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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.

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

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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

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

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.

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 evolu-

tionary link that may reflect visceral defense mechanisms responding to pain as a signal of danger.¹¹ This may help explain the multi-systemic 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.

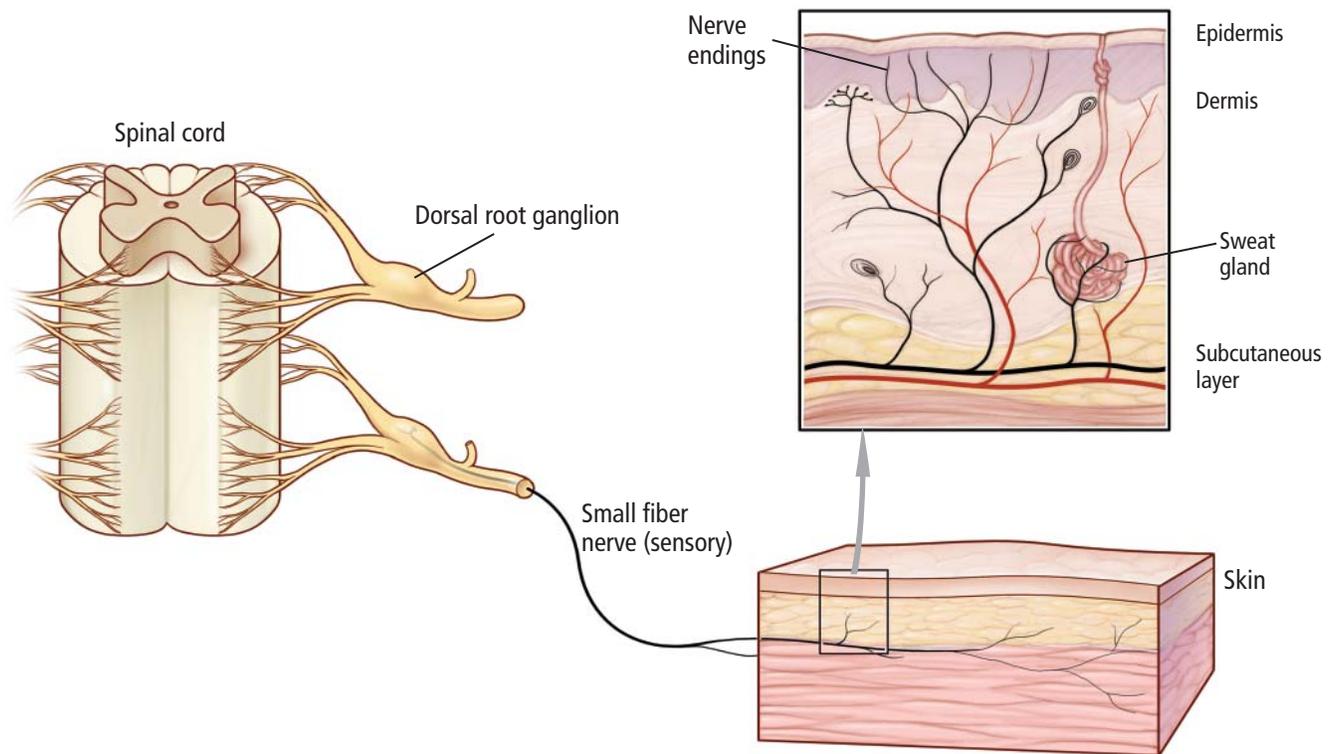
Evidence of a systemic disorder should also be sought, as it may indicate an underlying etiology.

DIAGNOSTIC TESTING

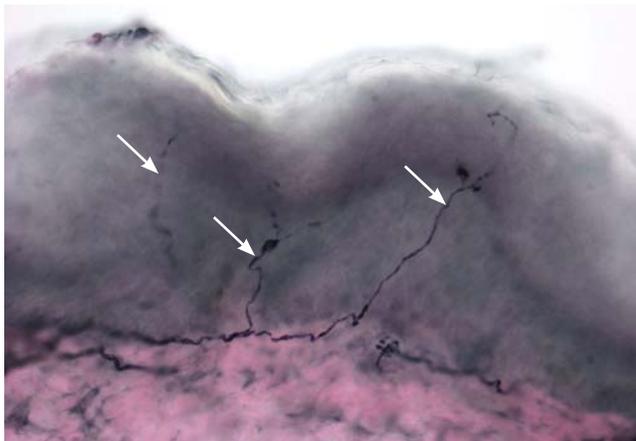
Although patients with either large or small fiber neuropathy may have subjective hyperesthesia or numbness of the distal lower extrem-

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.

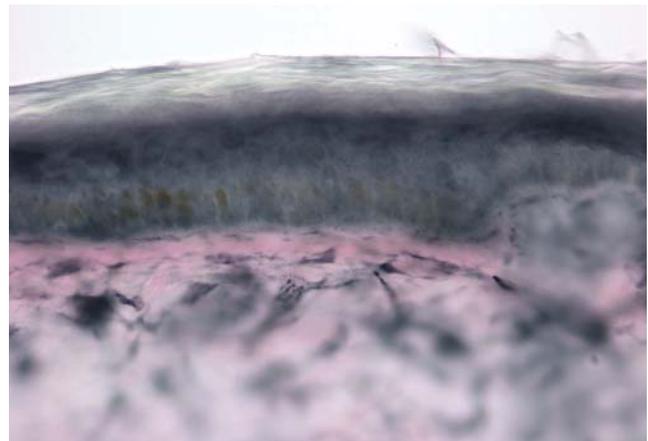


Normal skin biopsy



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.

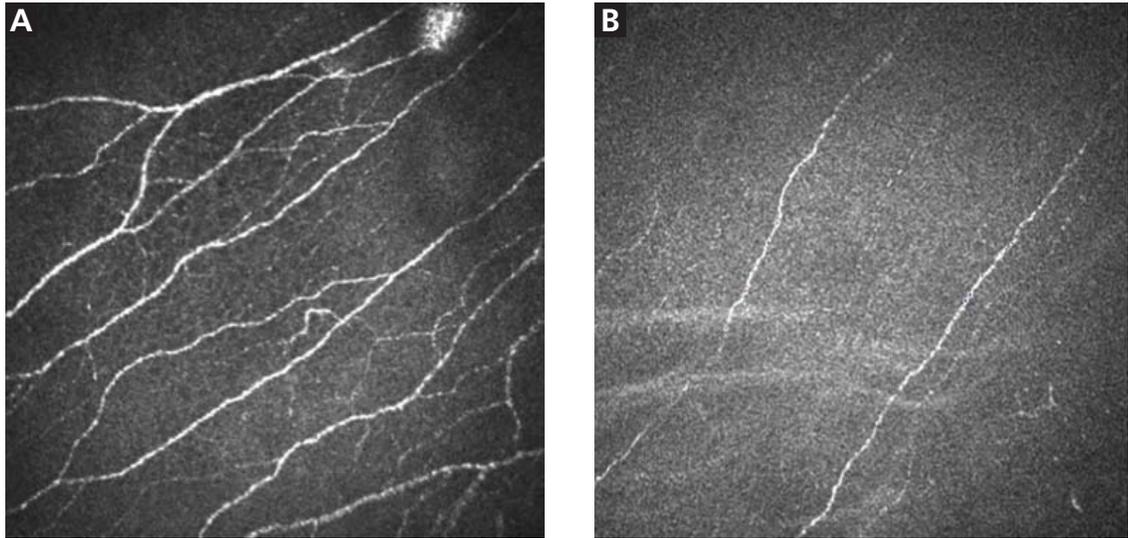


Figure 2. Corneal confocal microscopy in small fiber neuropathy: A, normal corneal nerve fibers and branching; B, marked reduction of corneal nerve fibers.

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

Electromyography worthwhile

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.

The physical examination should search for involvement of large nerve fibers

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 | |
| <i>SCN9A</i> and <i>SCN10A</i> genes | Hereditary small fiber neuropathy |
| <i>GLA</i> gene | Fabry disease |
| Transthyretin gene | Familial amyloidosis |
| <i>ABCA1</i> 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

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 B₁₂ deficiency testing

Vitamin B₁₂ 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 B₁₂ deficiency include reduced intake, pernicious anemia, and medi-

cations that can affect absorption of vitamin B₁₂ (eg, proton pump inhibitors, histamine 2 receptor antagonists, metformin).

Testing should include:

- Complete blood cell count to evaluate for vitamin B₁₂-related macrocytic anemia and other hematologic abnormalities
- Serum vitamin B₁₂ level
- Methylmalonic acid or homocysteine level in patients with subclinical or mild vitamin B₁₂ deficiency, manifested as low to normal vitamin B₁₂ levels (< 400 pg/mL); methylmalonic acid and homocysteine require vitamin B₁₂ as a cofactor for enzymatic conversion, and either or both may be elevated in early vitamin B₁₂ 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

Diabetes is the most common identifiable cause

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 B₁ (thiamine), or vitamin B₆ (pyridoxine) deficiency testing. Although vitamin B₆ toxicity may also result in neuropathy due to its toxic effect on the dorsal root ganglia, the mildly elevated vitamin B₆ 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 B₆ 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}

■ 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-

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

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.

■ 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 B₁₂ deficiency. As reduced absorption rather than low dietary intake is the primary cause of vitamin B₁₂ 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 B₁₂ 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 al³⁸ found that cibinetide, an experimental erythropoietin 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.

Targeted treatment may halt progression, improve symptoms

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. ■

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