CME CREDIT

JINNY O. TAVEE, MD
Medical Director, Neuromuscular Division,
Associate Professor, Department of Neurology,
Northwestern University Feinberg School of
Medicine, Chicago, IL

Office approach to small fiber neuropathy

ABSTRACT

Small fiber neuropathy is often characterized by neuropathic pain in the feet with normal nerve conduction studies and neurologic examination. Diagnosis requires specialized nerve tests, including autonomic studies and a skin biopsy study showing reduced intraepidermal nerve fiber density. Small fiber neuropathy has numerous causes but is often idiopathic. A practical approach to identifying an underlying cause is to first screen for common ones and then proceed with further testing as needed. Treatment consists of correcting the underlying cause, managing pain, and modifying lifestyle.

KEY POINTS

Patients typically develop a symmetric "stocking-glove" pattern of sensory loss in the feet and hands.

The diagnosis may be confirmed with skin biopsy for nerve fiber density, which can easily be done in a clinic setting with commercially available kits.

Diabetes is the most common identifiable cause of small fiber neuropathy.

Serologic testing can help uncover a vitamin deficiency or other potentially treatable condition.

Antiepileptics, antidepressants, and topical agents are first-line drugs for managing pain.

doi:10.3949/ccjm.85a.17124

Peripheral neuropathy is the most common reason for an outpatient neurology visit in the United States and accounts for over $10 billion in healthcare spending each year.[1,2] When the disorder affects only small, thinly myelinated or unmyelinated nerve fibers, it is referred to as small fiber neuropathy, which commonly presents as numbness and burning pain in the feet.

This article details the manifestations and evaluation of small fiber neuropathy, with an eye toward diagnosing an underlying cause amenable to treatment.

OLDER PATIENTS MOST AFFECTED

The epidemiology of small fiber neuropathy is not well established. It occurs more commonly in older patients, but data are mixed on prevalence by sex.[3–6] In a Dutch study,[3] the overall prevalence was at least 53 cases per 100,000, with the highest rate in men over age 65.

CHARACTERISTIC SENSORY DISTURBANCES

Characteristic clinical features are summarized in **Table 1**.

Sensations vary in quality and time

Patients with small fiber neuropathy typically present with a symmetric length-dependent ("stocking-glove") distribution of sensory changes, starting in the feet and gradually ascending up the legs and then to the hands.

Commonly reported neuropathic symptoms include various combinations of burning, numbness, tingling, itching, sunburn-like, and frostbite-like sensations. Nonneuropathic symptoms may include tightness, a vise-like squeezing of the feet, and the sensation of a

TABLE 1

Features of small fiber neuropathy

Neuropathic pain: burning, numbness, tingling, itching, "frostbite-like" sensations
Commonly "stocking-glove" pattern, but may be random, migratory, and intermittent
Symptoms of dysautonomia (eg, skin changes, sweating abnormalities, dry eyes, dry mouth, gastrointestinal dysmotility, orthostasis, palpitations, bowel or bladder changes, sexual dysfunction)
Normal neurologic examination, nerve conduction studies, needle electromyography

sock rolled up at the end of the shoe. Cramps or spasms may also be reported but rarely occur in isolation.[7]

Symptoms are typically worse at the end of the day and while sitting or lying down at night. They can arise spontaneously but may also be triggered by something as minor as the touch of clothing or cool air against the skin. Bedsheet sensitivity of the feet is reported so often that it is used as an outcome measure in clinical trials. Symptoms can also be exacerbated by extremes in ambient temperature and are especially worse in cold weather.

Small fiber neuropathy commonly presents as numbness and burning in the feet

Random patterns suggest an immune cause

Symptoms may also have a non–length-dependent distribution that is asymmetric, patchy, intermittent, and migratory, and can involve the face, proximal limbs, and trunk. Symptoms may vary throughout the day, eg, starting with electric-shock sensations on one side of the face, followed by perineal numbness and then tingling in the arms lasting for a few minutes to several hours. While such patterns may be seen with diabetes and other common etiologies, they often suggest an underlying immune-mediated disorder such as Sjögren syndrome or sarcoidosis.[8–10] Although large fiber polyneuropathy may also be non–length-dependent, the deficits are usually fixed, with no migratory component.

Autonomic features may be prominent

Autonomic symptoms occur in nearly half of patients and can be as troublesome as neuropathic pain.[3] Small nerve fibers mediate somatic and autonomic functions, an evolutionary link that may reflect visceral defense mechanisms responding to pain as a signal of danger.[11] This may help explain the multisystemic nature of symptoms, which can include sweating abnormalities, bowel and bladder disturbances, dry eyes, dry mouth, gastrointestinal dysmotility, skin changes (eg, discoloration, loss of hair, shiny skin), sexual dysfunction, orthostatic hypotension, and palpitations. In some cases, isolated dysautonomia may be seen.

TARGETED EXAMINATION

History: Medications, alcohol, infections

When a patient presents with neuropathic pain in the feet, a detailed history should be obtained, including alcohol use, family history of neuropathy, and use of neurotoxic medications such as metronidazole, colchicine, and chemotherapeutic agents.

Human immunodeficiency virus (HIV) and hepatitis C infection are well known to be associated with small fiber neuropathy, so relevant risk factors (eg, blood transfusions, sexual history, intravenous drug use) should be asked about. Recent illnesses and vaccinations are another important line of questioning, as a small-fiber variant of Guillain-Barré syndrome has been described.[12]

Assess reflexes, strength, sensation

On physical examination, particular attention should be focused on searching for abnormalities indicating large nerve fiber involvement (eg, absent deep tendon reflexes, weakness of the toes). However, absent ankle deep tendon reflexes and reduced vibratory sense may also occur in healthy elderly people.

Similarly, proprioception, motor strength, balance, and vibratory sensation are functions of large myelinated nerve fibers, and thus remain unaffected in patients with only small fiber neuropathy.

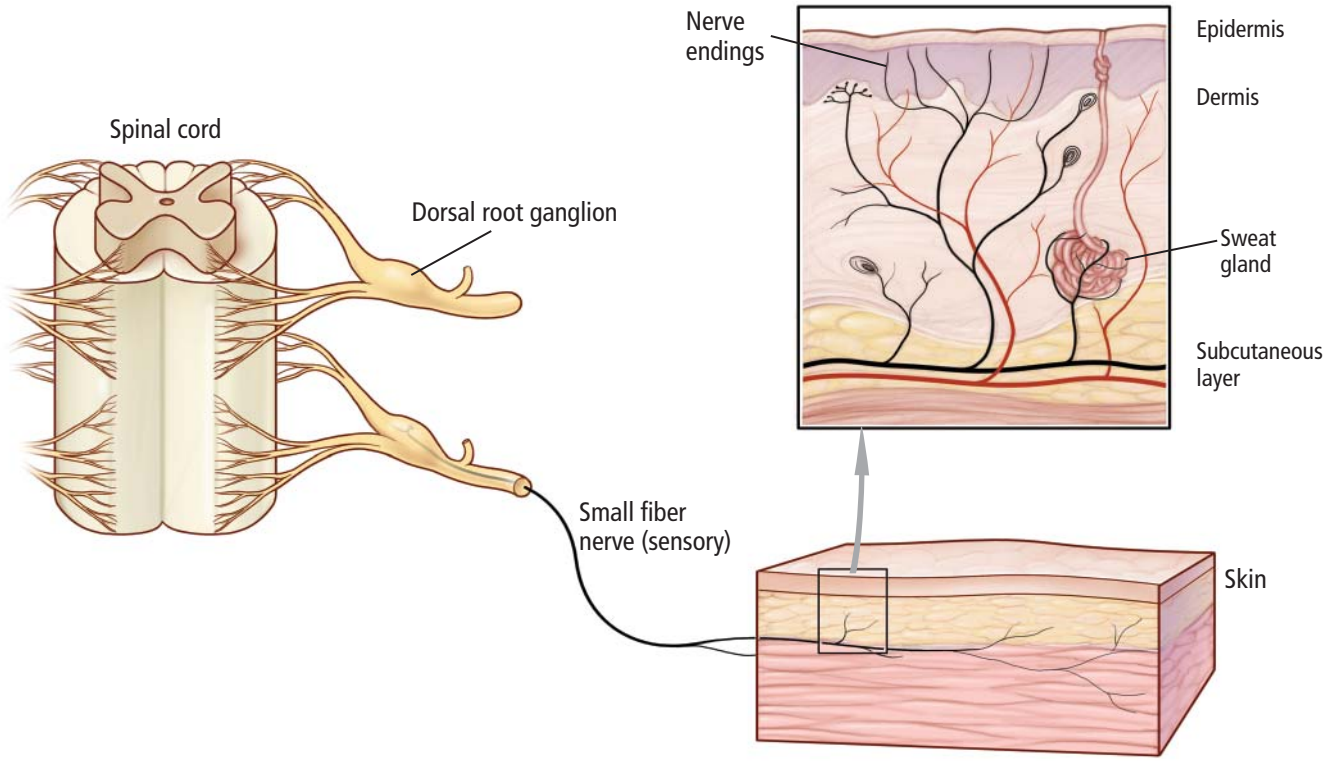
Evidence of a systemic disorder should also be sought, as it may indicate an underlying etiology.

DIAGNOSTIC TESTING

Although patients with either large or small fiber neuropathy may have subjective hyperesthesia or numbness of the distal lower extrem-

Small fiber neuropathy affects sensory nerves

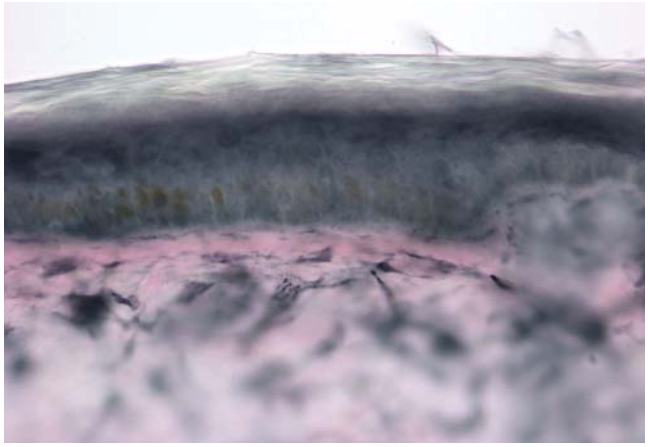
Small fiber neuropathy is a major cause of pain in the hands and feet, especially in the elderly. Diabetes mellitus is the most common identifiable cause, but there are many others. The nerve fibers affected are small-diameter myelinated A-delta fibers and unmyelinated C fibers, which mediate pain, thermal sensation, and autonomic function. Large fibers that innervate muscles are not affected. Skin biopsy may show a paucity of nerve fibers. Quantitative sudomotor axon reflex testing may show a lack of sweating in response to acetylcholine.



Normal skin biopsy

Normal innervation with small nerve fibers seen in the epidermis (arrows). Skin biopsy specimens with protein gene product 9.5 immunostaining.

Small fiber neuropathy biopsy



A specimen from a patient with small fiber neuropathy shows denervation, with no small nerve fibers seen in the epidermis.

Tavee J, Zhou L. Small fiber neuropathy: a burning problem. Cleve Clin J Med 2009; 76(5):297–305. doi:10.3949/ccjm.76a.08070

Figure 1.

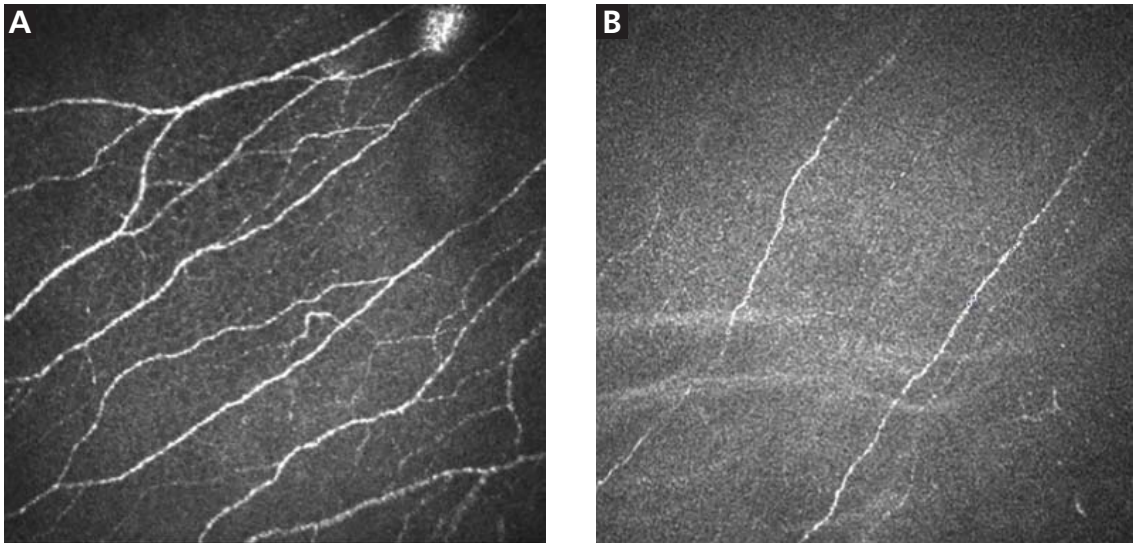


Figure 2. Corneal confocal microscopy in small fiber neuropathy: A, normal corneal nerve fibers and branching; B, marked reduction of corneal nerve fibers.

ities, the absence of significant abnormalities on neurologic examination should prompt consideration of small fiber neuropathy.

Electromyography worthwhile

The physical examination should search for involvement of large nerve fibers

Nerve conduction studies and needle electrode examination evaluate only large nerve fiber conditions. While electromyographic results are normal in patients with isolated small fiber neuropathy, the test can help evaluate subclinical large nerve fiber involvement and alternative diagnoses such as bilateral S1 radiculopathy. Nerve conduction studies may be less useful in patients over age 75, as they may lack sural sensory responses because of aging changes.[13]

Skin biopsy easy to do

Skin biopsy for evaluating intraepidermal nerve fiber density is one of the most widely used tests for small fiber neuropathy. This minimally invasive procedure can now be performed in a primary care office using readily available tools or prepackaged kits and analyzed by several commercial laboratories.

Skin specimens are obtained by 3-mm punch biopsy of the distal leg and thigh and are sent to a laboratory for analysis. The sample is immunostained against a panaxonal marker nerve, and fiber densities are calculated (**Figure 1**).[14] The results are compared with normative data for age and sex, and a formal report with the diagnosis is sent to the ordering physician. The test has a sensitivity of 88%.[5,15]

Reduced intraepidermal nerve fiber density on skin biopsy has been described in various other conditions such as fibromyalgia and chronic pain syndromes.[16,17] The clinical significance of these findings remains uncertain.

Quantitative sudomotor axon reflex testing

Quantitative sudomotor axon reflex testing (QSART) is a noninvasive autonomic study that assesses the volume of sweat produced by the limbs in response to acetylcholine. A measure of postganglionic sympathetic sudomotor nerve function, QSART has a sensitivity of up to 80% and can be used to diagnose small fiber neuropathy.[18] In a series of 115 patients with sarcoidosis small fiber neuropathy,[9] the QSART and skin biopsy findings were concordant in 17 cases and complementary in 29, allowing for confirmation of small fiber neuropathy in patients whose condition would have remained undiagnosed had only one test been performed. QSART can also be considered in cases where skin biopsy may be contraindicated (eg, patient use of anticoagulation). Of note, the study may be affected by a number of external factors, including caffeine, tobacco, antihistamines, and tricyclic antidepressants; these should be held before testing.

TABLE 2

Serologic testing to find the cause of small fiber neuropathy

First-tier studies	Associated conditions
2-hour oral glucose tolerance test, hemoglobin A_{1c}	Diabetes, impaired glucose tolerance
Extractable nuclear antigen testing for Sjögren syndrome A and B antibodies	Sjögren syndrome
Thyroid-stimulating hormone, free T_4, T_3 levels	Hypothyroidism
Vitamin B_{12}, methylmalonic acid, homocysteine levels	Vitamin B_{12} deficiency
Serum and urine monoclonal protein analysis	Paraproteinemia
Tissue transglutaminase, antigliadin antibodies	Celiac disease
Complete metabolic panel	Renal, hepatic impairment
Complete blood cell count	Hematologic abnormalities
Human immunodeficiency virus (HIV) and hepatitis C virus antibodies (may be second-tier tests if no risk factors)	HIV, hepatitis C
Fasting lipid panel	Hyperlipidemia
Erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody	Inflammatory disease
Liver function tests, gamma-glutamyltransferase	Alcohol abuse
Second-tier studies	
Angiotensin-converting enzyme	Sarcoidosis
Thiamine (vitamin B_1)	Vitamin B_1 deficiency
Pyridoxine (vitamin B_6)	Vitamin B_6 deficiency
Copper	Copper deficiency
Serum and urine monoclonal protein analysis, fat pad analysis, nerve biopsy	Systemic amyloidosis
Paraneoplastic autoantibody panel	Paraneoplastic disease
Ganglionic acetylcholine receptor antibody	Autoimmune autonomic ganglionopathy
Genetic studies	
SCN9A and *SCN10A* genes	Hereditary small fiber neuropathy
GLA gene	Fabry disease
Transthyretin gene	Familial amyloidosis
ABCA1 gene	Tangier disease

Start with a battery of tests that cover the most common causes

Other diagnostic studies

Other tests may be helpful, as follows:

Tilt-table and cardiovagal testing may be useful for patients with orthostasis and palpitations.

Thermoregulatory sweat testing can be used to evaluate patients with abnormal patterns of sweating, eg, hyperhidrosis of the face and head.

Corneal confocal microscopy is a promising new noninvasive diagnostic tool that provides objective quantification of small nerve fibers in the subbasal layer of the cornea, which holds the densest concentration of these fibers (**Figure 2**).[19] Routine corneal confocal microscopy is currently limited to ophthalmology, but the growing use of the corneal findings as a marker for therapeutic interventions in neuropathy studies may prompt more widespread availability soon.

INITIAL TESTING FOR AN UNDERLYING CAUSE

Although up to half of cases of small fiber neuropathy are idiopathic, it is important to search for an identifiable underlying cause amenable to treatment.[5,20] A cost-effective approach is to start with a battery of blood tests that cover the most common causes, and then proceed with second-tier testing as needed (**Table 2**).

Glucose tolerance test for diabetes

Diabetes is the most common identifiable cause of small fiber neuropathy and accounts for about a third of all cases.[5] Impaired glucose tolerance is also thought to be a risk factor and has been found in up to 50% of idiopathic cases, but the association is still being debated.[21]

Diabetes is the most common identifiable cause

While testing for hemoglobin A_{1c} is more convenient for the patient, especially because it does not require fasting, a 2-hour oral glucose tolerance test is more sensitive for detecting glucose dysmetabolism.[22]

Lipid panel for metabolic syndrome

Small fiber neuropathy is associated with individual components of the metabolic syndrome, which include obesity, hyperglycemia, and dyslipidemia. Of these, dyslipidemia has emerged as the primary factor involved in the development of small fiber neuropathy, via an inflammatory pathway or oxidative stress mechanism.[23,24]

Vitamin B_{12} deficiency testing

Vitamin B_{12} deficiency, a potentially correctable cause of small fiber neuropathy, may be underdiagnosed, especially as values obtained by blood testing may not reflect tissue uptake. Causes of vitamin B_{12} deficiency include reduced intake, pernicious anemia, and medications that can affect absorption of vitamin B_{12} (eg, proton pump inhibitors, histamine 2 receptor antagonists, metformin).

Testing should include:

- Complete blood cell count to evaluate for vitamin B_{12}-related macrocytic anemia and other hematologic abnormalities
- Serum vitamin B_{12} level
- Methylmalonic acid or homocysteine level in patients with subclinical or mild vitamin B_{12} deficiency, manifested as low to normal vitamin B_{12} levels (< 400 pg/mL); methylmalonic acid and homocysteine require vitamin B_{12} as a cofactor for enzymatic conversion, and either or both may be elevated in early vitamin B_{12} deficiency.

Celiac antibody panel

Celiac disease, a T-cell mediated enteropathy characterized by gluten intolerance and a herpetiform-like rash, can be associated with small fiber neuropathy.[25] In some cases, neuropathy symptoms are preceded by the onset of gastrointestinal symptoms, or they may occur in isolation.[25]

Inflammatory disease testing

Sjögren syndrome accounts for nearly 10% of cases of small fiber neuropathy. Associated neuropathic symptoms are often non–length-dependent, can precede sicca symptoms for up to 6 years, and in some cases are the sole manifestation of the disease.[10] Small fiber neuropathy may also be associated with vasculitis, systemic lupus erythematosus, and other connective tissue disorders.

Testing should include:

- Erythrocyte sedimentation rate, C-reactive protein, and antinuclear antibodies: though these are nonspecific markers of inflammation, they may support an immune-mediated etiology if positive
- Extractable nuclear antigen panel: Sjögren syndrome A and B autoantibodies are the most important components in this setting[5,11]
- The Schirmer test or salivary gland biopsy should be considered for seronegative patients with sicca or a suspected immune-mediated etiology, as the sensitivity of antibody testing ranges from only 10% to 55%.[10]

Thyroid function testing

Hypothyroidism, and less commonly hyperthyroidism, are associated with small fiber neuropathy.

Metabolic tests for liver and kidney disease

Renal insufficiency and liver impairment are well-known causes of small nerve fiber dysfunction. Testing should include:

- Comprehensive metabolic panel
- Gamma-glutamyltransferase if alcohol abuse is suspected, since heavy alcohol use is one of the most common causes of both large and small fiber neuropathy.

HIV and hepatitis C testing

For patients with relevant risk factors, HIV and hepatitis C testing should be part of the initial workup (and as second-tier testing for others). Patients who test positive for hepatitis C should undergo further testing for cryoglobulinemia, which can present with painful small fiber neuropathy.[26]

Serum and urine immunoelectrophoresis

Paraproteinemia, with causes ranging from monoclonal gammopathy of uncertain significance to multiple myeloma, has been associated with small fiber neuropathy. An abnormal serum or urine immunoelectrophoresis test warrants further investigation and possibly referral to a hematology-oncology specialist.

SECOND-TIER TESTING

Less common treatable causes of small fiber neuropathy may also be evaluated.

Copper, vitamin B_1 (thiamine), or vitamin B_6 (pyridoxine) deficiency testing. Although vitamin B_6 toxicity may also result in neuropathy due to its toxic effect on the dorsal root ganglia, the mildly elevated vitamin B_6 levels often found in patients being evaluated for neuropathy are unlikely to be the primary cause of symptoms. Many laboratories require fasting samples for accurate vitamin B_6 levels.

Angiotensin-converting enzyme levels for sarcoidosis. Small fiber neuropathy is common in sarcoidosis, occurring in more than 30% of patients with systemic disease.[27] However, screening for sarcoidosis by measuring serum levels is often falsely positive and is not cost-effective. In a study of 195 patients with idiopathic small fiber neuropathy,[11] 44% had an elevated serum level, but no evidence of sarcoidosis was seen on further testing, which included computed tomography of the chest in 29 patients.[12] Thus, this test is best used for patients with evidence of systemic disease.

Amyloid testing for amyloidosis. Fat pad or bone marrow biopsy should be considered in the appropriate clinical setting.

Paraneoplastic autoantibody panel for occult cancer. Such testing may also be considered if clinically warranted. However, if a patient is found to have low positive titers of paraneoplastic antibodies and suspicion is low for an occult cancer (eg, no weight loss or early satiety), repeat confirmatory testing at another laboratory should be done before embarking on an extensive search for malignancy.

Ganglionic acetylcholine receptor antibody testing for autoimmune autonomic ganglionopathy. This should be ordered for patients with prominent autonomic dysfunction. The antibody test can be ordered separately or as part of an autoantibody panel. The antibody may indicate a primary immune-mediated process or a paraneoplastic disease.[28]

Genetic mutation testing. Recent discoveries of gene mutations leading to peripheral nerve hyperexcitability of voltage-gated sodium channels have elucidated a hereditary cause of small fiber neuropathy in nearly 30% of cases that were once thought to be idiopathic.[29,30] Genetic testing for mutations in *SCN9A* and *SCN10* (which code for the Nav1.7 and Nav1.8 sodium channels, respectively) is commercially available and may be considered for those with a family history of neuropathic pain in the feet or for young, otherwise healthy patients.

Fabry disease is an X-linked lysosomal disorder characterized by angiokeratomas, cardiac and renal impairment, and small fiber neuropathy. Treatment is now available, but screening is not cost-efficient and should only be pursued in patients with other symptoms of the disease.[31,32]

Less common treatable causes of small fiber neuropathy may also be evaluated

OTHER POSSIBLE CAUSES

Guillain-Barré syndrome

A Guillain-Barré syndrome variant has been reported that is characterized by ascending limb paresthesias and cerebrospinal fluid albuminocy-

tologic dissociation in the setting of preserved deep tendon reflexes and normal findings on EMG.[12] The clinical course is similar to that of typical Guillain-Barré syndrome, in that symptoms follow an upper respiratory or gastrointestinal tract infection, reach their nadir at 4 weeks, and then gradually improve. Some patients respond to intravenous immune globulin.

Vaccine-associated

Postvaccination small fiber neuropathy has also been reported. The nature of the association is unclear.[33]

Parkinson disease

Small fiber neuropathy is associated with Parkinson disease. It is attributed to a number of proposed factors, including neurodegeneration that occurs parallel to central nervous system decline, as well as intestinal malabsorption with resultant vitamin deficiency.[34,35]

Rapid glycemic lowering

Aggressive treatment of diabetes, defined as at least a 2-point reduction of serum hemoglobin A_{1c} level over 3 months, may result in acute small fiber neuropathy. It manifests as severe distal extremity pain and dysautonomia.

In a retrospective study,[36] 104 (10.9%) of 954 patients presenting to a tertiary diabetic clinic developed treatment-induced diabetic neuropathy with symptoms occurring within 8 weeks of rapid glycemic control. The severity of neuropathy correlated with the degree and rate of glycemic lowering. The condition was reversible in some cases.

Targeted treatment may halt progression, improve symptoms

TREATING SPECIFIC DISORDERS

For patients with an identified cause of neuropathy, targeted treatment offers the best chance of halting progression and possibly improving symptoms. Below are recommendations for addressing neuropathy associated with the common diagnoses.

Diabetes, impaired glucose tolerance, and metabolic syndrome. In addition to glycemic- and lipid-lowering therapies, lifestyle modifications with a specific focus on exercise and nutrition are integral to treating diabetes and related disorders.

In the Look AHEAD (Action for Health in Diabetes) study,[37] which evaluated the effects of intensive lifestyle intervention on neuropathy in 5,145 overweight patients with type 2 diabetes, patients in the intervention group had lower pain scores and better touch sensation in the toes compared with controls at 1 year. Differences correlated with the degree of weight loss and reduction of hemoglobin A_{1c} and lipid levels.

As running and walking may not be feasible for many patients owing to pain, stationary cycling, aqua therapy, and swimming are other options. A stationary recumbent bike may be useful for older patients with balance issues.

Vitamin B_{12} deficiency. As reduced absorption rather than low dietary intake is the primary cause of vitamin B_{12} deficiency for many patients, parenteral rather than oral supplementation may be best. A suggested regimen is subcutaneous or intramuscular methylcobalamin injection of 1,000 µg given daily for 1 week, then once weekly for 1 month, followed by a maintenance dose once a month for at least 6 to 12 months. Alternatively, a daily dose of vitamin B_{12} 1,000 µg can be taken sublingually.

Sjögren syndrome. According to anecdotal case reports, intravenous immune globulin, corticosteroids, and other immunosuppressants help painful small fiber neuropathy and dysautonomia associated with Sjögren syndrome.[10]

Sarcoidosis. Sarcoidosis-associated small fiber neuropathy may also respond to intravenous immune globulin, as well as infliximab and combination therapy.[9] Culver et al[38] found that cibinetide, an experimental erythropoetin agonist, resulted in improved corneal nerve fiber measures in patients with small fiber neuropathy associated with sarcoidosis.

Celiac disease. A gluten-free diet is the treatment for celiac disease and can help some patients.

GENERAL MANAGEMENT

For all patients, regardless of whether the cause of small fiber neuropathy has been identified, managing symptoms remains key, as pain and autonomic dysfunction can markedly impair quality of life. A multidisciplinary approach that incorporates pain medications, physical therapy, and lifestyle modifications is ideal. Integrative holistic treatments such as natural supplements, yoga, and other mind-body therapies may also help.

TABLE 3

Pain management for small fiber neuropathy

Therapy	Dosages (per day)	Common adverse effects
Anticonvulsants		
Gabapentin	300–3,600 mg	Sedation, dizziness, peripheral edema, weight gain
Pregabalin	150–600 mg	Similar to gabapentin
Topiramate	25–400 mg	Weight loss, sedation, cognitive slowing, depression with suicidal ideation, renal stones, paresthesias, glaucoma
Zonegran	100–400 mg	
Antidepressants		
Amitriptyline	20–100 mg	Sedation, weight gain, anticholinergic effects, sexual dysfunction, arrhythmia (side effects most prominent with amitriptyline)
Nortriptyline	20–100 mg	
Desipramine	20–200 mg	
Duloxetine	60–120 mg	
Topical anesthetics		
Lidocaine 5% patch	3 patches for 12 hours	Local edema, burning, erythema
Lidocaine 5% cream or gel	5 g to affected areas up to 20 g total	Local edema, burning, erythema
Capsaicin 0.75%	Apply up to 4 times daily	Burning
Capsaicin 8% patch	60–90 minutes (applied by the clinician)	Burning
Other		
Tramadol	50–400 mg	Sedation, dizziness, seizures, nausea, constipation
Mexiletine	200–600 mg	Nausea, vomiting, abdominal pain, dry mouth (not helpful for diabetic neuropathy)

Regardless of cause, managing symptoms remains key

Pain control

Antiepileptics, antidepressants, and topical agents are first-line therapies for small fiber neuropathy pain (**Table 3**). The efficacy of each drug varies among individuals, so initial treatment choice is often based on cost or side-effect profiles. For example, topiramate should be avoided in patients with a history of renal stones but can be beneficial for metabolic syndrome, as it promotes weight loss.

Mexiletine, a voltage-gated sodium channel blocker used as an antiarrhythmic, may help refractory pain or hereditary small fiber neuropathy related to sodium channel dysfunction. However, it is not recommended for diabetic neuropathy.[39]

Combination regimens that use drugs with different mechanisms of action can be effective. In one study, combined gabapentin and nortriptyline were more effective than either drug alone for neuropathic pain.[40]

Inhaled cannabis reduced pain in patients with HIV and diabetic neuropathy in a number of studies. Side effects included euphoria, somnolence, and cognitive impairment.[41,42] The use of medical marijuana is not yet legal nationwide and may affect employability even in states in which it has been legalized.

Owing to the opioid epidemic and high addiction potential, opioids are no longer a preferred recommendation for chronic treat-

TABLE 4

Over-the-counter treatments for small fiber neuropathy

Treatments	Dosage	Comments
Oral supplements		
Acetyl-L-carnitine	1,000 mg 3 times a day	Some benefit seen in diabetic and human immunodeficiency virus neuropathy,[45,47] but may worsen chemotherapy-induced neuropathy[48]
Alpha lipoic acid	600 mg/day	Early studies found benefit with intravenous dosing but no data on optimal oral dose[46]
Glutamine	15 g twice a day	Possible neuroprotective effect in chemotherapy-induced neuropathy with oral dose,[49] pain reduction with intravenous dosing[50]
Curcumin	Dose varies	Some benefit in pain reduction for diabetic and chemotherapy-induced neuropathy[51,52]
Omega-3 fatty acids	1,000–3,000 g/day	Possible pain reduction seen in mouse models; increased nerve growth in patients with diabetic small fiber neuropathy[53,54]
Topical products		
Vicks VapoRub	Apply as needed	May cause increased pain on initial contact
Horse liniment cream	Apply as needed	May cause increased pain on initial contact
Frankincense oil	Apply as needed	Reduces neuropathic pain in mice[55]
Hemp cream or oil	Apply as needed	Noncannabidiol form legal in all states

Patients on chronic opioid therapy had worse functional outcomes

ment of noncancer-related neuropathy. A population-based study of 2,892 patients with neuropathy found that those on chronic opioid therapy (≥ 90 days) had worse functional outcomes and higher rates of addiction and overdose than those on short-term therapy.[43] However, the opioid agonist tramadol was found to be effective in reducing neuropathic pain and may be a safer option for patients with chronic small fiber neuropathy.[44]

Integrative, holistic therapies

Many patients with chronic illness are turning toward complementary and alternative medicine owing to lack of perceived benefit from conventional treatments, medication side effects, or a desire for more "natural" therapies. Limited data from small clinical trials have shown marginal improvement in neuropathic pain with a number of over-the counter-supplements, including acetyl-L-carnitine and alpha lipoic acid (**Table 4**).[45–55] In one study,[54] omega-3 fatty acids from seal oil improved corneal fiber density in patients with diabetic neuropathy. Acupuncture, as well as mentholated ointments and essential oils in combination with massage of the feet, may also provide temporary relief.[55] Mind-body therapies such as yoga, meditation, and tai chi may help pain, balance, and quality of life in patients with neuropathy.[56]

PROGNOSIS

For many patients, small fiber neuropathy is a slowly progressive disorder that reaches a clinical plateau lasting for years, with progression to large fiber involvement reported in 13% to 36% of cases; over half of patients in one series either improved or remained stable over a period of 2 years.[5,57] Long-term studies are needed to fully understand the natural disease course. In the meantime, treating underlying disease and managing symptoms are imperative to patient care. ■

REFERENCES

1. **Burke JF, Skolarus LE, Callaghan BC, Kerber KA**. Choosing Wisely: highest-cost tests in outpatient neurology. Ann Neurol 2013; 73(5):679–683. doi:10.1002/ana.23865
2. **Gordois A, Scuffham P, Shearer A, Oglesby A, Tobian JA**. The health care costs of diabetic peripheral neuropathy in the US. Diabetes Care 2003; 26(6):1790–1795. pmid:12766111
3. **Peters MJ, Bakkers M, Merkies IS, Hoeijmakers JG, van Raak EP, Faber CG**. Incidence and prevalence of small-fiber neuropathy: a survey in the Netherlands. Neurology 2013; 81(15):1356–1360. doi:10.1212/WNL.0b013e3182a8236e
4. **Periquet MI, Novak V, Collins MP, et al**. Painful sensory neuropathy: prospective evaluation using skin biopsy. Neurology 1999; 53(8):1641–1647. pmid:10563606
5. **Devigili G, Tugnoli V, Penza P, et al**. The diagnostic criteria for small fibre neuropathy: from symptoms to neuropathology. Brain 2008; 131(pt 7):1912–1925. doi:10.1093/brain/awn093
6. **Lacomis D**. Small-fiber neuropathy. Muscle Nerve 2002; 26(2):173–188. doi:10.1002/mus.10181
7. **Lopate G, Streif E, Harms M, Weihl C, Pestronk A**. Cramps and small-fiber neuropathy. Muscle Nerve 2013; 48(2):252–255. doi:10.1002/mus.23757
8. **Khan S, Zhou L**. Characterization of non-length-dependent small-fiber sensory neuropathy. Muscle Nerve 2012; 45(1):86–91. doi:10.1002/mus.22255
9. **Tavee JO, Karwa K, Ahmed Z, Thompson N, Parambil J, Culver DA**. Sarcoidosis-associated small fiber neuropathy in a large cohort: clinical aspects and response to IVIG and anti-TNF alpha treatment. Respir Med 2017; 126:135–138. doi:10.1016/j.rmed.2017.03.011
10. **Berkowitz AL, Samuels MA**. The neurology of Sjogren's syndrome and the rheumatology of peripheral neuropathy and myelitis. Pract Neurol 2014; 14(1):14–22. doi:10.1136/practneurol-2013-000651
11. **Lang M, Treister R, Oaklander AL**. Diagnostic value of blood tests for occult causes of initially idiopathic small-fiber polyneuropathy. J Neurol 2016; 263(12):2515–2527. doi:10.1007/s00415-016-8270-5
12. **Seneviratne U, Gunasekera S**. Acute small fibre sensory neuropathy: another variant of Guillain-Barré syndrome? J Neurol Neurosurg Psychiatry 2002; 72(4):540–542. pmid:11909922
13. **Tavee JO, Polston D, Zhou L, Shields RW, Butler RS, Levin KH**. Sural sensory nerve action potential, epidermal nerve fiber density, and quantitative sudomotor axon reflex in the healthy elderly. Muscle Nerve 2014; 49(4):564–569. doi:10.1002/mus.23971
14. **Tavee J, Zhou L**. Small fiber neuropathy: a burning problem. Cleve Clin J Med 2009; 76(5):297–305. doi:10.3949/ccjm.76a.08070
15. **Herrmann DN, Griffin JW, Hauer P, Cornblath DR, McArthur JC**. Epidermal nerve fiber density and sural nerve morphometry in peripheral neuropathies. Neurology 1999; 53(8):1634–1640. pmid:10563605
16. **Oaklander AL, Herzog ZD, Downs HM, Klein MM**. Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia. Pain 2013; 154(11):2310–2316. doi:10.1016/j.pain.2013.06.001
17. **Üçeyler N, Zeller D, Kahn AK, et al**. Small fibre pathology in patients with fibromyalgia syndrome. Brain 2013; 136(pt 6):1857–1867. doi:10.1093/brain/awt053
18. **Stewart JD, Low PA, Fealey RD**. Distal small fiber neuropathy: results of tests of sweating and autonomic cardiovascular reflexes. Muscle Nerve 1992; 15(6):661–665. doi:10.1002/mus.880150605
19. **Malik RA, Kallinikos P, Abbott CA, et al**. Corneal confocal microscopy: a non-invasive surrogate of nerve fibre damage and repair in diabetic patients. Diabetologia 2003; 46(5):683–688. doi:10.1007/s00125-003-1086-8
20. **de Greef BTA, Hoeijmakers JGJ, Gorissen-Brouwers CML, Geerts M, Faber CG, Merkies ISJ**. Associated conditions in small fiber neuropathy - a large cohort study and review of the literature. Eur J Neurol 2018; 25(2):348–355. doi:10.1111/ene.13508
21. **Smith AG**. Impaired glucose tolerance and metabolic syndrome in idiopathic neuropathy. J Peripher Nerv Syst 2012; 17(suppl 2):15–21. doi:10.1111/j.1529-8027.2012.00390.x
22. **Hoffman-Snyder C, Smith BE, Ross MA, Hernandez J, Bosch EP**. Value of the oral glucose tolerance test in the evaluation of chronic idiopathic axonal polyneuropathy. Arch Neurol 2006; 63(8):1075–1079. doi:10.1001/archneur.63.8.noc50336
23. **Vincent AM, Hinder LM, Pop-Busui R, Feldman EL**. Hyperlipidemia: a new therapeutic target for diabetic neuropathy. J Peripher Nerv Syst 2009; 14(4):257–267. doi:10.1111/j.1529-8027.2009.00237.x
24. **Wiggin TD, Sullivan KA, Pop-Busui R, Amato A, Sima AA, Feldman EL**. Elevated triglycerides correlate with progression of diabetic neuropathy. Diabetes 2009; 58(7):1634–1640. doi:10.2337/db08-1771
25. **Chin RL, Sander HW, Brannagan TH, et al**. Celiac neuropathy. Neurology 2003; 60(10):1581–1585. pmid:12771245
26. **Gemignani F, Brindani F, Alfieri S, et al**. Clinical spectrum of cryoglobulinaemic neuropathy. J Neurol Neurosurg Psychiatry 2005; 76(10):1410–1414. doi:10.1136/jnnp.2004.057620
27. **Bakkers M, Merkies IS, Lauria G, et al**. Intraepidermal nerve fiber density and its application in sarcoidosis. Neurology 2009; 73(14):1142–1148. doi:10.1212/WNL.0b013e3181bacf05
28. **Vernino S, Low PA, Fealey RD, Stewart JD, Farrugia G, Lennon VA**. Autoantibodies to ganglionic acetylcholine receptors in autoimmune autonomic neuropathies. N Engl J Med 2000; 343(12):847–855. doi:10.1056/NEJM200009213431204
29. **Faber CG, Hoeijmakers JG, Ahn HS, et al**. Gain of function Nav1.7 mutations in idiopathic small fiber neuropathy. Ann Neurol 2012; 71(1):26–39. doi:10.1002/ana.22485
30. **Brouwer BA, Merkies IS, Gerrits MM, Waxman SG, Hoeijmakers JG, Faber CG**. Painful neuropathies: the emerging role of sodium channelopathies. J Peripher Nerv Syst 2014; 19(2):53–65. doi:10.1111/jns5.12071
31. **Samuelsson K, Kostulas K, Vrethem M, Rolfs A, Press R**. Idiopathic small fiber neuropathy: phenotype, etiologies, and the search for Fabry disease. J Clin Neurol 2014; 10(2):108–118. doi:10.3988/jcn.2014.10.2.108
32. **de Greef BT, Hoeijmakers JG, Wolters EE, et al**. No Fabry disease in patients presenting with isolated small fiber neuropathy. PLoS One 2016; 11(2):e0148316. doi: 10.1371/journal.pone.0148316
33. **Souayah N, Ajroud-Driss S, Sander HW, Brannagan TH, Hays AP, Chin RL**. Small fiber neuropathy following vaccination for rabies, varicella or Lyme disease. Vaccine 2009; 27(52):7322–7325. doi:10.1016/j.vaccine.2009.09.077
34. **Nolano M, Provitera V, Manganelli F, et al**. Loss of cutaneous large and small fibers in naive and l-dopa–treated PD patients. Neurology 2017; 89(8):776–784. doi:10.1212/WNL.0000000000004274
35. **Zis P, Grünewald RA, Chaudhuri RK, Hadjivassiliou M**. Peripheral neuropathy in idiopathic Parkinson's disease: a systematic review. J Neurol Sci 2017; 378:204–209. doi:10.1016/j.jns.2017.05.023
36. **Gibbons CH, Freeman R**. Treatment-induced neuropathy of diabetes: an acute, iatrogenic complication of diabetes. Brain 2015; 138(pt 1):43–52. doi:10.1093/brain/awu307
37. **Look AHEAD Research Group**. Effects of a long-term lifestyle modification programme on peripheral neuropathy in overweight or obese adults with type 2 diabetes: the Look AHEAD study. Diabetologia 2017; 60(6):980–988. doi:10.1007/s00125-017-4253-z
38. **Culver DA, Dahan A, Bajorunas D, et al**. Cibinetide improves corneal nerve fiber abundance in patients with sarcoidosis-associated small nerve fiber loss and neuropathic pain. Invest Ophthalmol Vis Sci 2017; 58(6):BIO52–BIO60. doi:10.1167/iovs.16-21291
39. **Bril V, England J, Franklin GM, et al; American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation**. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. PM R 2011; 3(4):345–352.e21. doi:10.1016/j.pmrj.2011.03.008
40. **Gilron I, Bailey JM, Tu D, Holden RR, Jackson AC, Houlden RL**. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. Lancet

2009; 374(9697):1252–1261. doi:10.1016/S0140-6736(09)61081-3
41. **Ellis RJ, Toperoff W, Vaida F, et al**. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology 2009; 34(3):672–680. doi:10.1038/npp.2008.120
42. **Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH**. Efficacy of inhaled cannabis on painful diabetic neuropathy. J Pain 2015; 16(7):616–627. doi:10.1016/j.jpain.2015.03.008
43. **Hoffman EM, Watson JC, St Sauver J, Staff NP, Klein CJ**. Association of long-term opioid therapy with functional status, adverse outcomes, and mortality among patients with polyneuropathy. JAMA Neurol 2017; 74(7):773–779. doi:10.1001/jamaneurol.2017.0486
44. **Harati Y, Gooch C, Swenson M, et al**. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. Neurology 1998; 50(6):1842–1846. pmid:9633738
45. **Sima AA, Calvani M, Mehra M, Amato A; Acetyl-L-Carnitine Study Group**. Acetyl-L-carnitine improves pain, nerve regeneration, and vibratory perception in patients with chronic diabetic neuropathy: an analysis of two randomized placebo-controlled trials. Diabetes Care 2005; 28(1):89–94. pmid:15616239
46. **Ziegler D, Hanefeld M, Ruhnau KJ, et al**. Treatment of symptomatic diabetic peripheral neuropathy with the anti-oxidant alpha-lipoic acid. A 3-week multicentre randomized controlled trial (ALADIN Study). Diabetologia 1995; 38(12):1425–1433. pmid:8786016
47. **Scarpini E, Sacilotto G, Baron P, Cusini M, Scarlato G**. Effect of acetyl-L-carnitine in the treatment of painful peripheral neuropathies in HIV+ patients. J Peripher Nerv Syst 1997; 2(3):250-252. pmid: 10975731
48. **Hershman DL, Unger JM, Crew KD, et al**. Randomized double-blind placebo-controlled trial of acetyl-L-carnitine for the prevention of taxane-induced neuropathy in women undergoing adjuvant breast cancer therapy. J Clin Oncol 2013; 31(20):2627-2633. doi:10.1200/JCO.2012.44.8738
49. **Amara S**. Oral glutamine for the prevention of chemotherapy-induced peripheral neuropathy. Ann Pharmacother 2008; 42(10):1481-1485. doi:10.1345/aph.1L179
50. **Huang JS, Wu CL, Fan CW, Chen WH, Yeh KY, Chang PH**. Intravenous glutamine appears to reduce the severity of symptomatic platinum-induced neuropathy: a prospective randomized study. J Chemother 2015; 27(4):235-240. doi:10.1179/1973947815Y.0000000011
51. **Banafshe HR, Hamidi GA, Noureddini M, Mirhashemi SM, Mokhtari R, Shoferpour M**. Effect of curcumin on diabetic peripheral neuropathic pain: possible involvement of opioid system. Eur J Pharmacol 2014; 723:202-206. doi:10.1016/j.ejphar.2013.11.033
52. **Mendonça LM, da Silva Machado C, Teixeira CC, de Freitas LA, Bianchi MD, Antunes LM**. Curcumin reduces cisplatin-induced neurotoxicity in NGF-differentiated PC12 cells. Neurotoxicology 2013; 34:205-211. doi: 10.1016/j.neuro.2012.09.011
53. **Wagner K, Lee KS, Yang J, Hammock BD**. Epoxy fatty acids mediate analgesia in murine diabetic neuropathy. Eur J Pain 2017; 21(3):456-465. doi:10.1002/ejp.939
54. **Lewis EJ, Perkins BA, Lovblom LE, Bazinet RP, Wolever TMS, Bril V**. Effect of omega-3 supplementation on neuropathy in type 1 diabetes: a 12-month pilot trial. Neurology 2017; 88(24):2294–2301. doi:10.1212/WNL.0000000000004033
55. **Hu D, Wang C, Li F, et al**. A combined water extract of frankincense and myrrh alleviates neuropathic pain in mice via modulation of TRPV1. Neural Plast 2017; 2017:3710821. doi:10.1155/2017/3710821
56. **Tavee J, Rensel M, Planchon SM, Butler RS, Stone L**. Effects of meditation on pain and quality of life in multiple sclerosis and peripheral neuropathy: a pilot study. Int J MS Care 2011; 13(4):163–168. doi:10.7224/1537-2073-13.4.163
57. **Khoshnoodi MA, Truelove S, Burakgazi A, Hoke A, Mammen AL, Polydefkis M**. Longitudinal assessment of small fiber neuropathy: evidence of a non-length-dependent distal axonopathy. JAMA Neurol 2016; 73(6):684–690. doi:10.1001/jamaneurol.2016.0057

***ADDRESS**: Jinny O. Tavee, MD, Department of Neurology, Northwestern University Feinberg School of Medicine, 710 N Lakeshore Drive, Abbott Hall, Suite 1114, Chicago, IL 60611; jinny.tavee@nm.org; htavee@hotmail.com*