Small Fiber Neuropathy

Small fiber neuropathy has a benign course but can affect quality of life; individualize treatment to control underlying causes and alleviate pain.

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Small fiber neuropathy (SFN) is common and can be associated with many medical conditions, including reports of an association with COVID-19. A Dutch study suggests a prevalence of 52.95 per 100,000 population that increases with age.[1] Standardized diagnostic criteria for SFN are not fully established and skin biopsy remains the diagnostic test considered most reliable. Autonomic testing is useful when autonomic symptoms are present. Screening for associated conditions is important for etiology-specific treatment to control symptoms and slow down disease progression. The significance of new association with autoantibodies, including antibodies to trisulfated heparin disaccharide (TS-HDS) and fibroblast growth factor 3 (FGFR3), needs further investigation. Treatment should be individualized to control underlying causes and alleviate pain. Intravenous immunoglobulin (IVIG) is ineffective for treatment of idiopathic painful SFN. Progression is slow, and most people affected by SFN do not develop large fiber involvement over time. Symptoms of SFN, including painful paresthesia and dizziness, and sedative side effects of pain medications can negatively affect quality of life. Early diagnosis and individualized treatment are important for controlling SFN symptoms and optimizing daily functions. Here, we review the recent advances in the diagnosis and management of SFN.

Clinical Presentation

SFN is a common type of peripheral neuropathy that predominantly affects small, myelinated $A\delta$ fibers and unmyelinated C fibers. SFN can affect somatic sensory fibers and autonomic C fibers, and most people with SFN have predominantly somatic sensory involvement that is often painful, especially when associated with amyloidosis, diabetes mellitus, HIV, sarcoidosis, sodium channelopathy, alcohol toxicity, and neurotoxic drug exposure. The pain is usually sharp and described as burning, pins and needles, stabbing,

lancinating, and electric shock like. Patients may also report squeeze sensation, coldness, or itchy skin. SFN sensory symptoms are usually worse at night. Examination may show allodynia, hyperalgesia, and reduced pinprick and thermal sensation in affected areas. Motor strength, proprioception, and deep tendon reflexes are usually preserved, because these are functions of large fibers. Impaired vibratory sensation at toes and reduced deep tendon reflexes at ankles, however, may be detected in people with SFN later in life, as this is not uncommon in this population without neuropathy.

SFN is mostly length-dependent (LD-SFN), displaying a stocking or stocking-glove pattern of involvement. Nonlength-dependent SFN (NLD-SFN) is relatively rare, accounting for 20% to 25% of cases of pure SFN.[2,3] Sensory symptoms and signs in NLD-SFN are usually patchy, asymmetrical, migrating or diffuse, and involve the trunk and face in addition to the limbs.[3] Compared with LD-SFN, NLD-SFN is more common in women, occurs earlier in life, and has a higher association with immune-mediated conditions (eg, Sjögren's syndrome, sarcoidosis, and paraneoplastic syndrome).[3]

Autonomic dysfunction is frequently seen in SFN associated with amyloidosis, sarcoidosis, Sjögren's syndrome, and diabetes mellitus. With autonomic involvement palpitations, orthostatic dizziness, skin discoloration, bowel constipation, urinary retention, sexual dysfunction, dry eyes, dry mouth, and sweating abnormalities may occur. Examination may detect dryness, coldness, and skin discoloration in the feet and distal legs (ie, red, white, and purple), as well as orthostatic tachycardia and hypotension.[4]

SFN often negatively impacts quality of life both physically and mentally because of neuropathic pain, numbness, and dizziness, which may affect gait and lead to falls especially later in life when falls are already more common.[5,6]

SFN Diagnosis

Evaluation of SFN consists of confirming the diagnosis (diagnostic evaluation) and identifying underlying etiologies (etiologic evaluation).

Diagnostic Evaluation

SFN diagnosis should combine symptoms, signs, and diagnostic test findings. Standardized diagnostic criteria for pure distal SFN are not yet established, although 2 sets of diagnostic criteria have been proposed to use for all forms of SFN regardless of etiology. These criteria sets are the Diabetic Neuropathy Study Group of the European Association for the Study of Diabetes (NEURODIAB) criteria, which are graded, and the Besta criteria (Table).[7,8]

Evaluation should include examination for SFN signs and exclude large fiber neuropathy signs, nerve conduction studies (NCS) to rule out large fiber polyneuropathy, and skin biopsy or quantitative sensory testing (QST). A recent reappraisal study showed a strict agreement of these 2 criteria sets for diagnosing pure SFN,[9] and showed sensory symptoms alone are not reliable, whereas sensory signs are reliable, for SFN. Skin biopsy with intraepidermal nerve fiber density (IENFD) quantification is more accurate than QST and so is considered the most reliable test to confirm the diagnosis.[7,10]

Skin biopsy is useful for diagnosing not only LD-SFN and NLD-SFN but also focal SFN (eg, diabetic truncal neuropathy, complex regional pain syndrome, and meralgia paresthetica).[10-14] The 3-mm skin punch biopsy is an in-office procedure that is easy to perform and minimally invasive. The sample for biopsy is routinely taken from the distal leg, 7 to 10 cm above lateral malleolus, and an additional sample may be taken from proximal thigh (7-10 cm below the greater trochanter) to evaluate the severity and pattern of SFN. If focal or unilateral small fiber impairment affects other sites, biopsy specimens may be taken from these sites along with contralateral unaffected sites for comparison. A diagnostic cutaneous nerve laboratory should be used for processing and interpretation.

SFN diagnosis is established when IENFD is reduced in comparison to age- and sex-adjusted worldwide normative values of IENFD at the distal leg.[15] A recent study suggests that IENFD at the distal leg might also be influenced by ethnic ancestry,[16] with normative values potentially needing further studies and adjustment for specific populations to improve the diagnostic sensitivity. Skin biopsy has been increasingly used for diagnosing SFN but is limited by a high cost. Medical insurance, however, usually approves the test after presence of SFN symptoms and absence of large fiber polyneuropathy (normal NCS) are documented.

There are significant limitations to QST,[17] including that it is not widely available and cannot differentiate whether impaired response to sensory stimuli is caused by a peripheral nerve disease or a central nervous system disorder, because a proper response requires an intact sensory pathway. QST also requires cooperation of patients, and a slow response may result from cognitive deficit, poor concentration, or other subjective issues. QST is not recommended as a stand-alone test for SFN.[18]

Autonomic testing is useful when autonomic symptoms are present. The quantitative sudomotor axon reflex test (QSART) evaluates postganglionic sympathetic unmyelinated sudomotor nerve function. QSART and skin biopsy combined can increase the diagnostic sensitivity for SFN,[19,20] but QSART is not widely available. Because QSART is very sensitive to antihistamines and antidepressants, which affect sweating, these medications should be discontinued 48 hours prior to the study. Cardiovascular autonomic testing is useful to evaluate those with cardiovascular autonomic symptoms (eg, orthostatic intolerance, palpitations, and tachycardia).

Etiology Evaluation

SFN can be associated with many medical conditions, including diabetes mellitus, immune-mediated disorders, vitamin B_{12} deficiency, thyroid dysfunction, monoclonal gammopathy, metabolic syndrome, celiac disease, HIV and hepatitis C infections, alcohol abuse, neurotoxic drug exposure, sodium channelopathy, amyloidosis, Fabry disease, autoinflammatory diseases, and paraneoplastic syndrome. Associated conditions can be identified in about half of the SFN cases,[3,7,21] with diabetes mellitus being the most common in the US.[3,22] Immune-mediated conditions (eg, sarcoidosis and Sjögren's syndrome) are more common with NLD-SFN than LD-SFN.[3] Thorough history taking can help identify or raise a suspicion for certain associated conditions (eg, metabolic syndrome, alcohol abuse, neurotoxic drug exposure, HIV and hepatitis C infections, rapid improvement of glycemic control in diabetic patients, and genetic causes). Neurotoxic drugs more likely to cause painful SFN include

TABLE. DIAGNOSTIC CRITERIA SETS FOR SMALL FIBER NEUROPATHY			
NEURODIAB		**Besta criteria**	
Possible	Length-dependent symptoms and/or signs of small fiber damage	At least 2 of:	Clinical signs of small fiber neuropathy
Probable	Above with normal sural nerve conduction study		Abnormal QST thermal thresholds at foot
Definitive	Both of above and reduced IENFD at ankle		Reduced IENFD at distal leg
	AND/OR abnormal QST thermal thresholds at foot	Without:	Large fiber neuropathy signs or
			abnormal NCS
Abbreviations: IENFD, intraepidermal nerve fiber density; NCS, nerve conduction studies; NEURODIAB, Diabetic Neuropathy Study Group of the European Association for the Study of Diabetes; QST, quantitative sensory testing.			

antibiotics (eg, metronidazole, nitrofurantoin, fluoroquino-lone, and linezolid), chemotherapeutic agents (eg, bortezo-mib, thalidomide, and vincristine), and tumor necrosis factor (TNF)-inhibitors. Rapid improvement of glycemic control in diabetic patients can induce acute painful neuropathy, which usually occurs when HbA1C level is reduced by 2 or more percentage points over a 3-month period. The pain is severe and refractory to treatment, but spontaneously improves after 12 to 24 months.[23]

Screening for SFN etiologies begins with a battery of blood tests that should be ordered for every person with SFN (Box), considering a recent study showed 26.7% of people with SFN known to have underlying associated conditions before evaluation had additional underlying conditions identified at diagnosis of SFN.[21] There is still no consensus on what blood tests should be done before diagnosing a patient with idiopathic SFN if all test results are negative.

Consider a lip biopsy if Sjögren's syndrome or seronegative sicca syndrome is suspected. Order a chest CT if sarcoidosis is suspected. If there is history of gastrointestinal symptoms or gluten intolerance, evaluate for celiac disease with tests for gliadin and tissue transglutaminase antibodies and small bowel biopsy. If amyloidosis is suspected, bone marrow or fat biopsy can be helpful (see *Neuromuscular Amyloidosis* in this issue). Skin biopsy may also show amyloid deposition. HIV and hepatitis C serology should be ordered if risk factors are present. Consider genetic testing if there is an early onset of SFN symptoms or a positive family history. Sodium channelopathy is not exceedingly rare in pure SFN, with a recent screening study detecting potential pathogenic variants of voltage-gated sodium channel genes, including *SCN9A*, *SCN10A*, and *SCN11A*,

in 132/1139 (11.6%) patients with pure SFN.[24] Genetic screening for Fabry disease in people with SFN is not cost-effective and should be done only if other clinical features are present.[25] Familial amyloidosis associated with *transthyretin* (*TTR*) gene mutations usually affects both large and small nerve fibers, and should be suspected if renal, cardiac, or hepatic abnormalities and bilateral carpal tunnel syndrome are present.[26]

New painful paresthesia and numbness within 2 months of SARS-CoV-2 infection has been observed,[27] and some individuals with these symptoms also develop intense SFN symptoms acutely and diffusely. In a study of 13 individuals with this presentation, NCS was normal in all, but skin biopsy showed reduced IENFD in 6 of 13, confirming SFN. Among the 6 persons with SFN confirmed by biopsy, 3 had preexisting but controlled associated conditions, whereas the others had no neuropathy etiologies identified. Neuropathy in some of these individuals was severe and did not respond well to symptomatic treatment. Another case series reported 27 patients with autonomic symptoms 0 to 122 days after acute SARS-CoV-2 infection. Autonomic testing showed postural orthostatic tachycardia syndrome in 22%, mild orthostatic intolerance in 11%, and sudomotor dysfunction in 36%.[28] A case report also described a person who developed burning dysesthesias 1 week after receiving a second dose of COVID-19 vaccine, and subsequent skin biopsy showed reduced IENFD. The patient responded to symptomatic treatment very well with resolution of the symptom.[29] These reports suggest that COVID-19 and COVID-19 vaccine reactions may represent new associated conditions for SFN. The neuropathy pathogenesis in these settings is not clear (see *Neuromuscular & Autonomic Complications of COVID-19* in this issue), but may be immune-mediated, similar to postviral or postvaccination Guillain-Barré yndrome. COVID-19 has also been reported to exacerbate SFN symptoms in a person with a history of SFN, and early immunotherapy is effective.[30]

Autoantibody association with SFN has been reported and studied, with a retrospective study of 155 people who had cryptogenic SFN and 77 who had amyotrophic lateral sclerosis (ALS) showing 48% of those with SFN had serum autoantibodies to TS-HDS and FGFR-3. AntiTS-HDS antibodies were more frequent in those with SFN compared with those with ALS. AntiTS-HDS and antiFGFR-3 were more common in female persons and those with NLD-SFN.[31] Another retrospective study of 322 people with pure SFN and dysautonomia detected antiTS-HDS in 28% and antiFGFR3 in 17%, but the presence of these antibodies did not correlate with neuropathy symptom scores, autonomic dysfunction, or IENFD reduction, making the significance of these antibodies questionable.[32] These findings suggest antiTS-HDS and antiFGFR3 are unlikely to be pathogenic, and it is uncertain whether presence of these antibodies is an epiphenomenon

BOX. BLOOD TESTS TO EVALUATE ETIOLOGIES OF SMALL FIBER NEUROPATHY

Complete blood count (CBC)

Comprehensive metabolic panel

Hemoglobin A1C

Oral glucose tolerance test (OGTT)

Thyroid stimulating hormone (TSH) and free thyroxine (T4)

Erythrocyte sedimentation rate (ESR)

Antinuclear antibodies (ANA)

SSA and SSB antibodies

Free light-chain IgG

Vitamin B_{12} and folate levels

HIV and hepatitis C tests

Immunofixation

Others based on clinical history

indicating immune-mediated SFN. Detection and quantification of antiFGFR-3 by enzyme-linked immunosorbent assay (ELISA) has been shown inconsistent, which may also confound these results.[33] Future studies are needed to clarify the significance of these antibodies, with improved and standardized antibody detection and quantification methods, so treating physicians can make decisions whether to order the antibody test and know what to do with the results.

SFN Management

Management of SFN consists of identifying and treating underlying causes, alleviating neuropathic pain, and optimizing function. Etiology-specific treatment is the key to improving symptoms and prevention of SFN progression. Lifestyle modifications helped reduce pain and improve IENFD in patients with prediabetic SFN.[34] Treatment of sarcoidosis, autoimmune diseases, and celiac disease improved SFN symptoms caused by these conditions. A case series of SFN-associated Sjögren syndrome showed persistent improvement after IVIG treatment.[35] IVIG also had therapeutic effects on SFN associated with sarcoidosis in a large cohort study.[19] In contrast, a recent double-blind, randomized, placebo-controlled trial of IVIG for painful idiopathic SFN had no significant effect on pain.[36] It is unknown whether IVIG improved numbness or IENFD in idiopathic SFN, but these findings suggest that IVIG should be used to treat SFN associated with Sjögren or sarcoidosis and not idiopathic painful SFN. Controlled trials of IVIG for SFN associated with sarcoidosis or Sjögren's syndrome are needed to confirm efficacy and facilitate insurance coverage of IVIG. Such trials, however, may be difficult to do because of the small population available to participate in clinical trials. Future controlled studies will be needed to address whether idiopathic SFN associated with autoantibodies responds to IVIg. Because we may see more people with painful SFN after COVID-19 and this may be immune-mediated, it would be helpful to study whether IVIG can expedite recovery, especially for those with severe neuropathy and poor response to symptomatic treatment.

Management of neuropathic pain, which is common in SFN and often negatively impacts quality of life, is crucial but can be challenging. Many pain medications have sedative side effects that can limit use of a therapeutic dose. Pain medications should be started at a low dose that is increased slowly, optimized before adding another pain medication, and tapered down whenever possible to achieve the lowest effective maintenance dose. Treatment should be individualized based on a person's comorbidities, drug tolerability, and potential drug-drug interactions.

Recommended first-line medications include tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), antiseizure medication pregabalin and gabapentin, and topical anesthetics.[37,38] Tramadol, a semisynthetic opioid analgesic, is a second-line choice. Pain medications can be used as monotherapy or in combination to increase efficacy, such as gabapentin with nortriptyline and pregabalin or gabapentin with tramadol. If pain is localized, topical anesthetics, such as lidocaine or capsaicin cream or patches, should be tried first to avoid systemic side effects and drug-drug interactions. The benefit of topical anesthetics, however, is often limited. Chronic opioid use for noncancer-related neuropathy is not recommended because of high rates of addiction and overdose and worsening of functional outcomes.[39] Nonpharmacologic management includes transcutaneous electrical nerve stimulation (TENS), heat, ice, and massage of painful areas.

The importance of safety cannot be overemphasized, considering that pain, numbness, dizziness, and drowsiness can lead to physical injuries especially with increasing age. Pain medications should be adjusted to minimize the sedative side effect. Wearing padded socks and supportive shoes can help foot protection and promote ulcer healing. Individuals should test their bath water with a body part without numbness before putting their feet into the water, be careful with cooking, and avoid sleeping with their feet near a fireplace.[40] Refer patients to physical therapy for gait training if a gait abnormality is reported or detected.

Patient counseling is also important. Most patients with SFN experience a slow progressive course, with only a small percentage developing large fiber involvement over time—11.9% in one cohort[22] and 13% in another.[7] Most individuals, however, do require chronic pain management and may be distressed by pain and worry about developing weakness or losing ambulation because of the neuropathy. Fear can aggravate pain and depression, making treatment difficult. It is thus important to reassure patients about the benign course of SFN. It is also important to explain that pain medications are used to control pain, burning, or tingling, but not numbness. There is no medication yet to promote nerve fiber regeneration to reduce numbness; however, numbness may improve once etiologies are controlled, especially if SFN is relatively mild. ∎

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