



# Understanding Small Fiber

Because so little is still understood about this disease, there continues to be controversy about its causes, methods of diagnosis and rates of progression.

By Jim Trageser

**SMALL FIBER NEUROPATHY (SFN)** remains one of the least understood diseases. Doctors have a challenging time diagnosing it, and treatment options are limited. There is only a cure if a cause is known, and there is no vaccine to prevent it. In addition, researchers hold contradictory views on how SFN progresses, what the risks are, how to diagnose it and how best to treat it.<sup>1</sup>

As a June 2016 column in the journal *JAMA Neurology* states: “Despite three decades of intense study, SFN remains an enigmatic condition that is often difficult to diagnose and manage successfully. ... The precise diagnostic criteria for SFN are debated, and the relative role of specific symptoms, signs, specialized investigations ... and skin biopsy for measurement of intraepidermal nerve fiber density is uncertain and somewhat controversial.”<sup>1</sup>

This lack of consensus about SFN in the medical community understandably leaves patients and their families confused and frustrated as they not only look for definitive answers, but an effective approach to ease what can be debilitating pain and other symptoms and restore their quality of life.

## What Is SFN?

SFN is a type of peripheral neuropathy, which is a disease of the nervous system outside the brain and spinal column. It is a perplexing disease since it is defined by the damage it causes, rather than what causes it. The damaged nerves that lead to symptoms of SFN are the small myelinated afferent fibers or the unmyelinated C fibers that extend into the limbs.<sup>2</sup> (Myelin is a protective coating around larger nerves; SFN seems to involve nerve cells with minimal or no myelin.) These are the nerve cells that carry information on all sensation, temperature and pain to the brain.

If physicians and researchers struggle to craft a single, testable diagnosis for SFN (sometimes called small fiber sensory neuropathy), those suffering from it have no such difficulty describing it: terrible pain, often with no discernible cause.

Patients may experience hyperalgesia, which is a heightened sensitivity to pain in general. They may also develop hypoesthesia, which occurs when normal stimulation such as the feeling of a sheet over the legs suddenly provokes intense pain.<sup>3</sup> In addition, they may experience allodynia, which

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causes nonpainful sensations to become painful (i.e., lightly touching a limb producing severe pain).

Other symptoms may include sensations of burning heat or freezing cold, or the inability to tell the difference between heat and cold. Patients may experience tingling, numbness and/or feelings of electrical shock. And, oftentimes, these symptoms manifest or worsen at night or during rest.<sup>2</sup>

Patients with SFN can also have damage to their autonomic nervous system, which can produce the following symptoms:<sup>2,4</sup>

- Urinary problems
- Erectile dysfunction
- Nausea
- Lightheadedness
- Blurred vision
- Skin discoloration
- Changes in sweating
- Dry mouth or eyes
- Rapid heartbeat

Many patients with SFN also complain of irregular sleep habits, generally due to the onset of symptoms at night.

Patients can develop SFN at any age. And, for some, the symptoms will spread from their feet and/or lower legs into their hands and lower arms.

However, the progression of the condition is the subject of deep disagreement among researchers. A 2016 study conducted at Johns Hopkins University showed nerve damage spread from the lower legs at a fairly rapid rate.<sup>5</sup> Yet, just a year later, a study at the University of Cologne in Germany determined the vast majority of cases of SFN will never worsen.<sup>6</sup> Clearly, both of these studies cannot be accurate, and other researchers suggest much work needs to be done to expand our understanding of the causes, progression and treatment of SFN.

The 2016 Johns Hopkins study did seem to answer another question, though, about whether SFN is length-dependent. The results strongly suggest that loss of small fiber nerves is consistent across the legs, meaning it is length-dependent. However, it can also be non-length-dependent or even

multifocal (present in more than one location in the leg). Other researchers commenting on the study theorize most cases of SFN first manifest in the feet and lower leg because there are fewer nerves in the feet than higher in the leg, so a consistent loss of nerve cells would be more noticeable there.<sup>7</sup>

What is known is, in rare cases, SFN can spread not only to the hands, but to the trunk and other areas of the body. In even rarer cases, it can be associated with a condition known as erythromelalgia, which increases blood flow to the affected areas (often the feet) without a corresponding increase in oxygenation. This causes the affected areas to feel hot or experience pain, and they may turn a deep red.<sup>8</sup>

## Causes of SFN

As stated above, SFN is caused by damage to the small myelinated afferent fibers or the unmyelinated C fibers that extend into the limbs (the nerve cells that carry information on all sensations, temperature and pain to the brain). That damage, however, can be caused by a variety of conditions, including:

- Diabetes and prediabetes
- HIV infection
- Lupus
- Celiac disease
- Sarcoidosis
- Guillain-Barré syndrome
- Scleroderma
- Hepatitis C
- Lyme disease<sup>9</sup>
- Sjögren's syndrome

In addition, certain drugs used in chemotherapy to treat cancer also may cause a form of SFN, a variant known as chemotherapy-induced peripheral neuropathy (CIPN).<sup>10</sup>

Roughly one-third of SFN cases are attributable to diabetes or prediabetes, making these the single largest cause. And, yet, even with all the above conditions known to lead to or contribute to SFN, there are many cases (between 20 percent and 50 percent) in which the underlying cause cannot be determined.<sup>11</sup> These cases are referred to as idiopathic SFN.

Researchers also think there may be some hereditary conditions related to SFN.<sup>2</sup> For instance, it is believed that, in some patients, there is an inherited gene malfunction behind SFN. Mutations in the SCN9A or SCN10A genes can affect the creation of sodium channels in nerve cells, impacting their ability to transmit electrical charges.<sup>3</sup> Such mutations may cause up to one-third of all cases of SFN. Also, amyloidosis with mutations in the transthyretin gene can trigger SFN.

## RESEARCH INTO THE CAUSES OF SFN AND MORE IMMEDIATE, PRACTICAL TREATMENT OPTIONS IS ONGOING.

### Diagnosing SFN

Because the initial symptoms of SFN are similar to other conditions, a firm diagnosis can take a bit of detective work. Indeed, it is often a process of elimination, removing other possible causes one by one.

In some cases, microscopic examination of the epidermal nerve fiber density in a skin biopsy from the affected area will show a lower-than-normal nerve cell count or the presence of weakened nerve cells.<sup>4</sup> However, one recent study found many patients with all the symptoms of SFN had no noticeable changes in their biopsy. Still, that same study did find nearly all patients with SFN had a loss of nerve density over time, meaning a definitive diagnosis may be possible over the course of several years.<sup>12</sup> (When both small- and large-fiber nerves show damage, this is grouped into a different family of conditions known as polyneuropathy.)<sup>13</sup>

In most instances, a physician will begin the diagnosis process by reviewing the patient's overall health history. Any of the conditions that cause SFN, along with its symptoms, can give the doctor and his or her patient a good starting point from which to work. If the patient has not previously been tested for any of the conditions that can cause SFN, the doctor may order a blood test to check for diabetes, hepatitis C and/or HIV, and depending on any other symptoms or factors in the patient's health

history, the doctor may explore any of the other known causes of SFN.<sup>13</sup>

In cases in which the patient is otherwise healthy with none of the possible associative conditions, the physician may order a skin biopsy. If that comes back negative, the doctor may order a quantitative sudomotor axon reflex test to measure the skin's ability to sweat, a possible indicator of SFN.<sup>2</sup> Other tests may measure heat or heat-pain thresholds.

What can be confusing to a patient and his or her family is the standard neurological examination given to flag most neuropathies will come back negative in an isolated SFN patient, meaning coordination, reflex and motor skills will appear normal. Light touch and vibration detection will also often be unaffected.<sup>2</sup> And, standard nerve conduction studies will be normal. But, generally, if a patient exhibits all the symptoms of SFN and no other cause can be ascertained, a physician should proceed as though the patient has SFN.<sup>2</sup>

### What Is Not SFN

Burning feet syndrome remains a popular description of the symptoms of SFN in some regions of the United States. More formally known as Grierson-Gopalan syndrome, this condition was previously associated with a burning sensation in the feet.<sup>14</sup> However, this is likely an outdated understanding of the symptoms, and researchers now believe this condition was in reality either SFN or, in specific instances, the result of extreme malnutrition (i.e., in prisoners of war or isolated small communities without access to adequate food sources).<sup>15</sup>

Charcot-Marie-Tooth disease, a hereditary nerve disorder, can also cause pain in the extremities, although it will often affect the hands and feet. It generally leads to atrophied muscles in the affected areas, differentiating its symptoms from those of SFN.<sup>16</sup>

### Treating SFN

If the cause of SFN can be identified, neurologists can be very effective in treating the disease and improving the nerve density of the small fibers. But, in cases of idiopathic SFN in which there is no known cause, doctors cannot treat the disease. So, instead, treatment focuses on relieving symptoms as much as possible.<sup>2</sup> For instance, controlling diabetes by managing one's diet, losing weight and exercising regularly can help reduce pain over time in patients with diabetes or prediabetes.<sup>11</sup>

For all cases, ceasing smoking and increasing exercise

can improve blood flow throughout the body, thus increasing the amount of oxygen available to damaged nerve cells.<sup>13</sup>

Medicines that have shown some efficacy in treating pain include anti-seizure medications and antidepressants.<sup>13</sup> However, researchers caution that the available literature on the efficacy of pain treatments with SFN is limited and offers little guidance.<sup>2</sup>

One recent study suggests one small subset of idiopathic patients — those with fibroblast growth factor receptor 3 antibodies — will respond well to intravenous immunoglobulin (IVIG), showing a marked decrease in both pain and numbness in the affected areas.<sup>17</sup> Other studies indicate IVIG can help treat SFN linked to celiac disease and Sjögren's syndrome.<sup>18</sup>

Patients with CIPN have no specific treatments available, so pain management is the recommended course of action.<sup>19</sup>

## Looking Ahead

Research into the causes of SFN and more immediate, practical treatment options is ongoing. However, somewhat surprisingly given the number of people who suffer from SFN, the number of these studies is startlingly small: Fewer than three dozen are currently listed on [ClinicalTrials.gov](https://clinicaltrials.gov).

Some of the more noteworthy areas of research include exploring how chemotherapy drugs cause SFN. CIPN, which may affect one-third of all cancer patients, involves a class of drugs known as taxanes. A new study discovered how taxanes lead to nerve damage and death, and suggested a pretreatment that might allow cancer patients to avoid CIPN in the future.<sup>20</sup>

Todd Levine, MD, director of Corinthian Reference Labs and a neuromuscular neurologist in Phoenix, Ariz., recently proposed dividing SFN patients into four subclassifications to allow physicians to better manage their condition:<sup>21</sup>

- Those with sodium channel dysfunction
- Those with classic neuropathic symptoms
- Those with widespread pain
- Those with autonomic symptoms

While his ideas may not have gained widespread traction, they are indicative of the desire researchers and physicians have for more information and options at their disposal as they work with their patients to address this puzzling condition.

Other studies listed on [ClinicalTrials.gov](https://clinicaltrials.gov) include one looking at whether the experimental sciatica pain reliever Vixotrigine may help in relieving symptoms of SFN, another examining whether IVIG might help even more SFN patients

than the subgroup already identified with autoantibodies, and another examining the effectiveness of the experimental pain medicine VX-150, among others.

## More Knowledge Is Needed

Without a fuller understanding of the causes of SFN, including deeper comprehension of the specific physiological changes behind this disease, researchers are unlikely to develop effective treatments, much less a cure, especially in light of the fundamental disagreements about the causes, methods of diagnosis and rates of progression existing among researchers and doctors.

For now, the process of diagnosing SFN from the exhibited symptoms and then working with a physician to craft an effective treatment regimen will remain a slow, frustrating process for patients and physicians alike. ■

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