



**EDUCATIONAL OBJECTIVE:** Readers will recognize the symptoms of small fiber neuropathy, list its causes, and formulate a plan for treating it

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# Small fiber neuropathy: A burning problem

## ABSTRACT

Small fiber neuropathy is increasingly being recognized as a major cause of painful burning sensations in the feet, especially in the elderly. Although strength remains preserved throughout the course of the disease, the pain and paresthesias are often disabling. Diabetes mellitus is the most common identifiable cause of small fiber neuropathy, and impaired oral glucose tolerance and individual components of the metabolic syndrome are often associated with it. Some cases, however, are idiopathic. Skin biopsy (with an evaluation of the density of intraepidermal nerve fibers) and tests of autonomic nerve function are useful for the diagnosis. Management involves controlling pain and identifying and aggressively treating the underlying cause.

## KEY POINTS

Symptoms of small fiber neuropathy typically start with burning feet and numb toes.

Causes and associated conditions can be found in over 50% of cases. These include glucose dysmetabolism, connective tissue diseases, sarcoidosis, dysthyroidism, vitamin B<sub>12</sub> deficiency, paraproteinemia, human immunodeficiency virus infection, celiac disease, neurotoxic drug exposure, and paraneoplastic syndrome.

Findings on routine nerve conduction studies and electromyography are typically normal in this disease.

Management includes aggressively identifying and treating the underlying cause, advising lifestyle modifications, and alleviating pain.

AN ESTIMATED 15 to 20 million people in the United States over age 40 have some type of peripheral neuropathy.<sup>1</sup> In many, the impairment is purely or predominantly in small nerve fibers, and the clinical presentation consists of pain, burning, tingling, and numbness in a length-dependent or stocking-glove distribution. (“Length” refers to distance from the trunk; distal fibers are affected first.) Symptoms typically begin in the feet and slowly ascend to the distal legs, at which point the hands may also be affected (FIGURE 1).

In many of these patients, the findings on neurologic examination, nerve conduction studies, and electromyography are normal, although some may show signs of mild distal sensory loss on physical examination. The lack of objective findings on routine nerve conduction studies and electromyography may lead many physicians to attribute the symptoms to other disorders such as plantar fasciitis, vascular insufficiency, or degenerative lumbosacral spine disease.

The past 2 decades have seen the development of specialized tests that have greatly facilitated the diagnosis of small fiber neuropathy; these include skin biopsy to evaluate the density of nerve fibers in the epidermis and studies of autonomic nerve function. Common etiologies have been identified for small fiber neuropathy and can be specifically treated, which is critical for controlling progression of the disease. Pain management is becoming easier with more available options but is still quite challenging.

## WHAT IS SMALL FIBER NEUROPATHY?

Small fiber neuropathy is a disorder of the peripheral nerves that primarily or exclusively



**FIGURE 1.** Symptoms are pain, burning, numbness, and autonomic dysfunction (lack of sweating) in the hands and feet in a stocking-glove distribution. Strength is not affected. Tendon reflexes are normal, as are nerve conduction studies.

**Small fiber neuropathy is often mistaken for plantar fasciitis, vascular insufficiency, or degenerative lumbosacral spine disease**

affects small somatic fibers, autonomic fibers, or both, resulting in sensory changes and autonomic dysfunction when both types are involved (FIGURE 2).<sup>2</sup>

Peripheral nerve fibers can be classified according to size, which correlates with the degree of myelination.

- Large nerve fibers are heavily myelinated and include A-alpha fibers, which mediate motor strength, and A-beta fibers, which mediate vibratory and touch sensation.
- Medium-sized fibers, known as A-gamma fibers, are also myelinated and carry information to muscle spindles.
- Small fibers include myelinated A-delta fibers and unmyelinated C fibers, which innervate skin (somatic fibers) and involuntary muscles, including cardiac and smooth muscles (autonomic fibers). Together, they mediate pain, thermal sensation, and autonomic function.

Small fiber neuropathy results from selec-

tive impairment of small myelinated A-delta and unmyelinated C fibers.

### **Sensory symptoms:**

#### **Pain, burning, tingling, numbness**

Damage to or loss of small somatic nerve fibers results in pain, burning, tingling, or numbness that typically affects the limbs in a distal-to-proximal gradient. In rare cases, small fiber neuropathy follows a non-length-dependent distribution in which symptoms may be manifested predominantly in the arms, face, or trunk.

Symptoms may be mild initially, with some patients complaining of vague discomfort in one or both feet similar to the sensation of a sock gathering at the end of a shoe. Others report a wooden quality in their feet, numbness in their toes, or a feeling as if they are walking on pebbles, sand, or golf balls. The most bothersome and fairly typical symptom is burning pain in the feet that extends proximally in a stocking-glove distribution and is often accompanied by stabbing or aching pains, electric shock-like or pins-and-needles sensations, or cramping of the feet and calves.

Symptoms are usually worse at night and often affect sleep. Some patients say that their feet have become so exquisitely tender that they cannot bear having the bed sheets touch them, and so they sleep with their feet uncovered. A small number of patients do not have pain but report a feeling of tightness and swelling in their feet (even though the feet appear normal).

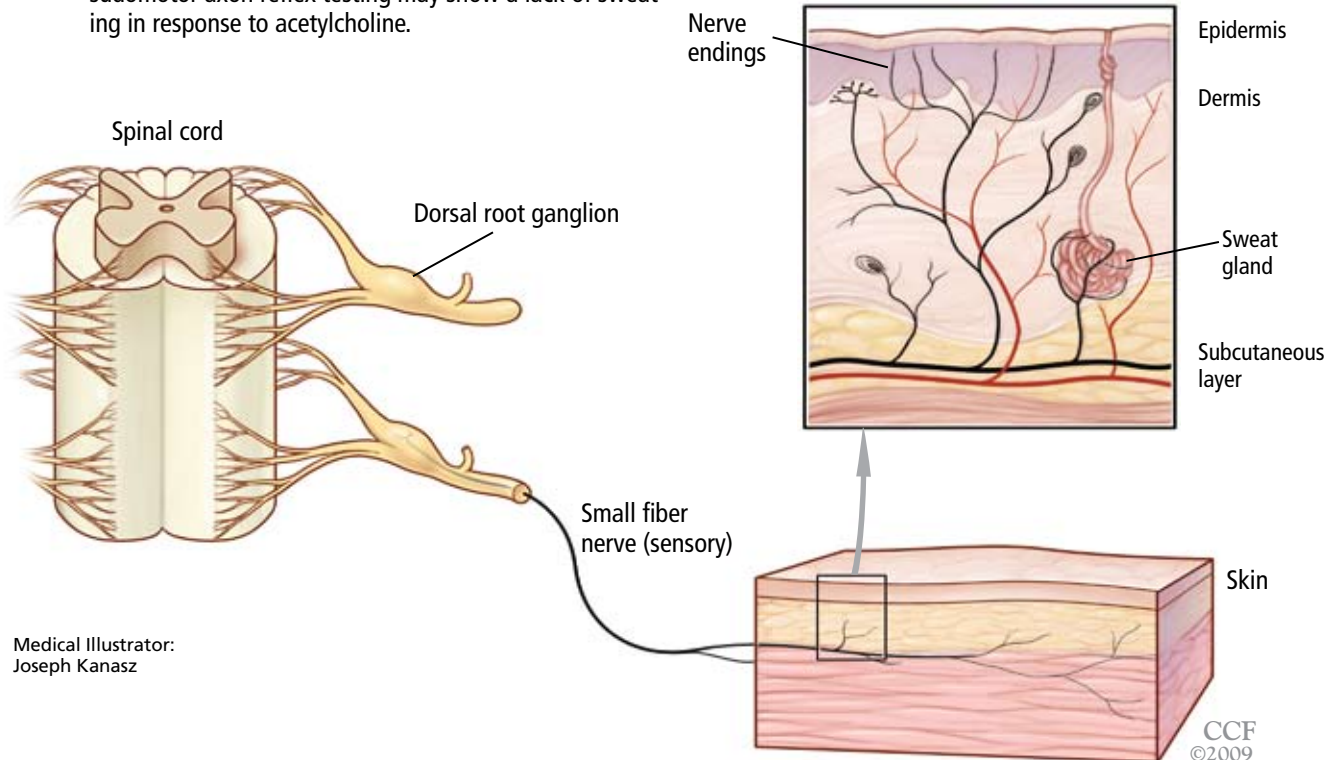
Examination often reveals allodynia (perception of nonpainful stimuli as being painful), hyperalgesia (perception of painful stimuli as being more painful than expected), or reduced pinprick and thermal sensation in the affected area. Vibratory sensation can be mildly reduced at the toes. Motor strength, tendon reflexes, and proprioception, however, are preserved because they are functions of large nerve fibers.

### **Autonomic symptoms**

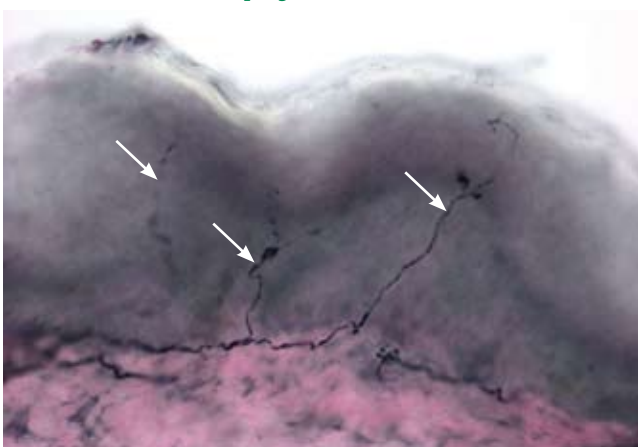
When autonomic fibers are affected, patients may experience dry eyes, dry mouth, orthostatic dizziness, constipation, bladder incontinence, sexual dysfunction, trouble sweating, or red or white skin discoloration.<sup>2</sup> Examination may show orthostatic hypotension and

## 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 affected nerve fibers are the 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.

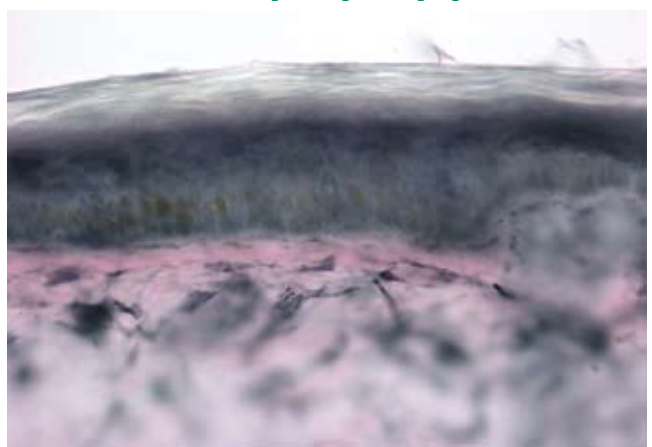


### Normal skin biopsy



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.

FIGURE 2

skin changes. The skin over the affected area may appear atrophic, dry, shiny, discolored, or mildly edematous as the result of sudomotor and vasomotor abnormalities.

### ■ WHAT CAUSES SMALL FIBER NEUROPATHY?

Small fiber neuropathy has been associated with many medical conditions, including glucose dysmetabolism,<sup>3</sup> connective tissue disease,<sup>4,5</sup> dysthyroidism,<sup>6</sup> vitamin B<sub>12</sub> deficiency, paraproteinemia, human immunodeficiency virus (HIV) infection,<sup>7</sup> hepatitis C virus infection, celiac disease,<sup>8</sup> restless legs syndrome,<sup>9</sup> neurotoxic drug exposure, hereditary diseases, and paraneoplastic syndrome. While most of these conditions cause a length-dependent small fiber neuropathy, others (Sjögren disease, celiac disease, and paraneoplastic syndrome) can cause a form of small fiber neuropathy that is not length-dependent.<sup>4,8,10</sup>

#### Diabetes and prediabetes

Glucose dysmetabolism, including diabetes and prediabetes with impaired oral glucose tolerance (a glucose level 140–199 mg/dL 2 hours after a 75-g oral dextrose load), is the most common identifiable associated condition, present in about one-third of patients with painful sensory neuropathy<sup>11</sup> and in nearly half of those with otherwise idiopathic small fiber neuropathy.<sup>12–14</sup>

Research findings strongly suggest that even prediabetes is a risk factor for small fiber neuropathy, and that so-called “impaired glucose tolerance neuropathy” may represent the earliest stage of diabetic neuropathy. Several recent studies have found a high prevalence of impaired glucose tolerance in patients with sensory peripheral neuropathy,<sup>12–14</sup> with a rate of up to 42% in cases initially thought to be idiopathic<sup>14</sup> compared with 14% in the general population.<sup>15</sup> Also, a dose-response relationship between the severity of hyperglycemia and the degree of neuropathy was demonstrated in one study, in which patients with impaired glucose tolerance more often had small fiber neuropathy, whereas those with diabetes more often had polyneuropathy involving both small and large fibers.<sup>14</sup> And studies in animals and cell cultures have shown that in-

termittent hyperglycemia, which can be seen in patients with impaired glucose tolerance, caused sensory neuron and nerve fiber damage and increased spontaneous C-fiber firing, resulting in neuropathic pain.<sup>8,16,17</sup>

#### Metabolic syndrome

Insulin resistance with prediabetes and diabetes is a part of the metabolic syndrome, which also consists of hypertension, hyperlipidemia, and obesity. The individual components of the metabolic syndrome have been implicated as risk factors not only for cardiovascular and cerebrovascular disease but also for small fiber neuropathy.

One study in 548 patients with type 2 diabetes showed that those with the metabolic syndrome were twice as likely to have neuropathy as those without.<sup>18</sup> Another study showed that in 1,200 patients with type 1 diabetes without neuropathy at baseline, hypertension, hyperlipidemia, and increased body mass index were each independently associated with a higher risk of developing neuropathy.<sup>19</sup>

A recent study of 219 patients with idiopathic distal symmetrical peripheral neuropathy and 175 diabetic patients without neuropathy found a higher prevalence of metabolic syndrome in patients with neuropathy than in normal populations. The prevalence of dyslipidemia (high levels of total and low-density lipoprotein cholesterol and triglycerides and low levels of high-density lipoprotein cholesterol), but not hypertension or obesity, was higher in patients with neuropathy than in patients with diabetes but no neuropathy.<sup>20</sup> The findings linked dyslipidemia to neuropathy and showed the need for further studies of the potential pathogenic role of dyslipidemia in neuropathy.

#### Hereditary causes

Hereditary causes of small fiber neuropathy are rare and include Fabry disease, Tangier disease, hereditary sensory autonomic neuropathy, and hereditary amyloidosis.

### ■ HOW DO YOU EVALUATE PATIENTS WITH SUSPECTED SMALL FIBER NEUROPATHY?

A thorough history should be taken to obtain details regarding onset and features of neu-

**The most bothersome symptom is burning pain in the feet that extends proximally in a stocking-glove distribution**

ropathy symptoms, exacerbating factors, and progression. It is also important to ascertain whether the patient has any associated conditions as mentioned above, a family history of neuropathy, risk factors for HIV or hepatitis C virus infection, or a history of neurotoxic drug exposure.

Clinical suspicion of small fiber neuropathy should be high if a patient presents with predominant small fiber symptoms and signs with preserved large fiber functions.

### Nerve conduction studies and electromyography

For diagnostic testing, routine nerve conduction studies and electromyography assess the function of large nerve fibers only and are thus normal in small fiber neuropathy. These tests should still be ordered to rule out subclinical involvement of large fibers, which may affect the diagnostic evaluation, prognosis, and treatment plan. However, if the results of these tests are normal, specialized studies are needed to evaluate small fibers.

Although several tests are available to evaluate somatic and autonomic small fibers, the two that have the highest diagnostic efficiency for small fiber neuropathy and that are used most often are skin biopsy, to evaluate intraepidermal nerve fiber density, and quantitative sudomotor axon reflex testing (QSART), to assess sudomotor autonomic function.<sup>21-23</sup>

### Skin biopsy

Skin biopsy is a minimally invasive procedure in which 3-mm-diameter punch biopsy specimens are taken from the distal leg, distal thigh, and proximal thigh of one lower limb. The procedure takes only 10 to 15 minutes.

Biopsy specimens are immunostained using an antibody against protein gene product 9.5, which is a panaxonal marker. Small nerve fibers in the epidermis are counted under a microscope, and intraepithelial nerve fiber densities are calculated and compared with established normative values. The diagnosis of small fiber neuropathy can be established if the intraepidermal nerve fiber density is lower than normal (FIGURE 1). Nerve fiber density may be normal in the early stage of small fiber neuropathy, but in this setting skin biopsy often

shows abnormal morphologic changes in the small fibers, especially large swellings,<sup>24</sup> and repeat biopsy in 6 to 12 months may be considered.

The diagnostic efficiency of skin biopsy is about 88%.<sup>21,23</sup> For diagnosing small fiber neuropathy, it is more sensitive than quantitative sensory testing<sup>21,25</sup> and more sensitive and less invasive than sural nerve biopsy.<sup>26</sup> Intraepidermal nerve fiber density also correlates well with a variety of measures of severity of HIV distal sensory neuropathy and thus may be used to measure the severity and treatment response of small fiber neuropathy.<sup>27</sup>

### Quantitative sudomotor axon reflex testing

QSART is an autonomic study that measures sweat output in response to acetylcholine, which reflects the function of postganglionic sympathetic unmyelinated sudomotor nerve fibers. Electrodes are placed on the arms and legs to record the volume of sweat produced by acetylcholine iontophoresis, in which a mild electrical stimulation on the skin allows acetylcholine to stimulate the sweat glands. The output is compared with normative values.

One prospective study showed that 67 (72.8%) of 92 patients with painful feet had abnormal results on QSART, ie, low sweat output.<sup>28</sup> A retrospective study found that 77 (62%) of 125 patients with clinical features of distal small fiber neuropathy had a length-dependent pattern of QSART abnormalities.<sup>22</sup> QSART abnormalities were detected in some patients without autonomic symptoms.

### If these tests are not available

Skin biopsy and QSART are objective, reproducible, sensitive, and complementary in diagnosing small fiber neuropathy. One or both can be ordered, depending on whether the patient has somatic symptoms, autonomic symptoms, or both. However, these two tests are not widely available. Only a few laboratories in the country can process skin biopsy specimens to evaluate intraepidermal nerve fiber density. Nevertheless, it is easy to learn the skin punch biopsy procedure, and primary care physicians and neurologists can perform it after appropriate training. (A concern is avoiding damage to the epidermis.) They can

**Nerve conduction studies assess large fibers only**

**TABLE 1**

**Drugs for pain control in small fiber neuropathy**

DRUG	DOSAGE (PER DAY)	COMMON SIDE EFFECTS
<b>Antidepressants</b>		
Amitriptyline (Elavil)	20–150 mg	Sedation, weight gain, anticholinergic effects, sexual dysfunction, arrhythmia (side effects most prominent with amitriptyline)
Nortriptyline (Aventyl)	20–150 mg	
Desipramine (Norpramin)	20–200 mg	
Duloxetine (Cymbalta)	60–120 mg	
<b>Anticonvulsants</b>		
Gabapentin (Neurontin)	600–3,600 mg	Sedation, dizziness, peripheral edema, weight gain
Pregabalin (Lyrica)	150–600 mg	Similar to gabapentin
Topiramate (Topamax)	25–400 mg	Weight loss, sedation, cognitive slowing, renal stones, paresthesias
Lamotrigine (Lamictal)	25–400 mg	Stevens-Johnson syndrome, rash, dizziness, nausea, sedation
Carbamazepine (Tegretol)	200–1,200 mg	Dizziness, sedation, ataxia, aplastic anemia, liver enzyme elevation
Oxcarbazepine (Trileptal)	600–2,400 mg	Dizziness, nausea, fatigue, leukopenia
<b>Topical anesthetics</b>		
5% Lidocaine patch (Lidoderm)	Every 12 hours	Local edema, burning, erythema
0.075% Capsaicin patch	Three or four times a day	Burning
<b>Opioids, opioid agonists</b>		
Tramadol (Ultram)	100–400 mg	Sedation, dizziness, seizures, nausea, constipation
Oxycodone (Oxycontin)	10–100 mg	Sedation, constipation, nausea; potential for addiction and abuse

then send specimens to one of the cutaneous nerve laboratories (but not to a routine reference laboratory).

A special technique, including unique fixative and cryoprotectant, is used to fix and process the biopsy specimens, because routine techniques for processing dermatologic punch biopsy specimens often result in lower intraepidermal nerve fiber densities. Therefore, it is very important to contact the laboratory regarding fixative and processing before performing a biopsy.

QSART requires specialized equipment and must be performed on site. In addition, the test is very sensitive to drugs that can affect sweating, such as antihistamines and an-

tidepressants, and such drugs must be discontinued 48 hours before the study.

**Basic laboratory tests to find the cause**

Once the diagnosis of small fiber neuropathy is established, the next important step is to order a battery of laboratory tests to search for an underlying cause. The tests should include the following:

- Complete blood cell count
- Comprehensive metabolic panel
- Lipid panel
- Erythrocyte sedimentation rate
- Thyroid-stimulating hormone level
- Free thyroxine (T4) level

- Antinuclear antibody
- Extractable nuclear antigens
- Angiotensin-converting enzyme (ACE) level
- Serum and urine immunofixation tests
- Vitamin B<sub>12</sub> level
- 2-hour oral glucose tolerance test.

Oral glucose tolerance testing is much more sensitive than measuring the hemoglobin A<sub>1c</sub> and fasting glucose levels in detecting diabetes and prediabetes. These two conditions were detected by oral glucose tolerance testing in more than 50% of patients with otherwise idiopathic sensory-predominant peripheral neuropathy and normal hemoglobin A<sub>1c</sub> and fasting glucose levels.<sup>13,14</sup> Therefore, every patient with small fiber neuropathy without a known history of diabetes or prediabetes should have an oral glucose tolerance test.

### Special laboratory tests in special cases

- If there is a history of gastrointestinal symptoms or herpetiform-like rash, then testing for gliadin antibody and tissue transglutaminase antibodies as well as small-bowel biopsy may be pursued to evaluate for celiac sprue.
- Serologic tests for HIV or hepatitis C should be ordered if the patient has risk factors.
- If there is a significant family history, further genetic testing should be considered.
- Lip biopsy or bone marrow biopsy should be considered if clinical suspicion is high for Sjögren disease, seronegative sicca syndrome, or amyloidosis.
- The serum ACE level has a low sensitivity and specificity; therefore, if sarcoid is suspected clinically, additional confirmatory testing, such as computed tomography of the chest, should be ordered despite a normal ACE value.

### ■ HOW DO YOU TREAT SMALL FIBER NEUROPATHY?

Treatment of small fiber neuropathy should target the underlying cause and neuropathic pain. Cause-specific treatment is a key in preventing small fiber neuropathy or slowing its progression.

#### Glucose control, weight control, and regular exercise

As glucose dysmetabolism is the condition most often associated with small fiber neu-

ropathy (and since individual components of the metabolic syndrome are potential risk factors for it), tight glycemic control and lifestyle modification with diet control, weight control, and regular exercise are of paramount importance in patients with these conditions.

The Diabetic Prevention Program,<sup>29</sup> a study in 3,234 people with prediabetes, found that diet and exercise were more effective than metformin (Glucophage) in preventing full-blown diabetes. At an average of 2.8 years of follow-up, the incidence of diabetes was 11.0 cases per 100 patient-years in a group assigned to receive placebo, compared with 7.8 in those assigned to receive metformin (31% lower), and 4.8 (58% lower) in those who were assigned to undergo a lifestyle intervention that included at least 150 minutes of physical activity per week with a weight-loss goal of 7%. Put another way, to prevent one case of diabetes over 3 years, 6.9 patients would have to undergo the lifestyle intervention program, or 13.9 would have to receive metformin. Since impaired glucose tolerance neuropathy may represent the earliest stage of diabetic neuropathy, the neuropathy at this stage may be reversible with lifestyle intervention and improvement of impaired glucose tolerance.

This concept is supported by a 3-year study in 31 people, which showed that lifestyle intervention significantly improved impaired glucose tolerance, reduced the body mass index, and lowered total serum cholesterol levels.<sup>30</sup> Changes in these metabolic variables were accompanied by significant improvement of neuropathy as evidenced by significantly increased intraepidermal nerve fiber density, increased foot sweat volume, and decreased neuropathic pain.<sup>30</sup>

#### Treatment of other diseases

It has also been reported that treatment of sarcoidosis, autoimmune diseases, and celiac disease improved the symptoms of small fiber neuropathy resulting from these conditions.<sup>8,31</sup> Therefore, it is important to identify the cause and treat it to prevent and slow the progression of small fiber neuropathy, and doing so may improve the disease in some mild cases.

**Only a few cutaneous nerve laboratories can process skin biopsy specimens to evaluate intraepidermal nerve fiber density**

### Pain management

Pain management is crucial in the treatment of small fiber neuropathy, as neuropathic pain can be debilitating and can cause depression. Pain management often requires a multidisciplinary team, including a primary care physician, a neurologist, a pain specialist, and a psychiatrist. Medications include antidepressants, anticonvulsants, and topical anesthetics (TABLE 1) as well as narcotic and non-narcotic analgesics and antiarrhythmics. Nonpharmacologic management includes transcutaneous electrical nerve stimulation (TENS), heat, ice, and massage of painful areas (reviewed by Chen et al<sup>32</sup> and Galluzzi<sup>33</sup>).

First-line choices of pain medications are the anticonvulsants gabapentin (Neurontin) and pregabalin (Lyrica), the tricyclic antidepressants amitriptyline (Elavil) and nortriptyline (Aventyl), a 5% lidocaine patch (Lidoderm), and the semisynthetic opioid analgesic tramadol (Ultram). These can be used alone or in combination.

**Gabapentin** is relatively well tolerated, but drowsiness can occur, especially with high starting doses. We usually start with 300 mg daily and increase it by 300 mg every week up to 1,200 mg three times a day as tolerated. Most patients need 600 to 900 mg three times a day.

**Pregabalin** is a newer antiepileptic drug, similar to gabapentin but less sedating. It can be started at 75 mg twice a day and gradually increased to 300 mg twice a day as needed. Weight gain and, rarely, swelling of the lower extremities may limit the use of both of these drugs.

**Tricyclic antidepressants**, such as amitriptyline, nortriptyline, and desipramine (Norpramin), are proven effective in controlling neuropathic pain, although no response with amitriptyline was seen in patients with painful HIV distal sensory neuropathy.<sup>34</sup>

**Lidocaine patch** is preferred if the painful area is small. Patients should be instructed to use the patch to cover the painful area 12 hours on and 12 hours off. If it does not provide relief within 1 week, it should be discontinued.

**Tramadol** is also helpful in treating neuropathic pain. It can be started at 50 mg two to four times a day as needed.

**Nonsteroidal anti-inflammatory drugs** and **selective serotonin reuptake inhibitors** are typically less effective than the other drugs mentioned.

**Opioids should be reserved for refractory cases**, given the potential for addiction, but they are sometimes necessary in patients with disabling pain that does not respond to other drugs.

**TENS** may be of benefit. The patient controls a pocket-size device that sends electrical signals to leads placed on affected areas.

**Alternative therapies** for small fiber neuropathy, such as meditation, yoga, and acupuncture, have yet to be studied.

It is also important to explain to patients that the typical course of small fiber neuropathy is relatively benign, as many patients worry about developing weakness and eventually not being able to walk. These concerns and fears can aggravate pain and depression, which can make treatment difficult.

### ■ WHAT IS THE PROGNOSIS OF SMALL FIBER NEUROPATHY?

Most patients with small fiber neuropathy experience a slowly progressive course, with symptoms and signs spreading proximally over time.

In one study, only 13% of 124 patients with small fiber neuropathy showed evidence of large-fiber involvement over a 2-year period.<sup>21</sup> None went on to develop Charcot joints, foot ulcers, weakness, or sensory ataxia, as is often seen in patients with long-standing or severe large fiber neuropathy. Neuropathic pain worsened in 30% and resolved spontaneously in 11%.<sup>21</sup>

Most patients with small fiber neuropathy require chronic pain management. Again, treatment of the underlying cause is important and can improve the prognosis.

We believe that the overall progression of small fiber neuropathy is slow. A longitudinal study with a follow-up longer than 2 years would be useful to confirm this.

### ■ TAKE-HOME POINTS

As the population continues to age and as more patients develop diabetes and the meta-

**All patients with small fiber neuropathy without known diabetes or pre-diabetes need an oral glucose tolerance test**



bolic syndrome, the prevalence of small fiber neuropathy will rise. Patients who present to their primary care physicians with painful, burning feet require a thorough diagnostic evaluation, which may include referral for

specialized neurodiagnostic testing. Aggressive cause-specific treatment, lifestyle modification, and pain control are key elements of a team approach to managing small fiber neuropathy. ■

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## CME ANSWERS

Answers to the credit test on page 319 of this issue

1D 2B 3A 4C 5D 6C 7B 8D