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Concordance between epidermal nerve fiber density and sensory examination in patients with symptoms of idiopathic small fiber neuropathy

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Abstract

Quantitation of epidermal nerve fiber (ENF) density is an objective diagnostic test of small fiber neuropathy (SFN). For a diagnostic test to be clinically useful it should correspond well with clinically meaningful physical findings. We performed a retrospective analysis of the concordance between foot ENF density and clinical findings in all patients seen at our institution with possible idiopathic SFN who underwent skin biopsy for ENF density determination. We found a high concordance between reduced foot ENF density and loss of pinprick sensitivity in this patient population. Our findings indicate that ENF density determination is a clinically relevant objective test in patients undergoing evaluation for possible SFN.

Keywords: Small fiber neuropathy; Painful neuropathy; Epidermal nerve fiber density; Skin biopsy; Pinprick testing

1. Introduction

Quantitation of epidermal nerve fiber (ENF) density in a skin biopsy has become an accepted method for confirming the clinical diagnosis of small fiber neuropathy (SFN) in patients with neuropathic symptoms and decreased distal sensation but preserved ankle reflexes, normal muscle bulk and strength, and normal nerve conduction studies. However, the utility of any diagnostic test for distal symmetric polyneuropathy rests in large part upon its concordance with clinical findings [1]. In the context of SFN, to demonstrate the value of epidermal nerve fiber (ENF) density as an objective diagnostic test, it must be shown that ENF density is concordant with patients' symptoms and signs. Because abnormal pinprick sensitivity is the clinical sign most commonly used to evaluate small fiber sensory function, we reviewed the concordance between pinprick sensitivity and ENF density in patients evaluated for possible idiopathic SFN.

2. Methods

Medical records of all patients referred from the University of Minnesota Medical Center neuromuscular clinic to our laboratory to evaluate foot ENF density between November 1999 and July 2005 were reviewed retrospectively. Patients with a clinical diagnosis of possible idiopathic painful SFN, defined as a syndrome of idiopathic symmetric burning, paresthesias, hyperalgesia, or allodynia in a length-dependent distribution with normal strength, reflexes, and nerve conduction studies, were included. It is the practice in our neuromuscular clinic to refer such patients for skin biopsy, regardless of whether sensory loss is present. Patients with a non-length dependent syndrome, clinically significant lumbar degenerative disease, other neurologic disease, exposure to known neurotoxins, alcohol abuse, or a documented family history of neuropathy were excluded. Patients with monoclonal

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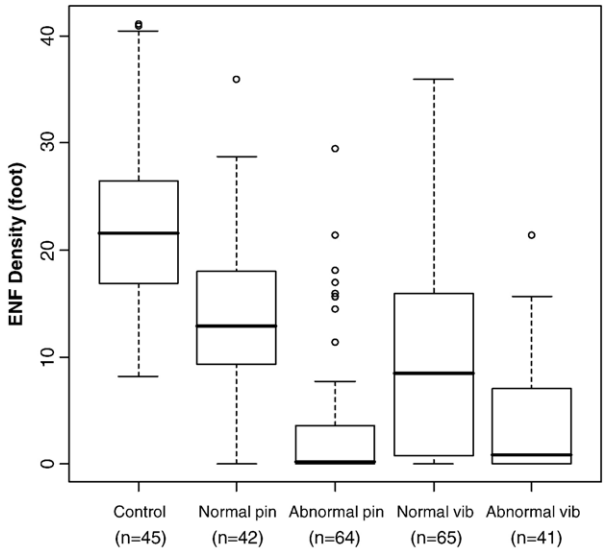

Fig. 1. ENF density for control subjects and patient groups. Foot ENF density data using R default boxplot function. The black center line indicates the median for each dataset, the edges of the box area are first and third quartiles, the plot whiskers extend to the most extreme data point which is no more than 1.5 times the length of the box away from the box, and circled points are outliers.

gammopathy, chronic hepatitis C infection, or vitamin B12 deficiency were also excluded from this analysis. All patients had a normal fasting blood glucose.

One hundred six of 178 patients referred for evaluation of ENF density during the study period met inclusion criteria. The remaining seventy-two patients were excluded for the following reasons: a non-length dependent presentation (35), diabetes (13), a second neurologic diagnosis (8), a history of lumbar spinal surgery (3), a history of vitamin B12 deficiency (3), hepatitis C infection (3), a documented family history of neuropathy (1), and insufficient information or inconsistent findings on examination (6). The mean age of the 106 subjects who met inclusion criteria was 53 (range 33–81). Sixty four were women and 42 were men.

All patients were examined in the neuromuscular clinic at the University of Minnesota Medical Center. Ninety patients were examined by one of the authors (DW), 14 by another neuromuscular specialist, and 3 by a third neuromuscular specialist. Sensory examination included assessment of pinprick sensitivity and a qualitative determination of vibration perception using a 128 Hz tuning fork at the great toe. All 3 clinicians used the same examination technique. Pinprick sensitivity was assessed by applying firm pressure, sufficient to indent the skin, with a safety pin. Patients were asked whether the pin felt normally sharp, or "the way a pin should feel," and whether it felt as sharp distally as it did in proximal areas in which the patient was not symptomatic. Testing was begun over

Table 1
ENF density as a predictor of pinprick sensation (all patients)

Density cutoff (ENF/mm)	Sensitivity	Specificity	Positive predictive value	Negative predictive value
6	0.80	0.86	0.89	0.73
7	0.83	0.83	0.88	0.76
8	0.88	0.81	0.88	0.81
9	0.88	0.76	0.85	0.80
10	0.88	0.71	0.82	0.79
11	0.88	0.69	0.81	0.78
12	0.89	0.60	0.77	0.78

Table 2
ENF density as a predictor of pinprick sensation (patients with normal vibration only)

Density cutoff (ENF/mm)	Sensitivity	Specificity	Positive predictive value	Negative predictive value
6	0.82	0.91	0.90	0.83
7	0.85	0.91	0.90	0.86
8	0.88	0.91	0.91	0.88
9	0.88	0.84	0.85	0.87
10	0.88	0.78	0.81	0.86
11	0.88	0.75	0.78	0.86
12	0.91	0.66	0.73	0.88

Sensitivity = Probability of an abnormal ENF density given abnormal pinprick sensation.
Specificity = Probability of normal ENF density given normal pinprick sensation.
Positive predictive value = probability of abnormal pinprick sensitivity given that ENF density is abnormal.
Negative predictive value = probability of normal pinprick sensitivity given that ENF density is normal.
Abnormal ENF density defined as < indicated cutoff.
Normal ENF density defined as ≥ indicated cutoff.

Table 3
Pinprick sensitivity and foot ENF density at an ENF density cutoff of 8/mm: number of subjects

	ENF <8	ENF ≥8	Total	Sensitivity and specificity (%)
Abnormal pin	56	8	64	88
Normal pin	8	34	42	81
Total	64	42	106	
Positive and negative predictive value	88%	81%		

Table 4
Foot ENF density compared with extent of sensory deficit

Pinprick sensation deficit	Mean foot ENF density (SD)	Min foot ENF density	Max foot ENF density
None (normal examination)	13.9 (7.7)	0	36.0
Deficit in distal half of foot only	3.3 (4.9)	0	17
Deficit extending proximal to midfoot but not above ankle	4.5 (8.0)	0	29.5
Deficit extending proximal to ankle	2.7 (5.7)	0	21.4