlafaxine)	Use with caution in cardiac disease as may cause tachycardia and hypertension; dosage adjustment needed for impaired renal and hepatic function
Duloxetine	Inhibits reuptake of serotonin and norepinephrine	Nausea, vomiting, dizziness, headache, sleep disturbance	60–120 mg/d; may be divided into twice daily dosing for doses greater than 60 mg/d	Avoid use in significant renal impairment or liver disease
Tricyclic antidepressants				
Amitriptyline	Inhibits serotonin, norepinephrine reuptake; blocks sodium channels and has anticholinergic properties	Anticholinergic effects (dry eyes/dry mouth, orthostatic hypotension, urinary retention), somnolence, weight gain, constipation	25–150 mg nightly	Use with caution in cardiac disease and conduction abnormalities
Nortriptyline	Inhibits serotonin, norepinephrine reuptake; blocks sodium channels and has anticholinergic properties	Anticholinergic effects (dry eyes/dry mouth, orthostatic hypotension, urinary retention), somnolence, weight gain	25–150 mg nightly	Use with caution in cardiac disease and conduction abnormalities
Desipramine	Inhibits serotonin, norepinephrine reuptake; blocks sodium channels and has anticholinergic properties	Anticholinergic effects (dry eyes/dry mouth, orthostatic hypotension, urinary retention), somnolence, weight gain	25–150 mg nightly	Use with caution in cardiac disease and conduction abnormalities

Continued on page 1424

TABLE 10-3 **Common Neuropathic Pain Medications** *Continued from page 1423*

Class/Drug	Mechanism of Action	Side Effects	Total Daily Dosing Range	Precautions
Calcium channel α2δ ligands				
Gabapentin	Acts on the α2δ subunit of voltage-gated calcium channels, decreasing central sensitization	Sedation, peripheral edema, weight gain, dizziness, incoordination	300–3600 mg divided 3 times a day; extended formulation available	Dose adjustment needed with renal dysfunction
Pregabalin	Acts on the α2δ subunit of voltage-gated calcium channels, decreasing central sensitization	Sedation, peripheral edema, weight gain, dizziness, incoordination	150–600 mg divided up to 3 times a day	Dose adjustment needed with renal dysfunction; use with caution in severe cardiovascular disease
Opioid agonist				
Tramadol	μ-Receptor agonist and norepinephrine and serotonin reuptake inhibitor	Constipation, nausea and vomiting, dizziness, somnolence, headache	100–400 mg divided up to 4 times a day	May lower seizure threshold; dosage adjustment needed with renal dysfunction; can be associated with serotonin syndrome when combined with other serotonergic drugs
Tapentadol	μ-Receptor agonist and norepinephrine reuptake inhibitor	Constipation, nausea and vomiting, dizziness, somnolence	100–500 mg divided twice daily; extended release formulation available	Dosage adjustment needed with hepatic dysfunction
Opioids (examples include oxycodone, hydromorphone, morphine)	μ-Receptor agonists	Constipation, nausea, vomiting, dizziness, somnolence	Varies depending on formulation	Dependency; opioid-induced respiratory depression in vulnerable individuals
Topical lidocaine patch	Sodium channel inhibition	Skin reaction, including erythema/pruritus	Up to three patches, on for 12 hours, off for 12 hours; also available as an ointment, cream, and gel	Do not use in individuals with a history of amide local anesthetic sensitivity

Continued on page 1425

TABLE 10-3 Common Neuropathic Pain Medications *Continued from page 1424*

Class/Drug	Mechanism of Action	Side Effects	Total Daily Dosing Range	Precautions
Capsaicin				
Patch	Transient receptor potential vanilloid 1 agonist and depletes substance P	Associated allodynia initially, erythema, elevated blood pressure	Apply to affected area, not more than four patches per application for 60 minutes; effective for 3 months	Use with caution in those with hypertension
Cream	Transient receptor potential vanilloid 1 agonist and depletes substance P	Associated allodynia initially, erythema, elevated blood pressure	Apply 4 times a day	Use with caution in those with hypertension
α-Lipoic acid	Antioxidant	Nausea, vomiting, dizziness, skin rash	600 mg/d in two divided doses	None

when the glycosylated hemoglobin decreases by more than 2 percentage points over 3 months.[49] The polyneuropathy is characteristically small fiber as supported by normal nerve conduction studies[5,50] and is characterized by loss of intraepidermal nerve fiber density on skin biopsy.[5] Although the pain may be refractory at first, it tends to improve within 24 months.[49] Relaxation of tight glucose control is not recommended.

Sodium Channelopathies

Mutations of voltage-gated sodium channels, both Nav1.7 and Nav1.8, have been reported to cause painful small fiber neuropathies and inherited erythromelalgia. Patients with inherited erythromelalgia present with episodic pain and reddening of the distal upper extremity and lower extremity skin.[51] It is genetically linked to a dominant gain-of-function mutation of the *SCN9A* gene encoding Nav1.7, which results in hyperpolarizing shifts in channel activation and dorsal root ganglia hyperexcitability.[51] Recently, 13 patients with inherited erythromelalgia due to Nav1.7 mutations were extensively phenotyped.[51] The majority of patients had onset of clinical signs within the first decade of life. Feet and hands were the most commonly affected parts of the body, showing reddening and swelling of the skin exacerbated by heat and exercise and alleviated by cooling. Most patients also had pain between the acute episodes. Inherited erythromelalgia is also associated with gain-of-function mutations of the *SCN10A* gene that encodes voltage-gated Nav1.8 channels, also expressed in the dorsal root ganglia and peripheral nerve axons.[52,53] These mutations result in dorsal root ganglia hyperexcitability.[53] In addition, Nav1.7 and Nav1.8 mutations have been reported to result in otherwise idiopathic painful small fiber neuropathy.[52–54]

KEY POINT

- Both Nav1.7 and Nav1.8 voltage-gated sodium mutations can result in a painful small fiber polyneuropathy.

Autoimmune Small Fiber Neuropathy

The small fiber neuropathies that have an underlying autoimmune mechanism include those associated with sarcoidosis, Sjögren syndrome, celiac disease, and paraneoplastic diseases

Case 10-1

A 16-year-old girl presented with a 4-week history of lower extremity pain and paresthesia. Seven weeks earlier, she was diagnosed with type 1 diabetes mellitus when she presented to the emergency department with vomiting and abdominal pain. She was found to have a blood glucose of 400 mg/dL. Her glycosylated hemoglobin was 14.8%. She was in diabetic ketoacidosis and was transferred to the pediatric intensive care unit. She was started on an insulin drip and ultimately discharged on insulin glargine and insulin lispro. In the weeks following her discharge, her blood sugars ranged from 100 mg/dL to 130 mg/dL.

Three weeks following hospitalization, she developed burning pain in her toes that was associated with sharp, shooting pain that progressed up to her knees over the next 2 to 3 weeks. The pain worsened in the evenings and interrupted her sleep. The patient also reported a purple discoloration of her toes and reduced sweating in her feet. She had lightheadedness with standing. She had a depressed mood and was unable to participate in her regular activities. She had tried acetaminophen, ibuprofen, aspirin, capsaicin cream, and a diabetic foot pain lotion without any improvement. Cold compresses and placing a fan near her feet helped with the burning.

Her neurologic examination showed normal muscle strength, bulk, and tone. She reported allodynia to pinprick in her feet and legs and hyperesthesia to light touch in the same distribution. She reported reduced sensation to cold temperature in her feet and legs but normal vibratory and proprioceptive sensation. Her muscle stretch reflexes were normal.

She was diagnosed with treatment-induced neuropathy of diabetes mellitus given the temporal association of her small fiber dysfunction to the rapid correction of her hyperglycemia. She was started on gabapentin and titrated up aggressively to 2700 mg/d, with improvement in her symptoms.

Comment. This is a classic case of treatment-induced neuropathy of diabetes mellitus. The patient presented with an acute small fiber neuropathy associated with refractory pain and autonomic features. Her neuropathy started 3 weeks after rapid correction of her hyperglycemia. A skin biopsy was not pursued given the straightforward diagnosis.

(**Case 10-2**). The recently described voltage-gated potassium channel complex–associated small fiber neuropathies are discussed in detail here, but **Table 10-1** provides a more complete list of autoimmune small fiber neuropathies. The voltage-gated potassium channel complex autoantibodies are distributed widely throughout the central and peripheral nervous systems. The autoantibodies do not bind to voltage-gated potassium channels but to contactin-associated proteinlike 2 (CASPR2), which is expressed in both the peripheral and central nervous systems, and leucine-rich glioma inactivated 1 protein (LGI1), which is isolated to the central nervous system.[55] Voltage-gated potassium channel complex autoimmunity and, in particular, CASPR2 antibodies have been reported with chronic idiopathic pain without evidence of peripheral nervous system dysfunction.[56] Patients with CASPR2 antibodies may also have a painful neuropathy, although in a 2016 series of five patients, most had evidence of large fiber involvement.[55]

Case 10-2

A 57-year-old man with a past medical history remarkable only for hyperlipidemia reported that he had acutely developed paresthesia in his feet 3 months earlier. Within weeks, the paresthesia spread to his hands, followed by his lips, tongue, and nose. The symptoms worsened over weeks, spreading up his legs and his arms. He denied any weakness. He was no longer able to play golf or exercise because of the severe neuropathic pain. He blinked frequently because of dry eyes and had frequent dry mouth. Gabapentin and duloxetine were not effective. His workup at an outside institution within 2 months of symptom onset included normal nerve conduction studies and EMG and normal heavy metal testing, paraneoplastic panel, serum protein electrophoresis, antinuclear antibodies, antineutrophil cytoplasmic antibodies, complement levels, erythrocyte sedimentation rate, C-reactive protein, glycosylated hemoglobin, and anti–Sjögren syndrome A (SSA)/Sjögren syndrome B (SSB) antibodies. Brain and cervical spine MRI were unremarkable.

His neurologic examination showed normal muscle bulk, tone, and strength throughout. He had normal symmetric reflexes. On sensory examination, he had a length-dependent loss of temperature and pinprick sensation, with relative preservation of vibratory and proprioceptive sensation. His gait was normal without a Romberg sign. His repeat nerve conduction studies and EMG were again normal. Testing for angiotensin-converting enzyme, hepatitis B and C, and vitamins B_6 and B_{12} was normal. A skin biopsy demonstrated abnormal intraepidermal nerve fiber density at all sites, consistent with a severe neuropathy affecting the small nerve fibers (**Figure 10-3**). A lip biopsy was obtained, which demonstrated minor salivary gland lobules with multiple foci of chronic inflammation. Based on this information and the rapid progression of his small fiber neuropathy, he was treated with 20 mg/d oral prednisone for presumed seronegative Sjögren syndrome–associated small fiber neuropathy. This resulted in dramatic improvement of his neuropathic pain and disability.

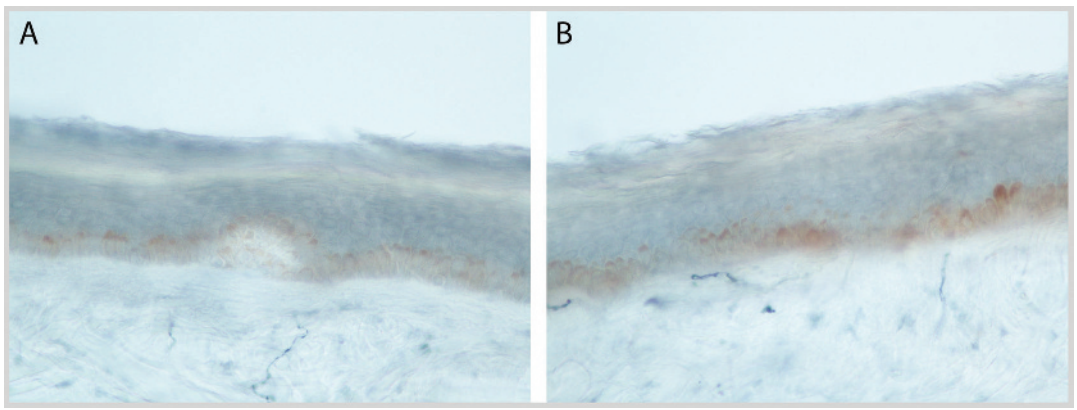

FIGURE 10-3 Epidermal nerve fiber analysis with protein gene product 9.5 stain of the patient in **Case 10-3**. *A*, Right foot: Nerve fiber density is significantly decreased to 0.0/mm (normal greater than 3.0/mm). *B*, Right calf: Nerve fiber density is significantly decreased to 0.0/mm (normal greater than 3.5/mm). Both specimens were stained with hematoxylin and eosin stain and Congo red. No abnormal Congo red staining was seen on either specimen.

Courtesy of Corinthian Reference Lab.

Comment. This case illustrates that autoimmune small fiber neuropathies may be acute in onset and progress rapidly. Taking a careful history led the physician to obtain a lip biopsy, which demonstrated inflammation and supported a diagnosis of seronegative Sjögren syndrome (up to 50% of patients with neuropathy and Sjögren syndrome will initially have negative antibodies). Making this diagnosis resulted in effective treatment for this patient who was otherwise unresponsive to conventional neuropathic pain medications.

KEY POINTS

- Autoimmune small fiber neuropathies, such as those associated with contactin-associated proteinlike 2 antibodies, may respond to treatment.
- Anti-Hu paraneoplastic sensory neuronopathy is characterized by subacute sensory ataxia and pain in the setting of malignancy.
- Treatment for the paraneoplastic sensory neuronopathies is broadly divided into three categories: tumor treatment, immunosuppression/immunomodulation, and symptomatic management.

The pathophysiologic basis of this autoimmune neuropathy is hyperexcitability of sensory fibers.[55] Recognizing these patients is important as they may respond to immunotherapy.[55]

Fibromyalgia

Fibromyalgia, characterized by widespread pain and fatigue, is prevalent in 2% to 8% of the population[57] and is likely a heterogeneous group of diseases with similar symptoms.[58] Studies have reported that nearly half of patients with fibromyalgia have small fiber neuropathy, characterized by decreased intraepidermal nerve fiber density.[28,58,59]

SPECIFIC SENSORY NEURONOPATHIES

Compared to axonal sensory neuropathies, relatively few causes of sensory neuronopathy are known. A description of the most common sensory neuronopathies follows.

Paraneoplastic Sensory Neuronopathies

Paraneoplastic sensory neuronopathy is one of the most common paraneoplastic syndromes.[60] It is characterized by an immune reaction that is directed against neuronal proteins or cross-reacting proteins expressed by cancer cells.[61] Chief among these, anti-Hu antibodies react against neural intracellular antigens through cell-mediated immune mechanisms.[62] The way in which anti-Hu antibodies react to intracellular antigens is still being investigated, and it appears that sensory neuronopathies are cytotoxic T-cell–mediated disorders.[63] Anti-Hu paraneoplastic sensory neuronopathy is characterized by subacute onset of sensory ataxia and often neuropathic pain.[19] Patients can develop concomitant motor neuropathy and weakness, cerebellar degeneration, limbic encephalitis, and brainstem involvement.[18] Autonomic nervous system involvement also occurs.[64] Less commonly, anti-CV2/collapsin response mediator protein-5 (CRMP-5) antibodies are associated with a mixed axonal and demyelinating motor polyneuropathy.[65]

A search for paraneoplastic autoantibodies is recommended in any patient with a sensory neuronopathy, although the absence of antibodies does not exclude an underlying malignancy, as the sensitivity is about 82%.[66] Although small cell lung cancer is the most common underlying malignancy, many other cancers have been reported.[18,67] Sensory neuronopathy may precede the cancer diagnosis by up to 8 months or longer.[19,64]

Imaging to look for an underlying malignancy is mandatory in the presence of antibodies and if no alternative diagnosis (such as Sjögren syndrome or chemotherapy-induced neuronopathy) is thought to be likely. Routine chest radiographs and CT of the chest are occasionally negative, in which case fludeoxyglucose positron emission tomography (FDG-PET) should be pursued.[68] If this is negative, then repeat imaging should be performed every 6 months for up to 4 years.[68] CSF analysis is almost always abnormal, with elevated protein, pleocytosis, and sometimes oligoclonal bands.[69]

Given the rarity of these disorders, treatment recommendations are mostly based on expert opinion. Treatment is very broadly divided into three categories: tumor treatment, immunosuppression/immunomodulation, and symptomatic management. Tumor treatment may stabilize or perhaps even improve the paraneoplastic syndromes associated with intracellular antigens.[70] Immunosuppressant medications used to treat paraneoplastic sensory neuronopathies include corticosteroids, cyclophosphamide, sirolimus, and rituximab.[64,67]

Immunomodulatory therapy includes IV immunoglobulin (IVIg) and plasma exchange.[64,67] One published treatment strategy supports using high-dose corticosteroids with or without IVIg followed by cyclophosphamide if the cancer is not found.[71] Symptomatic treatment consists of neuropathic pain medications (**Table 10-3**).

In general, patients with anti-Hu–associated paraneoplastic syndromes have a poor prognosis with a median survival of less than 1 year and a 20% survival at 36 months.[70] Early identification of the tumor and initiation of treatment results in improved outcomes.

Immune-mediated Sensory Neuronopathies

Sjögren syndrome is the autoimmune disease most frequently associated with sensory neuronopathies. Others, such as systemic lupus erythematosus, autoimmune hepatitis, and celiac disease (**Table 10-2**), are not discussed in detail here. Sjögren syndrome is characterized by sicca symptoms (xerophthalmia and xerostomia) and affects between 1% and 2% of the population.[72] In a large series of patients, over half developed neurologic symptoms before other symptoms of Sjögren syndrome and over half had isolated neurologic symptoms.[73] Sjögren syndrome may have peripheral nervous system manifestations in 5% to 15% of patients, although the estimates vary widely from 0% to 56%.[74,75] Up to 40% of patients with Sjögren syndrome–related polyneuropathies will have sensory neuronopathies (5% of all patients with Sjögren syndrome).[72] The presentation of sensory neuronopathy in patients with Sjögren syndrome is usually subacute, with the average age in the sixties to seventies (**Case 10-3**).[72] In contrast to other forms of sensory neuronopathy, trigeminal and autonomic involvement is common.[76]

It is recommended to screen all sensory neuronopathy patients for Sjögren syndrome by checking for anti–Sjögren syndrome A (SSA [anti-Ro]) and anti–Sjögren syndrome B (SSB [anti-La]), although they are often negative.[73] Should the initial laboratory screen be negative, additional testing should be obtained, including the Schirmer test, rose bengal test, and lip or salivary gland biopsy.[74] The sensitivity of the Schirmer test and salivary gland biopsy were both excellent (93%) in one series of patients.[76]

As with paraneoplastic sensory neuronopathies, no randomized controlled treatment trials exist to guide treatment of the Sjögren-associated sensory neuronopathies. A number of treatments have been used, including plasma exchange, IVIg, rituximab, corticosteroids, cyclophosphamide, and azathioprine.[18,72,75] One protocol proposes treating with IVIg (2 g/kg divided over 5 days) followed by monthly infusions.[75]

Toxic Sensory Neuronopathies

Toxic sensory neuronopathies may be caused by chemotherapeutic agents and megadoses of pyridoxine (vitamin B_6). Certain platinum-based chemotherapeutic agents are particularly toxic to the dorsal root ganglia, including cisplatin, carboplatin, and oxaliplatin.[77] These drugs result in apoptosis of the sensory neurons in the dorsal root ganglia[78,79] and slow fast axonal transport.[80] Cisplatin is associated with a dose-dependent neurotoxicity, and patients experience neuropathic pain typically after a cumulative dose of 300 mg/m^2.[15] Because of the coasting effect, patients may experience worsening of their neuropathy for several months after treatment.[77]

KEY POINTS

- Sjögren syndrome is the autoimmune disease most frequently associated with sensory neuronopathy.
- Toxic sensory neuronopathies are caused by platinum-based chemotherapy and megadoses of pyridoxine.

Case 10-3

A 76-year-old woman presented with progressive ataxia. She went from working 9-hour shifts to being wheelchair dependent within 2 weeks. She denied any weakness and reported she could not walk because her legs were numb and ''did not know where they wanted to go.'' Initially diagnosed with Guillain-Barré syndrome, she was hospitalized and given 2 g/kg IV immunoglobulin (IVIg) over a 5-day course, with some improvement in her symptoms. She received four more monthly IVIg infusions. She reported progression of her numbness and neuropathic pain despite these infusions, ascending to her waist, hands, and then forearms. Her pain was adequately controlled on gabapentin, duloxetine, and oxycodone.

She had carried a diagnosis of Sjögren syndrome for 2 years in the setting of a several-year history of sicca symptoms and a positive anti–Sjögren syndrome A (SSA) antibody. Erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody, serum protein electrophoresis, antineutrophil cytoplasmic antibodies, vitamin B_{12}, thyroid-stimulating hormone (TSH), paraneoplastic panel, and hepatitis B and C studies obtained prior to her referral were unremarkable. She had previously had an unremarkable MRI of the brain and full spine. CSF analysis had demonstrated 0 white blood cells and a protein level of 89 mg/100 mL.

Her examination showed normal muscle bulk, tone, and strength. She had decreased pinprick sensation in the bilateral lower extremities to the level of the waist and in her upper extremities up to the mid forearms. Proprioception was severely impaired in the legs to the level of the hips and in the upper extremities to the level of the wrists. Pseudoathetosis of the fingers was present and more pronounced with her eyes closed. Reflexes were normal in the upper extremities and absent in the lower extremities. She was unable to ambulate without maximum assistance because of severe ataxia.

Her nerve conduction studies demonstrated absent sensory responses throughout. Motor responses were normal apart from mildly low-amplitude left ulnar and fibular (peroneal) compound muscle action potentials (CMAPs). Concentric needle EMG was entirely normal. Her nerve conduction velocity/EMG was interpreted as electrophysiologic evidence of a sensory neuronopathy.

She had already been previously prescribed mycophenolate mofetil, high-dose corticosteroids, and hydroxychloroquine in addition to the IVIg without any benefit. A trial of rituximab was recommended.

Comment. This case is a classic description of Sjögren syndrome–associated sensory neuronopathy, which is characterized by acute to subacute onset of severe sensory ataxia. Often patients will be very treatment refractory. Although this patient carried a diagnosis of Sjögren syndrome at the time of neuronopathy onset, it is not uncommon for a patient to have sensory neuronopathy as the initial manifestation of the disease.

Pyridoxine is an essential vitamin that plays a role in amino acid metabolism. The original cases of pyridoxine-associated neuropathy/neuronopathy were reported in the 1980s in patients who were taking over 2 g/d for several months.[81] The recommended daily intake of pyridoxine is 1.3 mg. Subsequently, pyridoxine toxicity with doses as low as 200 mg/d has been

TABLE 10-4 Causes of Small and Large Fiber Sensory Neuropathies

Etiology	Evaluation
Diabetes mellitus	Glycosylated hemoglobin, fasting glucose, 2-hour glucose tolerance
Sporadic amyloidosis	Serum and urine protein electrophoresis, immunofixation, light chains, fat aspirate, rectal mucosa biopsy, or nerve biopsy with Congo red staining
Sjögren syndrome	Sicca symptoms, anti-Ro (SSA)/anti-La (SSB) antibodies, rose bengal test, Schirmer test, lip/salivary gland biopsy
Celiac disease	Antigliadin antibodies (serum IgA endomysial and tissue transglutaminase antibody), IgG-deamidated gliadin peptides, small bowel biopsy, testing for HLA DQ2/DQ8
Sarcoidosis	Chest x-ray, serum angiotensin-converting enzyme, lymph node or other tissue biopsy for necrotizing granulomas
Leprosy	Serum antibodies to PGL-1, skin biopsy or nerve biopsy for acid-fast bacilli
Systemic lupus erythematosus	ANA, antiphospholipid antibodies, complement levels, ESR, CRP, anti-dsDNA and anti-Smith antibodies
Sensory chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	Diagnosis is supported by nerve conduction studies and CSF analysis
Human immunodeficiency virus (HIV)	Fourth-generation antigen/antibody immunoassay, HIV viral load testing
Hepatitis C virus	Anti–hepatitis C virus antibody, hepatitis C virus RNA
Cryoglobulinemia (typically associated with hepatitis C virus)	Cryoglobulin levels, hepatitis C virus antibody and PCR
Lyme disease	Tick exposure, serum ELISA with Western blot confirmation
Vitamin deficiencies	Vitamin B_{12} and methylmalonic acid levels; folic acid, vitamin E, vitamin B_6 and thiamine levels
Tangier disease	ATP binding cassette (ABC) transporter mutation
Toxins	Chemotherapy (taxols, platinum drugs, bortezomib), metronidazole, phenytoin, ethambutol, isoniazid, thallium, mercury, lead
Alcohol	History of drinking alcohol
Hypothyroidism	TSH, free T4 levels
Hereditary neuropathies	Genetic testing for hereditary sensory and autonomic neuropathies, mitochondrial mutation testing
Familial amyloid	Genetic testing for transthyretin (*TTR*), apolipoprotein A1 (*APOA1*), and gelsolin (*GSN*) mutations
Paraneoplastic	Voltage-gated potassium channel antibodies (CASPR2 specifically), anti-Hu antibodies, anti-CV2/CRMP-5 antibodies
Other antibody-mediated	Sulfatide antibodies, GD1b antibodies, anti-galactocerebroside antibodies
Idiopathic	Diagnosis of exclusion

ANA = antinuclear antibody; ATP = adenosine triphosphate; CASPR2 = contactin-associated proteinlike 2; CRMP-5 = collapsin response mediator protein-5; CRP = C-reactive protein; CSF = cerebrospinal fluid; dsDNA = double-stranded deoxyribonucleic acid; ELISA = enzyme-linked immunosorbent assay; ESR = erythrocyte sedimentation rate; HLA = human leukocyte antigen; IgA = immunoglobulin A; IgG = immunoglobulin G; PCR = polymerase chain reaction; PGL-1 = phenolic glycolipid-1; RNA = ribonucleic acid; SSA = Sjögren syndrome A; SSB = Sjögren syndrome B; T4 = thyroxine; TSH = thyroid-stimulating hormone.

KEY POINT

■ The most common sensory polyneuropathy is caused by diabetes mellitus.

reported,[82] and daily doses greater than 50 mg should be discouraged. Pyridoxine-associated sensory neuronopathy results in large fiber dysfunction and prominent sensory ataxia.[81] Discontinuation of the pyridoxine may result in some improvement of symptoms, but residual deficits are possible.[81]

Differential Diagnosis of Sensory Neuronopathies

In nearly half of patients, an underlying etiology of the sensory neuronopathy is not identified and the disease is considered to be idiopathic.[14,16] In contrast to the autoimmune and paraneoplastic sensory neuronopathies, patients with idiopathic sensory neuronopathy have an indolent slowly progressive course.[16] The diagnosis of idiopathic sensory neuronopathy is a diagnosis of exclusion and thought to have an autoimmune pathophysiology.[16] Despite treatment with immunosuppressants in a small series, patients had relatively poor outcomes.[16]

Sensory loss, ataxia, and areflexia may also be seen in distal acquired demyelinating symmetric (DADS) neuropathy and sensory chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). For more information, refer to the article ''Chronic Demyelinating Polyneuropathies'' by Jeffrey A. Allen, MD,[83] in this issue of *Continuum*. When sensory ataxia, areflexia, and extensor plantar responses coexist, consideration should be made for conditions such as Friedreich ataxia, vitamin B_{12} deficiency, and tabes dorsalis.

SMALL AND LARGE FIBER SENSORY POLYNEUROPATHIES

Although the majority of this article has focused on disorders of the dorsal root ganglia (sensory neuronopathies) that present with ataxia and the small fiber neuropathies that present primarily with pain, in clinical practice, sensory-predominant polyneuropathies with involvement of both small fibers (Aδ fibers and small unmyelinated C fibers) and large sensory fibers (Aβ fibers) is frequently encountered. By far the most common cause of small and large fiber sensory polyneuropathies worldwide is diabetes mellitus.[35] **Table 10-4** provides a comprehensive list of small and large sensory fiber polyneuropathies.

CONCLUSION

The presentations of sensory polyneuropathies are varied. Patients will often present with painful burning feet. This, in combination with normal nerve conduction studies, supports localization to the small nerve fibers. Infrequently, patients present with dramatic sensory ataxia early in the course of the neuropathy, which supports localization to the dorsal root ganglia, dorsal columns, or the large heavily myelinated nerves. These different presentations are associated with distinct diagnostic and treatment algorithms.

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