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Small Fiber Neuropathy is Present in Nonpainful Conditions

Editor – Small fiber neuropathy (SFN) is traditionally classified as a disorder of neuropathic pain involving thinly myelinated or unmyelinated fibers. However, a number of SFN phenotypes are emerging, which are not associated with pain. These three other conditions, which are not characterized by chronic pain, but that are frequently associated with reduced intra-epidermal nerve fiber density (IENFD) and/or sweat glad density consistent with SFN are (1) Postural orthostatic tachycardia syndrome (POTS) and dysautonomia;[1] (2) Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS); and (3) Mast cell activation syndrome (MCAS) (Figure 1). These conditions, all of which are associated with SFN, may be linked via neuroimmune etiology involving neuroinflammation and immune dysregulation.[2]

Additional conditions that may be associated with minimal neuropathic pain or painless SFN are Long COVID and other post-acute infectious syndromes, hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorders, irritable bowel syndrome and other gastrointestinal disorders, genital arousal disorders and sexual dysfunction, skin conditions involving itching and urticaria, Sjogren's disease, celiac disease and other autoimmune disorders.[3-8] Neurodegenerative disorders, such as Parkinson's disease, multiple system atrophy and Alzheimer's disease, can also be associated with findings of SFN in the absence of pain[9,10] (Figure 1). Importantly, large studies with skin biopsy or quantitative sudomotor axon reflex test (QSART)-confirmed SFN in patients with these diverse conditions are needed to confirm the presence of SFN in broad patient populations rather than small subsets of patients with these disorders.

Recently, a study by Murin et al demonstrated another important and not uncommon phenotype of SFN – one that has little to no neuropathic pain, but significant fatigue and autonomic symptoms.[11] In fact, only 20% of the cohort in that study consisting of 203 patients had classical neuropathic pain; 80% had less classical presentations, but all patients had a skin biopsy with epidermal nerve fiber density below the 5th percentile for sex and age and a normal EMG with nerve conduction studies.[12] Importantly, most patients experienced fatigue and other autonomic symptoms rather than neuropathic pain suggesting that evaluation for dysautonomia in patients with SFN and evaluation for SFN in patients with dysautonomia are warranted to optimize diagnostic accuracy and improve treatment outcomes.[11] Therefore, it should emphasized that SFN can be present in the absence of not only neuropathic pain, but chronic pain in general. Patients with POTS/dysautonomia, ME/CFS and MCAS should be routinely screened for SFN with a skin biopsy, quantitative sudomotor

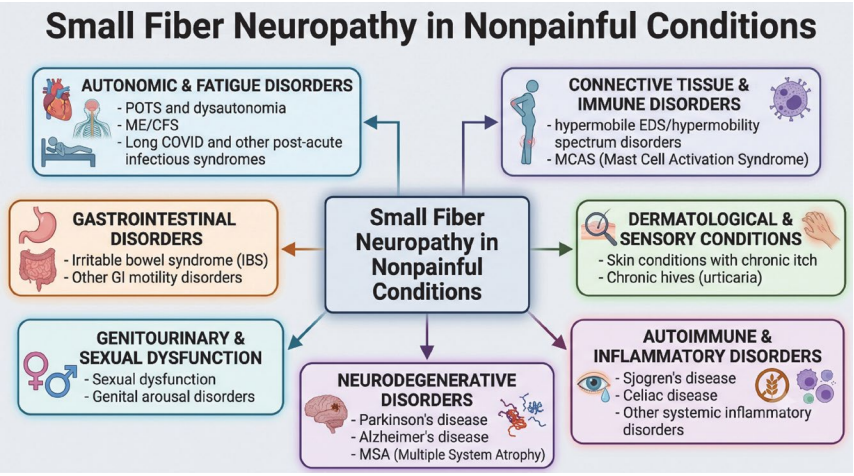

Figure 1. Small fiber neuropathy in nonpainful conditions.
Disclaimer: Figure 1 was generated using Gemini AI.

axon reflex test or corneal confocal microscopy, even in the absence of pain.

A second important point is that a significant subset of patients with SFN, whether with or without chronic pain, may have autoimmune etiology even when standard autoimmune and inflammatory markers available to clinicians return unremarkable. Additional testing that may show elevated autoantibodies include anti-TS HDS, anti-FGFR3, anti-Plexin D1, anti-Sulfatide, anti-voltage gated potassium channel antibodies and others; unfortunately, these blood tests are only available at specialized reference laboratories significantly limiting their use and accessibility in clinical medicine. Especially when accompanied by significant autonomic symptoms, these patients with autonomic and small fiber neuropathy may have substantial improvement with intravenous immunoglobulin (IVIG).[13,14] In a recent study by Novak et al,[13] IENFD on a follow-up skin biopsy demonstrated greater improvement in patients treated with IVIG than in patients treated with symptomatic management (P=0.017) as part of the standard of care providing further evidence to numerous case reports and case series documenting the benefits of long-term IVIG use in patients with autonomic disorders and autoimmune SFN.[13,14]

Lastly, besides immunoglobulin therapy, which is often inaccessible to many patients who need it, other therapies, both existing and emerging, may need to be considered in patients with SFN, particularly in those who do not tolerate first- and second-line therapies, or who are still symptomatic despite these therapies.[15] These may include low-dose naltrexone, cannabis in oral and topical forms, clonidine, doxepin, benzodiazepines (to be used cautiously due to the risk of dependance), histamine receptor blockers, ketogenic and gluten-free diets, non-invasive vagus nerve stimulation (n-VNS) and compounded creams that include ketamine, diclofenac, gabapentin, amitriptyline, baclofen and other ingredients (Table 1). Although most of these treatments have not been validated in randomized placebo-controlled trials, many are low-risk, cost-effective and available for treatment of other conditions. If comorbid dysautonomia is present, pharmacologic and non-pharmacologic therapies, including increased fluid and sodium chloride intake, compression garments, beta blockers, midodrine, ivabradine, fludrocortisone and

Table 1. Treatment of small fiber neuropathy: A comprehensive approach.

First Line	Second Line	Other: Pharmacologic	Other: Non-pharmacologic
Amitriptyline	Duloxetine	**Immunotherapies:**	TENS
Nortriptyline	Venlafaxine	IVIG, SCIG, PLEX	n-VNS
Pregabalin	Tramadol	Corticosteroids	Acupuncture
Gabapentin	Opioids, as needed		Spinal cord stimulator
Topiramate		**Repurposed Neuropathic**	Compounded creams
Lidocaine patches or		**Agents**	Vitamin D3
cream		Low-dose naltrexone	Vitamin B complex
Capsaicin cream		Cannabis oral or topical	Alpha lipoic acid
		Clonidine patch or tablets	Curcumin
		Doxepin	Ketogenic diet
		Clonazepam	Gluten-free diet
		Hydroxyzine	
		Low-dose ketamine	
		Memantine	
		Mexiletine	
		Lacosamide	
		Tapentadol	
		Suzetrigine	

Abbreviations: IVIG, intravenous immunoglobulin; SCIG, subcutaneous immunoglobulin; PLEX, plasmapheresis; TENS, transcutaneous electrical nerve stimulation; n-VNS, non-invasive vagus nerve stimulation.

pyridostigmine, aimed at reducing the autonomic symptom burden should be utilized.[1]

Besides expanding therapeutic landscape with novel and repurposed therapies, future direction in SFN should include accessibility to and inclusion of corneal confocal microscopy as part of the diagnostic criteria, more comprehensive autoantibody panels, proinflammatory cytokines, mitochondrial dysfunction testing and tailored genetic panels that are covered by commercial insurance.

Keywords: Small fiber neuropathy; Dysautonomia; Postural orthostatic tachycardia syndrome; Nonpainful conditions; Treatment

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