Ratio of distal to proximal epidermal nerve fiber density in small fiber neuropathy

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ABSTRACT

Intraepidermal nerve fiber density (IENFD) assessment is an important tool for diagnosing small fiber neuropathy (SFN), with distal leg and proximal thigh biopsies commonly performed to evaluate length dependency. Although age-dependent normative data exist for distal leg IENFD, some patients with paresthesias exhibit normal values at both sites but a markedly lower distal IENFD compared to proximal density. The aim of this study is to assess the diagnostic value of the distal-to-proximal IENFD ratio in SFN. Charts of patients who underwent skin biopsy for evaluation of SFN between May 2020 and May 2023 at the Neurology Department, University of Kansas Medical Center, were retrospectively reviewed. IENFD was measured at the distal leg and proximal thigh, and the distal-to-proximal ratio calculated. Patients were classified as having possible or probable SFN based on NEURODIAB criteria, or as not meeting diagnostic criteria. Of 64 charts reviewed, 56 were enrolled, the female-to-male ratio was 3:1 and mean age was 50±26 years. Forty-six patients met clinical criteria for SFN (16 possible, 30 probable), with IENFD abnormal in 23 and normal in 23, showing mean ratios of 0.5 and 0.6, respectively. Patients without a clinical diagnosis of neuropathy had a mean ratio of 0.9, and among patients with clinical SFN but normal biopsy results, the mean ratio was significantly lower than in those without clinical SFN (p=0.02). These findings suggest that, in patients with normal IENFD but high clinical suspicion for SFN, the distal-to-proximal IENFD ratio may serve as an additional parameter to improve diagnostic sensitivity.

Introduction

Small fiber neuropathy (SFN) is a condition that selectively affects small unmyelinated C-fibers and thinly myelinated Aδ-fibers, which are responsible for pain, temperature perception, and autonomic regulation.[1,2] It may present with burning pain, paresthesias, or autonomic disturbances like orthostatic hypotension, and may follow a length-dependent or non–length-dependent distribution. Common causes include metabolic disorders (eg diabetes, glucose intolerance) autoimmune diseases (e.g., Sjögren's syndrome, sarcoidosis), infections, toxins, hereditary (e.g., SCN9A mutation), and idiopathic origins.[1-3] Given the diversity of etiologies and lack of large fiber involvement, diagnosis is often delayed or missed.

The underlying pathophysiology of SFN is multifactorial. Mechanisms such as immune-mediated injury, neuroinflammation, metabolic dysregulation, and ion channel dysfunction lead to distal axonopathy or patchy proximal fiber loss.[1,4,5] Dysfunction within the dorsal root ganglia and epidermis is thought to underlie the neuropathic pain symptoms. Notably, the clinical presentation can vary by etiology. In metabolic neuropathies, degeneration typically follows a distal-to-proximal gradient, whereas autoimmune SFN may show non–length-dependent or proximal-predominant involvement.[2,6] This anatomical variability complicates clinical recognition and highlights the need for more nuanced diagnostic approaches.

Diagnosis is established using clinical features, exclusion of large fiber neuropathy with normal nerve conduction studies, and confirmatory tests. An objective test to confirm is intraepidermal nerve fiber density (IENFD) measurement with 3-mm skin punch biopsy, often performed at the distal leg and proximal thigh.[1,7,8] Decreased IENFD is diagnostic, and normative values adjusted for age and sex guide interpretation at distal site are available.[8-10] Skin biopsy has excellent specificity but variable sensitivity (45–80%) depending on site selection, disease distribution, and methodology.[2,3,8,11] Recent efforts have focused on optimizing technique and standardizing thresholds to reduce false negatives.[1,12]

One limitation of current IENFD-based diagnostics is the reliance on absolute fiber density values, which may miss patients with significant symptoms but normal fiber counts. We hypothesize that calculating the ratio of distal leg to proximal thigh IENFD could enhance diagnostic sensitivity. In metabolic SFN, distal loss exceeds proximal, whereas in autoimmune SFN, proximal loss may predominat.[12,13] In cases with borderline or normal values, a significantly reduced ratio could reflect subtle but pathologically relevant fiber gradient changes. Our study aims to retrospectively assess this IENFD ratio in patients with suspected SFN undergoing skin biopsy at a tertiary neuromuscular center. The NEURODIAB criteria have been established to diagnose clinically small fiber neuropathy in diabetic patients.[14] There is no prior literature looking at the IENFD ratio in patients being evaluated for small fiber neuropathy.

Design and methods

After Institutional review board approval was obtained, we retrospectively evaluated charts of subjects who underwent skin biopsy for evaluation of SFN between May 2020 to May 2023, at the Outpatient Neurology Clinics, KUMC. All patients who had a normal nerve

Table 1: Symptoms of small fiber neuropathy.

Sensory symptoms
• Pain (burning sensations, tingling, painful cold sensation, shooting pain, pins and needles) • Dysesthesia (e.g. sensation of feet constriction) • Allodynia in response to rubbing • Hypoesthesia to heat, cold, and pinprick
Dysautonomic symptoms
• Hypo/anhydrosis • Hyperhydrosis • Sicca syndrome • Erythromeralgia • Cutaneous vasoparalysis • Gastrointestinal symptoms (early gastric empty, constipation, diarrhea, intestinal pseudo-obstruction) • Urinary incontinence or retention • Erectile dysfunction • Disorders of accommodation with blurred vision, photophobia, tonic pupil • Orthostatic hypotension, orthostatic intolerance

Table 2: Demographic and Clinical Characteristics of Patients included

		Possible SFN	Probable SFN	Not meeting Criteria
Total number of patients		16	30	10
Mean age at onset		46	47	35
Male:Female		2:14	8:30	3:07
Most common sign*	Numbness	2/16 (12.5%)	5/30 (17%)	0
	Decreased pinprick	5/16 (31%)	26/30 (87%)	0
	Hyperesthesia	1/16 (6%)	6/30 (20%)	0
Most common presenting symptom		Tingling and numbness (100%),	Tingling and numbness (85%), dysautonomia (70%)	Tingling (90%), itching (50%)
Pain		14 (87.5%)	19(63%)	2/20 (20%)
Associated diseases		Sjogren (44%)	RA (20%), Sjogren (20%)	ATTR 1/10 (10%)
Diabetes		7(44%)	10 (33%)	0
Time from onset to diagnosis (years)		5.8	4.9	2.4
Body parts involved (A:arms, L:legs, F:face)		A+L (44%), L (29%), A+L+F (25)	A+L (40%), A+L+F (27%), L (24%)	A+L (30%), L (20%)

*11/16 (69%) of the possible SFN group did not have any finding on examination

conduction study (NCS), without evidence of large fiber neuropathy or radiculopathy were included. Skin biopsies were processed using the standard technique and PGP9.5 protein marker. The distal leg and proximal thigh IENFD information was collected, and the distal-to-proximal ratio was calculated for all subjects. Subjects were categorized as having "possible SFN" with presence of either signs on examination or symptoms (Table 1); "probable SFN" with having both signs and symptoms, based on the clinical criteria established by Diabetic Neuropathy Study Group of the European Association for the Study of Diabetes (NEURODIAB), or not fitting criteria for diagnosis.[1,15,16] Descriptive and correlation analysis was performed.

Results

Total of 64 charts were reviewed. 8 subjects were excluded due to abnormal NCS findings. Sixteen (16/56) subjects had a possible diagnosis of SFN, 30/56 had a probable diagnosis of SFN, and 10/56 subjects did not meet the NEURODIAB criteria for diagnosis (Table 2)

There was no significant difference between the mean age at onset of symptoms for subjects with possible and probable diagnosis and those that did not fulfill the criteria 37±17 and 35±15 (p=0.73). More female subjects were seen in all groups. The most frequent symptom reported in all groups was tingling and numbness. The most common sign was decreased pin prick sensation. Diabetes and other autoimmune conditions were seen in 20-40% of subjects in the possible and probable group while one patient was positive for transthyretin (TTR) gene mutation in the subjects that did not meet the criteria. In the possible SFN group, 9/16 had a normal IENFD results on skin biopsy and 7/16 had an abnormal IENFD results. In the probable SFN group, 14/30 had a normal IENFD results and 16/30 had an abnormal IENFD results. In the group not meeting criteria for diagnosis, all subjects had a normal IENFD results (Table 3). In total (all groups included), 23 of the 46 subjects had abnormal IENFD results, and 23/46 subjects had normal IENFD results (Table 4), with mean distal to proximal ratio of 0.5 and 0.6 respectively. Among the subjects with normal IENFD 69.7% fulfilled the criteria for possible or probable SFN. Using the cutoff ratio of less than 0.5, 96.1% of subjects with normal IENFD met diagnostic criteria for SFN and using cutoff less than 0.6, 94.1% met the SFN criteria (Fig 1 and 2).

Table 3: Epidermal Nerve Fiber Density Findings

	Possible SFN (n=16)	**Probable SFN(n=30)**	**Not meeting Criteria (n=10)**
Normal IENFD result	9 (56%)	14(46%)	10 (100%)
Abnormal IENFD result	7(44%)	16(54%)	0
Average distal IENFD (SD)	7.2 (4.0)	5.7 (4.6)	11.0 (4.4)
Average proximal IENFD (SD)	10.2 (6.2)	11.1 (5.2)	13.0 (4.8)
Average distal/proximal IENFD ratio(SD)	0.8 (0.4)	0.5 (0.3)	0.8 (0.3)

Table 4: Mean IENFD ratio in subjects with normal IENFD results vs those with abnormal IENFD results

	Normal IENFD result	Abnormal IENFD result
Number of patients	23(50%)	23(50%)
Average distal IENFD	9.5	3.7
Average proximal IENFD	13.8	7.2
Average distal/proximal IENFD ratio	0.6	0.5

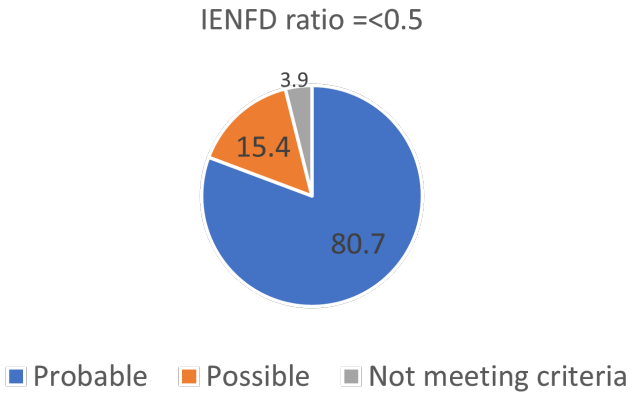

Fig. 1. Using IENFD cutoff ratio of 0.5, 96.1 % of patients with normal IENFD meet the diagnostic criteria of SFN

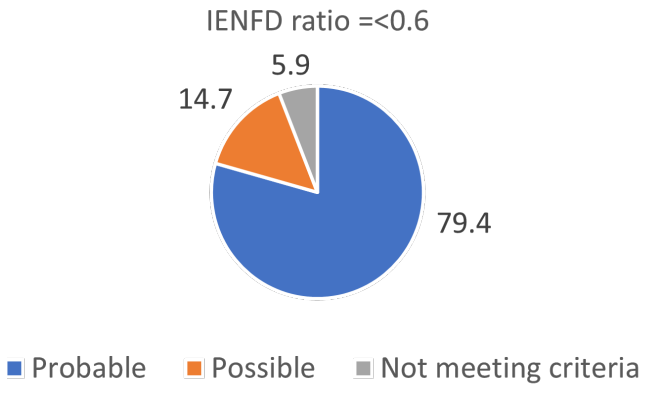

Fig. 2. Taking IENFD ratio cutoff < 0.6; 94.1 % of patients with normal IENFD meet the diagnostic criteria of SFN

Discussion

SFN is a disease of somatic and autonomic, thinly myelinated and unmyelinated nerve fibers. The classical presentation is that of a length-dependent neuropathy, however further clinical presentations have been proposed. Definitive diagnostic criteria have yet to be established, affecting the approach to patient's management and treatment. Devigili et al. demonstrated that a combined approach including clinical, functional and structural assessment of small nerve fibers, improves the reliability of diagnosis. However, given the differences in phenotypic presentations, genetic, racial and gender variability, some patients with high clinical suspicion for SFN might turn out to have normal IENFD on skin biopsy. Even with normal fiber density, some patients may have borderline values at distal site and very high fiber density at proximal site. To our knowledge, the use of IENFD ratio was not previously assessed in the diagnosis of SFN. In this study, we found that patients who had probable SFN when applying the NEURODIAB criteria had a low IENFD ratio mean of 0.5, compared with a mean of 0.8 for patients with possible SFN, and those who did not meet the criteria for neuropathy. Interestingly, when calculating the IENFD ratio for all patients with abnormal skin biopsies regardless of which group they belonged to, the mean IENFD ratio was 0.5, compared to 0.6 for the patients with normal skin biopsy results. Using the IENFD ratio cutoff of less than 0.5, 96.1% of subjects with normal IENFD met the criteria for SFN. Patients with probable SFN are more likely to have abnormal IENFD compared to patients with possible SFN. This study shows that IENFD ratio is a better diagnostic tool compared to IENFD alone, with a cut-off of 0.6, in patients with clinical suspicion for SFN, increasing the sensitivity of skin biopsy from 67% to around 95%. The limitations of this study are the small sample size and sensitivity analysis was not performed.

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