Small Fiber Neuropathy
Differential Diagnosis and Treatment Implications

Stephen L. Barrett, DPM, MBA[a], A. Lee Dellon, MD, PhD[b,*]

KEYWORDS

• Small fiber neuropathy • Intraepidermal nerve ending • Skin biopsy

KEY POINTS

- When the unmyelinated and small myelinated nerve fibers are symptomatic, patients' complaints are of burning extremity pain.
- Skin biopsy is now standardized to identify abnormal intraepidermal nerve fiber density, which correlates with a patient's small fiber disease.
- *Pure small fiber neuropathy is rare*. Treatment with neuropathic drugs and topical creams is appropriate. Nerve decompression is not appropriate.
- Abnormal cutaneous pressure or vibratory thresholds and/or abnormal nerve conduction velocity or distal latency document that pure small fiber neuropathy is *not* present, because these are tests of large fiber function.
- Chronic nerve compression and mixed (large and small) fiber neuropathy, as in diabetes, also can give an abnormal skin biopsy for intraepidermal nerve fibers, in which case, nerve decompression surgery may be appropriate.

INTRODUCTION

Burning sensation in the feet is a common problem encountered in podiatric medicine. When this pain is bilateral, symmetric, and includes the top and bottom of both feet, small nerve fiber involvement must be considered in the differential diagnosis. These "small nerve fibers" include the unmyelinated C-fibers and the thinly myelinated group A-delta fibers, which transmit perception of hot and cold and burning or itching pain.[1] *Small nerve fibers do not transmit the perception of numbness*. It is the large, myelinated A-beta fibers that transmit the perception of touch, including vibratory perception and pressure perception.[1] Abnormal perception of touch is described as numbness, not pain. Numbness can be described as unpleasant, or paresthesias, but is not burning pain. Documentation of small fiber function requires quantitative sensory

[a] Arizona School of Podiatric Medicine, Midwestern University College of Health Sciences, Glendale, AZ, USA; [b] Johns Hopkins University, Baltimore, MD, USA
* Corresponding author. 1122 Kenilworth Drive, Suite 18, Towson, MD 21204.
E-mail address: aldellon@dellon.com

Clin Podiatr Med Surg 33 (2016) 185–189
http://dx.doi.org/10.1016/j.cpm.2015.12.001 **podiatric.theclinics.com**
0891-8422/16/$ – see front matter

testing with cutaneous warmth or cold thresholds, but this testing is not usually available.[2] Documentation of large fiber function is commonly done with either the Semmes-Weinstein monofilaments, to give an estimate of a range for 1-point static touch, or with the pressure-specified sensory device, to give a direct measurement of the pressure required to discriminate 1-point from 2-point static touch.[2] Traditional electrodiagnostic testing of the sensory conduction velocity or the distal sensory latency are also traditional measures of large fiber function.[2] A computer-assisted sensory evaluation with the CASE IV, developed by the Neurology Department at the Mayo Clinic, which incorporates thermal testing, vibration testing, and 1-point static testing thresholds has been used to quantitate both small and large fiber function demonstrating them to be abnormal in patients with diabetes and with subclinical problems related to running,[3–5] but this device is not generally available.

The realization that the terminal endings of the small fibers innervate the skin in the epidermis, lead the way to a quantitative measurement of these endings in a skin biopsy. This testing was developed and standardized by the Neurology Department at Johns Hopkins Hospital and published in 1998.[6] Decreased intraepidermal nerve fiber density correlated with the presence of pain in this study. The presence of pure small fiber neuropathy is rare, with this same neurology group reporting on just 32 such patients in their now classic article on this disease.[7]

Prevalence and incidence of pure small fiber neuropathy has been reported recently in the Netherlands: it was found in 55 patients over a 5-year time period in a clinic devoted to the treatment of these types of problems, with an incidence of 11.7 per 100,000 population.[8]

An abnormal intraepidermal nerve fiber density report from a skin biopsy must be considered as a finding, not as a diagnosis of pure small fiber neuropathy. Chronic nerve compression and the commonest forms of polyneuropathy also can have decreased intraepidermal nerve fiber density.

DIFFERENTIAL DIAGNOSIS

Does the presence of abnormal intraepidermal nerve fibers exclude the diagnosis of mixed fiber neuropathy, or of chronic nerve compression, or of neuropathy with superimposed chronic nerve compression? It is clear from the following articles, including the original article from the Johns Hopkins Neurology group, that many forms of neuropathy have both large and small fiber abnormalities.[6,7,9,10] It is also clear from studies on humans with chronic nerve compression,[11–13] and on rats with chronic nerve compression,[14] that small fibers are affected in these conditions too: chronic nerve compression has abnormalities of both large and small nerve fibers.

A positive skin biopsy for decreased intraepidermal nerve fibers is, therefore, consistent with the diagnosis of pure small fiber neuropathy, mixed fiber neuropathy, or chronic nerve compression. A differential diagnosis should be included in the skin biopsy reporting format, and understood by the physician ordering that test.[15]

TECHNIQUE FOR A SKIN BIOPSY TO EVALUATE SMALL FIBER DENSITY

What you will need:

- Betadine
- Small pair of dissecting scissors
- Disposable forceps
- 3-mm punch biopsy
- Labeled vial
- 5.0 nylon suture (optional) (**Fig. 1**A)