

## A Proposed Taxonomy of Isolated Small Fiber Neuropathy

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### Introduction

The term small fiber neuropathy (SFN) is used to define a group of heterogeneous disorders that affect peripheral nerves and cause structural injury of myelinated A $\delta$ -fibers and unmyelinated C-fibers.<sup>1</sup> In the somatosensory nervous system, these fibers control information about temperature, pain, and itch, and in the autonomic nervous system, they mediate thermoregulatory, cardiovascular, and gastrointestinal autonomic functions.<sup>2</sup> Patients can have a peripheral neuropathy with predominant small fiber symptoms such as pain, burning, and numbness, but on exam or electrophysiology one finds evidence for damage to medium and large fibers such as decreased reflexes or abnormal nerve conduction studies. These patients are considered to have mixed fiber neuropathies.<sup>3,4</sup> There is a second population of patients who have small fiber neuropathic symptoms but no evidence for mixed fiber involvement on exam or electrophysiology. This second group of patients is diagnosed objectively by demonstrating reduced intraepidermal nerve fiber density on skin biopsy, and these patients should be considered to have isolated small fiber neuropathy (ISFN).<sup>1,5</sup>

The reported prevalence of peripheral neuropathies in the United States is 2% in the general population, but in people older than 65 years the prevalence rises to about 20%. The exact frequency of SFN is unknown but has been estimated at 12 cases per 100,000.<sup>6</sup>

Although advances in the diagnosis of SFN have evolved over the past two decades, SFN has a poorly under-

stood pathophysiology, and despite extensive evaluations approximately 50% of cases are idiopathic.<sup>5,8</sup> In a recently published series of 921 patients with biopsy-proven ISFN, immunological conditions were found in 19%, sodium channel variants were found in 16.7%, diabetes in 7.7%, Vitamin B12 deficiency in 4.7%, alcohol abuse in 3%, exposure to chemotherapy in 2.2%, and monoclonal gammopathy of unknown significance in 2.2%.<sup>9</sup> Other potential causes include impaired glucose tolerance, hepatitis C virus, human immunodeficiency virus (HIV), paraneoplastic syndromes, and both acquired and inherited forms of amyloid neuropathies. Familial amyloid neuropathies, familial amyloid cardiomyopathy, and leptomeningeal amyloidosis are associated with mutation of transthyretin (TTR), a transport protein that carries holo-retinol binding protein and thyroxine. Mutations of the TTR gene have been associated with the development of SFN and autonomic neuropathy.<sup>7,10</sup>

### Diagnosis

Neuropathic pain and symptoms dominate the clinical presentation of ISFN. Symptom severity and their progression vary between patients, but typically the sensory symptoms present distally, manifesting as foot or leg pain and spread proximally to the upper limbs and trunk. Pain can be extremely severe and debilitating and is often described as burning or shooting. Other symptoms include hyperesthesia, paresthesia, numbness, restless leg syndrome, and dry eyes and mouth.

Patients with ISFN might also present with erythromelalgia and paroxysmal extreme pain disorder, which indicate small fiber sodium channel dysfunction (SFSCD).<sup>7,11</sup> The hallmark feature of SFSCD is normal intraepidermal nerve-fiber density (IENFD) on biopsy associated with nociceptive dysfunction. Patients with small fiber-mediated painful neuropathy (SFMPN) often have symptoms such as burning, tingling, stabbing, and numbness with normal electromyography and nerve conduction velocity.<sup>12-14</sup> Genetic testing for disorders of the NaV 1.7, 1.8, and 1.9 can help identify these patients.

Some patients develop small fiber-mediated autonomic dysfunction (SFMAD) that is characterized by cardiovascular, gastrointestinal, urinary, pupillary, and metabolic disturbances and sweating. Cardiac symptoms include syncope, palpitations, symptomatic postural hypotension, and postural orthostatic tachycardia syndrome.

Another clinical phenotype is small fiber-mediated widespread pain (SFMWP). Patients from this group often experience muscle cramps or muscle pain and have reduced

IENFD. These patients may represent a significant percentage of patients with fibromyalgia and in some reports ISFN damage can be seen in 40-60% of these patients.<sup>15,16</sup>

Patients with isolated SFN (without large nerve fibers involvement) present with intact deep tendon reflexes, normal strength, normal sensory examinations, and normal motor coordination. Normal nerve conduction studies also suggest isolated SFN.

Diagnosis of SFN can be challenging and is often based on the combination of clinical signs, physical examination, and quantification of IENFD. Ancillary testing includes functional test measures such as a quantitative sensory testing (QST) and quantitative sudomotor axon reflex testing (QSART) that require special equipment and are only available in specialized centers. Nerve conduction studies can be done to establish large nerve fiber involvement but have limited diagnostic efficacy for ISFN.

### Using Pathophysiology to Delineate the Underlying Pathology

The diagnosis of ISFN can be confirmed on a skin biopsy assessed for IENFD. The procedure is fast and straightforward, and it can be easily performed in the office or clinic. When performing skin biopsy for the measurement of IENFD, it is best to biopsy three separate sites, especially in cases of widespread bilateral symptoms. The preferred sites are the calf, the distal thigh, and the proximal thigh. Using these three sites the reported sensitivity and specificity of IENFD are 80% and 90% respectively.<sup>17</sup>

Normal IENFD varies by region of the body, and reference values ideally should be adjusted for sex, age, and site. Decreased IENFD has been correlated with clinical symptoms and abnormalities on sensory testing, for example, pain and length-dependent symptoms predict abnormal biopsy results. Furthermore, patients with an abnormal skin biopsy have a higher likelihood to respond to typical neuropathic medications than controls.<sup>18</sup>

Skin biopsy of upper and lower thigh and calf is very well tolerated with a very low rate of complications and can be performed in almost all patients apart from those with skin abnormalities at the biopsy site. Skin punch should be taken from upper thigh (10 cm below the greater trochanter), lower thigh (10 cm above the lateral knee) and the calf (10 cm above the lateral malleolus) for diagnostic purposes. Biopsies can also be repeated several times to monitor treatment efficacy and disease progression. Utilizing these three sites the clinician can classify patients into one of four distinct pathologic phenotypes. Several papers have shown

a poor correlation between the distribution of the clinical complaints and the pathologic abnormalities.<sup>19</sup> For example, a patient with a proximal ganglionopathy may have their most severe symptoms initially localized distally to the feet. Only by examining three sites with a gradient from proximal to distal can one accurately classify these patients.

### Pathologically defined phenotypes

Although there may sometimes be significant overlap between somatic and autonomic symptoms, we believe patients with ISFN can be classified into four clinical phenotypes: ISFN-1, ISFN-2, ISFN-3, and ISFN-4.

#### *Non-length dependent form: ISFN-1*

These patients will have abnormalities in the proximal thigh and/or distal thigh but relative preservation of the distal foot IENFD. There are no studies that evaluate to what degree the proximal sites must be abnormal compared to the distal sites, so currently we rely on normal versus abnormal, but this binary distinction may be insufficient. For example, if the proximal thigh has a 90% reduction below the lower limits of normal and the calf has a ten percent reduction below the lower limits of normal should this be considered as both abnormal or more abnormal proximally. This question requires further analysis.

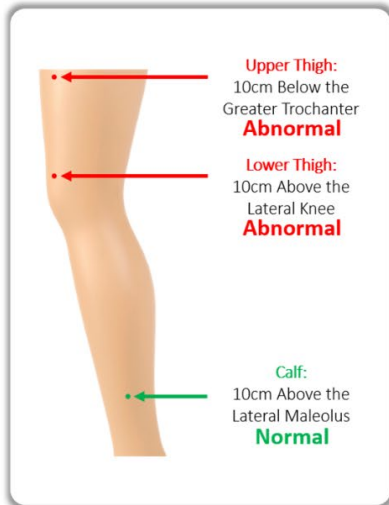
However, in cases where only the proximal sites are abnormal, studies have shown that this pathologic phenotype is distinct from other forms of SFN. This finding indicates that the disease process has begun proximally and has been shown to often represent a ganglionopathy. ISFN-1 is more common in women, often presents at a younger age and is more likely associated with diseases of acute onset that are related to immune-mediated disorders (Table 1). It is important to clinically exclude other mixed fiber conditions such as mononeuropathies (meralgia paresthetica), radiculopathies, and patchy forms of plexopathies.

#### *Length dependent: ISFN-2*

Typically, SFN presents in a length-dependent pattern in which patients present with symmetrical neuropathic pain occurring in a distal “stocking-and-glove” distribution. The skin biopsies would confirm predominant damage in the calf and/or distal thigh with relative preservation of the IENFD in the proximal thigh. This traditional pattern follows a distal-to-proximal gradient and is associated with diseases such as diabetes and impaired glucose tolerance, Vitamin B12 deficiency, lymphoproliferative disorders and Sjogren's syndrome (Table 2).

## A Diagnostic Algorithm for Evaluating Small Fiber Neuropathies

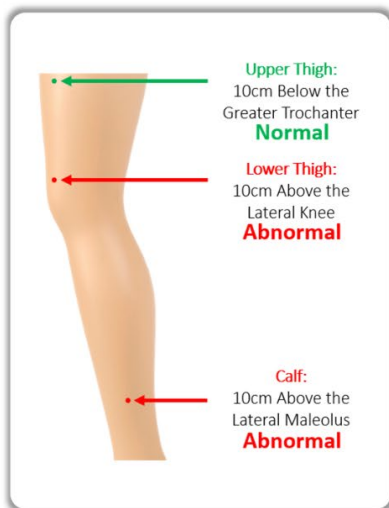
### Non Length Dependent Form: ISFN-1



Disease State	Diagnostic Tests	Potential Therapies
Sjogrens Syndrome	SS-A, SS-B	IVIG, Steroids, IST <sup>23,24</sup>
Immune Mediated Neuronopathy	FGFR-3 antibodies	IVIG <sup>19,25</sup>
Immune Mediated Neuronopathy	TS-HDS antibodies	IVIG <sup>19,25</sup>
Immune Mediated Neuropathy	Lumbar Puncture	IVIG, steroids <sup>19,25</sup>
CISP	CSF Protein	IVIG, Steroids <sup>26</sup>
CISP	IgG Synthesis rate	IVIG, Steroids <sup>26</sup>

Table 1: Etiologies and potential treatments of non-length dependent small fiber neuropathies

### Length Dependent: ISFN-2



Disease Association	Diagnostic Testing	Potential Treatments
Diabetes	HgbA1C	Glucose control
Diabetes	2 hour OGTT	Glucose Control
Sjogren's Syndrome	SS-A, SS-B	IVIG, Steroids, IST <sup>23,24</sup>
Sarcoid	ACE	IVIG, Steroids, IST <sup>27,28</sup>
Lymphoproliferative Disorder	Serum Immunofixation Quantitative Immunoglobulins	Heme/Onc Evaluation

Table 2: Etiologies and potential treatments of length dependent small fiber neuropathies

### Multifocal presentation: ISFN-3

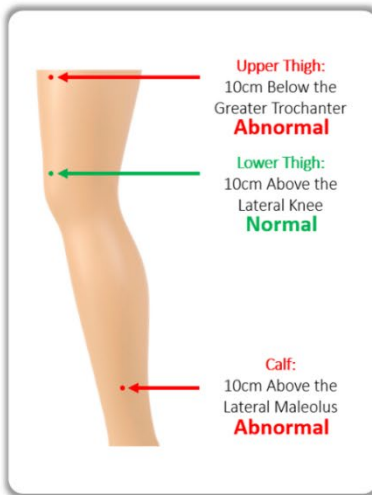
More rarely, the clinical presentation of ISFN is characterized by multifocal sensory symptoms. On the biopsy one might see the distal thigh damaged but the proximal thigh and distal calf having preserved IENFD. Multifocal SFN can present very asymmetrically, involving only a single limb, or as truncal pain, face or scalp pain. The multifo-

cal presentation is associated with glucose dysmetabolism, cryoglobulinemia, systemic vasculitis, sarcoidosis, and HIV infection (Table 3).

### Autonomic predominant: ISFN-4

Patients with ISFN-4 have significant autonomic complaints and findings. They may have abnormal autonomic

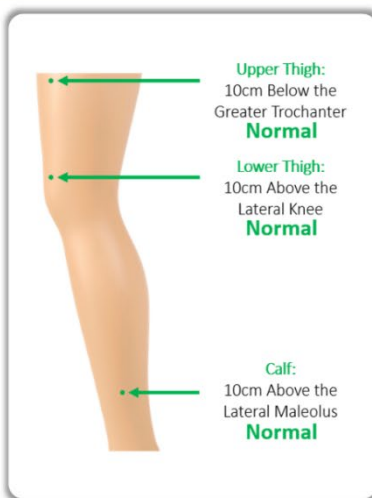
**Multifocal Presentation: ISFN-3**



Disease State	Diagnostic Tests	Treatment
Glucose Dysmetabolism	2 hour OGTT Fasting glucose	Glucose Control
Cryoglobulinemia	Cryoglobulins	Rituximab, IFN, Antiviral <sup>29</sup>
Systemic Vasculitis	ANA; ANCA	Steroids, IST <sup>30</sup>
Sarcoid	ACE	Steroids, IVIG, IST <sup>28</sup>
HIV	HIV	Retroviral Therapy

**Table 3: Etiologies and potential treatments of multifocal small fiber neuropathies**

**Autonomic Predominant: ISFN-4**



Disease State	Diagnostic Tests	Possible Therapies
Lymphoproliferative D/O	Serum Immunofixation Quantitative Immunoglobulins	Heme/Onc evaluation
Acute autonomic ganglionopathy	Anti Nicotinic Ganglionic Receptor antibodies Gad-65 antibodies	Heme/Onc evaluation
Acquired Amyloid	Serum free light chains	Heme/Onc evaluation
Inherited Amyloid	TTR Sequencing	Patiseran Inotersen

**Table 4: Etiologies and potential treatments of autonomic predominant small fiber neuropathies**

testing but the IENFD is normal at all three sites; yet when one examines the density of Protein Gene Product 9.5 (PGP 9.5) positive nerves in the sweat glands in the dermis there is a marked reduction. In this scenario acquired or inherited amyloidosis should be considered. Laboratory testing for inherited amyloidosis includes TTR gene mutations as well fat-pad biopsies or aspirates, rectal biopsy, and biopsies of affected organs such as heart or kidney.<sup>20-22</sup> Lymphoproliferative disorders and acute autonomic ganglionopathy have been described in ISFN-4 (Table 4).

**Treatments options**

Treatment of SFN should primarily focus on addressing the underlying cause. Skin biopsy at the proximal thigh, distal thigh, and calf can help place patients into one of the four recognized pathologic phenotypes. Utilizing the differential in Table 1-4 can help identify treatable causes in up to 50% of these ISFN patients.

There is very limited evidence for medications to treat pain associated with ISFN. Novel drugs that primarily affect sodium channels are in late stage trials. But until we

have medications approved for ISFN patients we must rely on pragmatic consensus guidelines including drugs in the treatment of other neuropathic pain syndromes (such as painful diabetic neuropathy). These agents include tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and gabapentinoids. Opioids are a second-line treatment option and should be considered in patients who have resistance to nonopioid therapy. Topical treatments such as 5% lidocaine plasters or high-dose (8%) capsaicin cream may also be used to alleviate pain.

We hope this novel algorithm to identifying the phenotypes of patients with ISFN can lead to a more thorough understanding of the underlying causes and prompt focused research in the future.

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