

Small Fiber Neuropathy in Sjogren's Syndrome: A Review

A lack of uniform diagnostic criteria for small fiber neuropathy and Sjogren's syndrome presents several challenges for treatment.

By Anna Chang, BS; Kevin Lazo, DO; Michael Malekan, DO; Steven Mandel, MD

Peripheral neuropathy is one of many extra-glandular manifestations in primary Sjogren's Syndrome (pSS), an autoimmune disease that affects approximately 0.6 percent to one percent of adults in the United States.¹ A review of the literature from 1990 to 2010 suggests that the prevalence of peripheral neuropathy seen in pSS ranges from 1.8 percent to 64 percent.² More recently, a 2013 study reported a prevalence of 20 percent (but ranging from five percent to 60 percent).³ This range may be attributed to highly variable presentation of symptoms in pSS including neuropathic pain.¹ The types of peripheral neuropathy described among patients with pSS are numerous, and have included ganglionopathic sensory neuropathy, axonal sensory or sensorimotor polyneuropathy, multiple mononeuropathy, autonomic neuropathy, small-fiber neuropathy, cranial neuropathy, and inflammatory myopathy.¹ Although peripheral neuropathy in pSS has not have been unequivocally identified or classified across studies, up to 40 percent of all patients with the disease have described "burning," "tearing," or "raking" sensations consistent with neuropathic pain.¹

Identification and Diagnosis

Small fiber neuropathy (SFN) has been identified in some cohorts of pSS patients as the most common peripheral neuropathy,^{1,4} producing symptoms by affecting small myelinated A-delta fibers and unmyelinated nociceptive C fibers. Both fibers have somatic and autonomic components that affect pain and temperature sensation. Autonomic dysfunction can manifest as dryness of the eye and mouth, dizziness, constipation, incontinence, skin discoloration, or anhidrosis.⁵ Symptoms include pain of burning quality and impaired temperature and pinprick

sensation with preserved vibratory sense and proprioception.¹ The SFN seen in pSS may not always present in the typical length-dependent fashion as it does in diabetes mellitus (a glove and stocking distribution defined by symmetric involvement of distal limbs associated with burning pain). Instead, some patients with pSS associated SFN have been described to experience lancinating and burning pain in the proximal areas of the body such as the torso and face.¹ One study described that 60 percent of 20 patients with pSS complaining of non-length dependent symptoms of neuropathic pain had corresponding low density skin biopsies,¹ which may be a result of toxic insult to small dorsal root ganglionic neurons.⁴

The onset of neuropathic symptoms on the timeline of pSS diagnosis is unclear. Some studies have reported presence of neuropathic symptoms preceding the development of sicca symptoms and often therefore prior to an official diagnosis of pSS.⁶ One possible explanation for this delay in diagnosis is that sicca symptoms such as xerostomia or xerophthalmia are emphasized over neuropathic symptoms in patients with whom the differential includes pSS.⁶ In fact, patients presenting with neuropathy with negative serology for anti-SSA/SSB will often be diagnosed with pSS only after later development of sicca symptoms.⁶ Some studies have reported a low prevalence of anti-SSA/SSB antibodies in their cohort of patients with pSS with associated neuropathy.⁶ Additionally, pSS patients with SFN have been reported to have an older age, lower titers of ANA, anti-SSA, anti-SSB, rheumatoid factor, and low serum C4 levels than compared to pSS patients without SFN.³ Similarly, in a cohort of 108 pSS patients, the prevalence and severity of neuropathic pain was significantly greater in seronegative patients (patients without anti-SSA

and anti-SSB).⁷ However, the seronegativity of pSS patients with neuropathy is not unanimous. In another study, a subset of patients in a cohort of 1010 patients with pSS patients had positive antibodies for SSA/SSB as well as the highest prevalence of peripheral neuropathy including SFN.⁸ These findings indicate the importance of considering pSS in patients presenting with symptoms of neuropathy, especially non-length dependent neuropathic pain, irrespective of seropositivity for SSA/SSB.

SFN is reported to be the most common type of peripheral neuropathy¹ in some samples of pSS patients, but not all. One study reported SFN as an uncommon finding in a cohort of 62 pSS patients. With the hopes of identifying only true autoimmune related neuropathy specific to pSS, investigators utilized the new international criteria for pSS from 2002. Their parameters for diagnosing SFN included a low intraepidermal nerve fiber density (<3.4 fibers per millimeter) in the leg and proximal thigh, and the absence of other causes for neuropathy (normal blood glucose, cobalamin, folic acid, and thyroid function tests). Their cohort identified a number of symptomatic patients who, although not meeting criteria for SFN, did have measurable decrease in density of nerve fibers when compared to those of healthy patients.⁹ These findings suggest that the normal fiber densities identified on biopsy may be confounded by method of biopsy collection or analysis rather than actual infrequency of SFN.⁹ Other studies have described patients with pSS and neuropathic pain in a non-length-dependent distribution to have normal, or even increased intraepidermal nerve fiber density (IENFD). These findings may overlap with sensory ganglionopathy, a pathology which may be more easily detected with alternative modalities such as high resolution magnetic resonance neurography.¹⁰

The “non-length-dependent” nature of SFN in patients with pSS may be due to lymphocytic infiltration resulting in damage to the dorsal root ganglion (DRG), the most proximal origin of the peripheral nervous system.¹⁰ Other mechanisms affecting the DRG may be in play, including hyperexcitability of the DRG, enhanced chemosensitivity of the DRG to proprioceptive cytokines or to the neurotrophin nerve growth factor.¹⁰ Neurotrophic growth factors may be upregulated by inflammatory processes in pSS, possibly contributing to heightened nerve growth and supranormal IENFD on skin biopsies in some patients, instead of the low nerve densities that usually classify SFN.¹⁰ Thus, peripheral neuropathy in pSS may not be characterized only by damage, degeneration, death, or transection of axons by neurotoxic causes, but also by increased chemosensitivity or hyperexcitability to cytokines or growth factors. In the setting of normal or supranormal skin biopsies, the noninvasive Magnetic

The cardinal finding for SFN is a density of intraepidermal nerve fibers on skin biopsy less than the fifth percentile, which is caused by axonal or small dorsal root ganglionic neuronal infiltration or degeneration by pathogenic mechanisms that are still unclear.

Resonance Neurography DRG (MRN DRG) protocol can characterize abnormal and normal DRG at each vertebral level in patients with pSS experiencing neuropathic pain symptoms. Birnbaum et al. classified abnormal findings as one or more of the following: an increase in the size of DRG, increase in the T2 signal of DRG, and increase in the enhancement of DRG in comparison to the contralateral, superior, or inferior spinal levels.¹⁰ In the patient group, those with abnormal MRN DRG study results correlated to increased IENFD in their skin biopsies.

The diagnosis of SFN does not utilize nerve conduction studies, due to the small diameter of affected fibers. The traditional electroneuromyographic (ENMG) test for peripheral neuropathies is sensitive in individuals with involvement of large nerves with diameters ranging from greater than 5-7 μ m. Small nerve fibers with a diameter less than 5-7 μ m are not detected by ENMG. Instead, histologic or neurophysiologic tests are helpful alternatives for diagnosis in SFN. The Intraepidermal Nerve Fiber Density (IENFD) is considered the most objective finding, measured by a biopsy of the epidermis which is predominately innervated by small fibers. The sample is stained with antineuropeptide (peptide gene product 9.5) antibodies; innervation densities that are below the fifth percentile are considered diagnostic for SFPN.¹⁰ Pain stimulation by laser produces Laser Evoked Potentials (LEP) while Quantitative Sensory Testing (QST) can measure response to warm and cold thermal stimuli. A review of 40 cases showed all patients with Sjogren’s related SFN had either abnormal LEP or QST,³ with altered LEP’s in 97.5 percent and abnormal QST thresholds in 67.5 percent of those studied. Sympathetic Skin Reflexes (SSR) recording to autonomic nervous testing is useful as well, with abnormal findings in 40 percent of the 40 studied patients.³ SSR, QST, and LEP may pose challenges to interpretation since results depend on patient cooperation in uncomfortable testing environments.⁴

In summary, common criteria of SFN are painful sensory symptoms, normal nerve conduction studies, low density of intraepidermal nerve fibers in a skin biopsy, and abnormal neurophysiologic test for small nerve fibers.^{3,11} Patients with atypical (normal or high IENFD) biopsy results, described above in patients with non-length dependent pattern of SFN, may require further testing by MRN DRG to identify pathology affecting the DRG.

Treatment Options

A number of symptomatic therapeutic options are available to manage symptoms associated with SFN. Neuropathic and nociceptive pain often occur together and may be addressed with the same pharmacologic agent(s). Anti-epileptic drugs (AED) such as gabapentin and pregabalin may be administered in a slow titration spanning over three to four months to avoid the common adverse effect of somnolence which is of particular concern in pSS patients where underlying fatigue is a common symptom.¹ Tricyclic antidepressants (TCA) should be avoided due to their anticholinergic side effects that can exacerbate sicca symptoms.¹¹ Duloxetine and venlafaxine may be of particular benefit in the setting of depression but these agents have not been formally studied with regard to pSS related neuropathic pain. The use of the tumor necrosis factor (TNF-alpha) inhibitor adalimumab was effective in SFN for other inflammatory diseases such as sarcoidosis, but has not yet been shown to be effective in pSS. Future studies might benefit from stratifying patients with pSS to identify a whether patients with pSS specifically benefit from treatment with TNF blockers.

As lymphocytic infiltration with T-cells in the DRG is a proposed pathogenic mechanism of non-length-dependent neuropathic pain in pSS patients, one would expect that immunologic therapeutic modalities may provide effective treatment.^{1,12} Currently, therapy with corticosteroids, plasmapheresis, and immunosuppressive drugs such as cyclophosphamide have not been as efficacious in treating pSS related neuropathies as they are in treating non-neuropathic pSS manifestations like sicca and pneumonitis.^{10,12,13} IVIG is one option that warrants further study as a number of case reports have described response to therapy. Formal evaluation of the benefits of IVIG is complicated by its cost as well as its need to be administered as an infusion.¹² IVIG is an expensive treatment prepared by the donation of thousands of healthy plasma donors and is recognized for those with Guillain Barre Syndrome and chronic inflammatory demyelinating polyneuropathy.¹² In a retrospective study evaluating the efficacy of IVIG therapy in 19 patients with peripheral neuropathy, those with non-ataxic sensory neuropathy with a mean duration of treatment for 15.2 months showed clinical improvement as measured by improved scores on the

The detection of SFN presents a number of challenges, one of which is a lack of uniform diagnostic criteria for both pSS and SFN across studies.

Modified Rankin Scale for Neurologic Disability.¹² One study compared the clinical response to IVIG therapy in six patients who experienced a mean decrease in the Visual Analog Scale score from 8.2 to 4.0 compared to four patients who only received symptomatic therapy due to denial of insurance reimbursement for IVIG therapy that experienced a mean decrease of 6.8-5.5. Two patients of the six had follow-up MRN DRG studies performed, which showed interval improvement after IVIG infusion.¹⁰

Future Paths

The detection of SFN presents a number of challenges, one of which is a lack of uniform diagnostic criteria for both pSS and SFN across studies. It is unclear whether the onset of peripheral neuropathy precedes or is a later development in pSS. There have been equivocal findings as to the relation of anti-SSA/SSB serology and the presence of neuropathy, and the clinical presentation of SFN often varies. For example, SFN in pSS may present in a length dependent or non-length dependent manner, and will escape detection in traditional nerve conduction stimulation tests, requiring skin biopsies and neurophysiologic tests specific to small fibers (LEP, SSR, QST) for diagnosis. The cardinal finding for SFN is a density of intraepidermal nerve fibers on skin biopsy less than the fifth percentile, which is caused by axonal or small dorsal root ganglionic neuronal infiltration or degeneration by pathogenic mechanisms that are still unclear.

Emerging research suggests a role for pro-inflammatory cytokines IL-2 and TGF-beta 1 in circulating blood, with increased IL-6 and IL-8 in skin biopsy present in those with SFN, though not SFN specific to pSS.¹³ The clinical presen-

PRACTICAL POINTER

When treating SFN in primary Sjogren's Syndrome, AEDs such as gabapentin and pregabalin may be administered in a slow titration spanning over three to four months to avoid somnolence, which is of particular concern in patients where underlying fatigue is a common symptom.

tation of impaired temperature and pinprick sensation, with burning, lancinating pain, and preserved vibratory and proprioceptive sense may in some cases present with normal or above-normal IENFD that do not fit with SFN. This may prompt further investigation into the dorsal root ganglion for pSS patients to detect sensory ganglionopathy, a different peripheral neuropathy which may in its early stages present without clinical manifestations of ataxia and mimic SFN. Several studies have shown the efficacy of IVIG therapy in peripheral neuropathies associated with pSS, including SFN with superiority over symptomatic pharmacologic agents such as AED's or TCA's. However, other agents such as TNF-alpha inhibitors (adalimumab) have not been formally studied in SFN specific to pSS. ■

Anna Chang, BS is a third year medical student at New York Medical College in Valhalla.

Kevin G. Lazo, DO is in the Department of Medicine at Northwell Health Lenox Hill Hospital in New York.

Michael Malekan, DO is in the Department of Medicine at Northwell Health Lenox Hill Hospital in New York.

Steven Mandel MD, PC is Clinical Professor of Neurology at Lenox Hill Hospital, Hofstra Northwell School of Medicine.

1. Birnbaum J. Peripheral nervous system manifestations of Sjogren syndrome: clinical patterns, diagnostic paradigms, etiopathologies, and therapeutic strategies. *The Neurologist*. 2010; 16(5): 287-297. <https://www.ncbi.nlm.nih.gov/proxy.nymc.edu/pubmed/20827117>
2. Pavlakis PP, Kosmidis AM, Mamali I et al. Peripheral neuropathies in Sjogren's Syndrome: A critical update on clinical features and pathogenic mechanisms. *Journal of Autoimmunity*. 2012; 39(1):27-33. <http://www.sciencedirect.com/proxy.nymc.edu/science/article/pii/S0896841112000042>.
3. Sene D, Cacoub P, Authier FJ, et al. Sjogren Syndrome-associated small fiber neuropathy: characterization from a prospective series of forty cases. *Medicine*. 2013; 92(5): 10-12. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4553978/#R17>
4. Pavlakis P, Haralampos A, Kosmidis E, et al. Peripheral neuropathies in Sjogren's syndrome: a new reappraisal. *HAL archives*. 2011 Jun; hal-00600751. <https://hal.archives-ouvertes.fr/hal-00600751>.
5. Tavee J, Zhou L. Small Fiber Neuropathy: a burning problem. *Cleveland Clinic Journal of Medicine*. 2009 May. 76(5):297-305. <http://www.ccm.org/past-issues/past-issue-single-view/small-fiber-neuropathy-a-burning-problem/2e6a5924d840eef79f213dd53bb68ccf.html>
6. Mori K, Lijima M, Koike H et al. The wide spectrum of clinical manifestations in Sjogren's syndrome-associated neuropathy. *Brain*. 2005 Nov; 128:2518-34. <https://www.ncbi.nlm.nih.gov/pubmed/16049042>
7. Segal B, Pogatchnik B, Henn L, et al. Pain and severity and neuropathic pain symptoms in primary Sjogren's syndrome: A comparison study of seropositive and seronegative Sjogren's syndrome. *Arthritis Care Res (Hoboken)*. 2013 Aug; 65(8): 1291-1298.
8. Ramos-Casals M, Solans R, Rosas J. Primary Sjogren syndrome in Spain: clinical and immunologic expression in 1010 patients. *Medicine*. 2008 Jul; 87(4):210-9. <https://www.ncbi.nlm.nih.gov/pubmed/18626304>.
9. Goransson L, Herigstad A, Tjensvoll A et al. Peripheral Neuropathy in Primary Sjogren Syndrome, A Population Based Study. *Arch Neurol*. 2006;63(11):1612-1615. doi:10.1001/archneur.63.11.1612
10. Birnbaum J, Duncan T, Owoyemi et al. Use of a Novel High-Resolution Magnetic Resonance Neurography Protocol to Detect Abnormal Dorsal Root Ganglia in Sjogren Patients With Neuropathic Pain: Case Series of 10 Patients and Review of the Literature. *Medicine*. 2014; 93(3): 121-134. <http://ovidsp.tx.ovid.com/proxy.nymc.edu/sp-3.23.1b/ovidweb.cgi?T=JS&PAGE=fulltext&D=ovft&AN=00005792-201405000-00001&NEWS=N&CSC=Y&CHANNEL=PubMed>.
11. Oaklander AL. Immunotherapy prospects for painful small fiber sensory neuropathies and gangliopathies. *Neurotherapeutics*. 2016; 13:108-117. https://www.ncbi.nlm.nih.gov/proxy.nymc.edu/pmc/articles/PMC4720682/pdf/13311_2015_Article_395.pdf.
12. Rist S, Sellam J, Hachulla E et al. Experience of intravenous immunoglobulin therapy in neuropathy associated with primary Sjogren's syndrome: A national multicentric retrospective study. *Arthritis Care and Research*. 2011 Aug; 63(9): 1339-1334. <http://onlinelibrary.wiley.com/proxy.nymc.edu/doi/10.1002/acr.20495/full>.
13. Uceyler N, Kafke W, Riediger N. Elevated Proinflammatory cytokine expression in affected skin in small fiber neuropathy. *Neurology*. 2010 Jun; 74(22): 1806-1813. <https://www.ncbi.nlm.nih.gov/proxy.nymc.edu/pubmed/?term=Elevated+proinflammatory+cytokine+expression+in+affected+skin+in+small+fiber+neuropathy>.