

PERIPHERAL NEUROPATHIES

Less sweat, more neuropathy

A novel technique to measure the density of autonomic nerve fibers that innervate sweat glands could help determine the extent and progression of peripheral neuropathy. “We could already quantify small sensory fibers using intra-epidermal nerve fiber density (IENFD) analysis of skin biopsies but, until now, had no means to quantify autonomic nerve fibers. These play an important role in the predisposition to foot ulceration and impaired wound healing that leads to limb amputation in patients with diabetic neuropathy,” explains Roy Freeman (Center for Autonomic and Peripheral Nerve Disorders, Beth Israel Deaconess Medical Center, Boston, MA, USA), who directed a detailed evaluation of the new method.

“...[autonomic nerve fibers] play an important role in the predisposition to foot ulceration...”

The researchers stained sections derived from skin biopsies originally obtained from 30 people with diabetes and 64 healthy controls for IENFD. Sweat gland nerve fiber density (SGNFD) was assessed by staining tissue with PGP 9.5 (Figure 1) and counting the fibers manually in sections viewed with a light microscope. The technique clearly differentiated patients with mild neuropathy from healthy controls, with diabetics showing

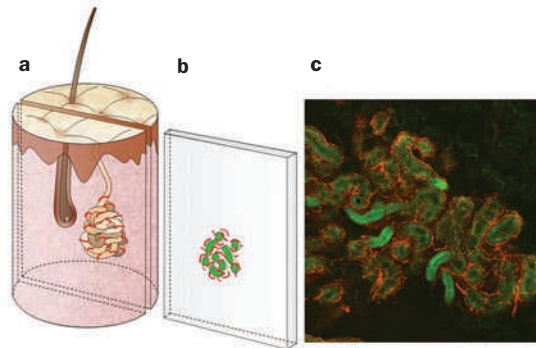


Figure 1 | Assessing sweat gland nerve fiber density. **a** | A punch skin biopsy containing a sweat gland is obtained and **b** | a tissue section containing a portion of the sweat gland is removed. **c** | The tissue is stained with the pan-axonal marker PGP 9.5 and nerve fibers (red) surrounding a sweat gland (green) are visualized. The fibers are quantified by placing a grid over the image and counting the intersections between the nerve fibers and the grid. Image provided by Prof. Roy Freeman.

lower SGNFD in the distal leg, distal thigh and proximal thigh regions.

The Neuropathy Impairment Score in the Lower Limb, a standard neuropathy scoring system, revealed a strong relationship between increasing severity of neuropathy and decreasing density of nerve fibers surrounding sweat glands in the distal leg. “Patients reporting very dry, cracked skin had significantly fewer nerve fibers surrounding sweat glands at this site,” notes lead author Christopher Gibbons.

Freeman suggests that quantification of SGNFD will complement the IENFD technique. “No additional staining or preparation of the skin biopsy is required, allowing the SGNFD technique to be done

by simple adaptation to ongoing studies,” he explains. Previous studies suggest that different populations of nerve fibers degenerate and regenerate at different rates and have differing susceptibility to various degenerative processes. “This technique will permit the evaluation of this population of nerve fibers and assess the response to interventions that seek to alter the natural history of neuropathies and neurodegenerative disorders,” predicts Freeman.

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Original article Gibbons, C. H., et al. Quantification of sweat gland innervations: a clinical-pathologic correlation. *Neurology* 72, 1479–1486 (2009).