Short Communication

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Use and Misuse of Epidermal Nerve Fiber Density for Assessment and Treatment of Peripheral Nerve Function and Dysfunction

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Abstract

Pathoanatomical examination procedures such as epidermal nerve fiber density (ENFD) was indicative of small-fiber dysfunction and the objective of this short communication was to throw light on ENFD and its use in assessment and treatment of peripheral neuropathies. Limited yet sufficient evidence shows that ENFD had established normative reference range, predictive equation with respect to age and gender, low inter-measurement variability; and was correlated to quantitative sensory test measures, morphometry, pain-related evoked potentials and C-fiber axon reflex flare size; was used in HIV-related peripheral neuropathy, sensory ganglionopathiesand Diabetic peripheral neuropathy; and, was influenced by topical treatments such as capsaicin and lidocaine patches. Thus ENFD is the one of earliest indicator of nerve function and dysfunction in peripheral nerve disorders.

Keywords: Neuroanatomy; Neurohistology; Skin Biopsy; Peripheral Neuropathy.

Pathoanatomical examination procedures such as epidermal nerve fiber density (ENFD) was indicative of small-fiber dysfunction and the objective of this short communication was to throw light on ENFD and its use in assessment and treatment of peripheral neuropathies.

McArthur et al [1] developed a reference range of epidermal nerve fiber density in humans, in 98 normal controls and its diagnostic utility was examined in 20 patients with sensory neuropathies. The study determined that the density of intraepidermal fibers in normal controls was 21.1+/-10.4 per millimeter in the thigh, and was 13.8+/-6.7 per millimeter at the distal part of the leg. "Significantly higher intraepidermal fiber densities were seen in the youngest age group, and Epidermal nerve fiber density was significantly reduced in patients with sensory neuropathies. With a cutoff derived from the fifth percentile of the normative range for the distal part of the leg, the technique had a positive predictive value of 75%, a negative predictive value of 90%, and a diagnostic efficiency of 88%."

Gøranssonet al [2] used immunohistochemical techniques with the panaxonal marker anti-protein gene product 9.5 (PGP 9.5) and established a reference range for ENFD in 106 healthy white volunteers. The density of ENF depended on age and gender as per the predictive equation (Y = 13.92 + 2.25 (gender) - 0.06 x age). The density of epidermal nerve fibers decreased with age and was lower in men compared with women.

Selim et al [3] evaluated QST measures (touch, mechanical pain, heat pain and innocuous cold sensations) for differences between genders and over time using ENFd as an objective-independent measure in 36 healthy volunteers and concluded that "most QST measures detect relatively large differences in epidermal innervation (12.2 ENFs/mm), but response to mechanical pain was the only sensory modality tested with the sensitivity to detect small changes in innervation (4.18 ENFs/mm)."

Umapathi et al [4]studied the relationship between epidermal innervation and age, gender, height, and weight in 84 normal individuals and found negative correlation between age and IENFD at the ankle. With increasing age the thigh IENFD/ankle IENFD ratio,

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a measure of the length-dependent distal-to-proximal gradient of epidermal nerve density, increased significantly. In normal individuals, distal epidermal innervation decreases in a length-dependent manner with advancing age.

Bickel et al [5] compared C-fiber axon reflex flare size (ARFS) and electrically evoked axon reflex sweating with intraepidermal nerve fiber density (IENF) in patients and found that ARFS was significantly correlated with IENF, while axon reflex sweating was not correlated to IENF.

Herrmann et al [6] investigated the associations of baseline epidermal nerve fiber (ENF) densities and morphology (percent ENF swellings) and quantitative sensory testing (QST) with clinically defined human immunodeficiency virus (HIV)-associated distal polyneuropathy (DSP) in 57 HIV-infected subjects with and without DSP and 19 controls participated. Mean ENF densities were lower at the distal leg and proximal thigh in asymptomatic or symptomatic DSP than in controls. A higher percent ENF swelling in the distal legwas associated with a shorter time to development of symptomatic DSP.

Herrmann et al [7] studiedintraepidermal nerve fiber (IENF) density in distal leg skin biopsies, sural nerve morphometry, electrophysiology, and clinical features in 26 patients with peripheral neuropathies. IENF density was found to be correlated with the densities of sural nerve total myelinated, small myelinated, and large myelinated fibers. Distal leg Intraepidermal nerve (IENF) density was more sensitive than sural nerve biopsy in identifying small fiber sensory neuropathies.

Obermann et al [8] assessed a method to identify small-fiber neuropathy using electrically evoked pain-related potentials and correlated the electrophysiological results with intraepidermal nerve fiber density in 19 patients with HIV associated sensory neuropathy and nine healthy HIV negative control subjects. Pain-related evoked potential latencies and amplitudes strongly correlated with intraepidermal nerve fiber density.

Walk et al [9] performed a retrospective analysis of the concordance between foot ENF density by skin biopsy and clinical findings in all patients with possible idiopathic SFN and found a high concordance between reduced foot ENF density and loss of pinprick sensitivity in this patient population.

Lauria et al [10] assessed the involvement of somatic unmyelinated fibers in sensory ganglionopathies by skin biopsy and quantitative sensory testing (QST) in 16 patients with ganglionopathy, 16 with axonal neuropathy, and 15 normal controls and found that healthy subjects and neuropathy patients showed the typical proximodistal gradient of IENF density; in neuropathies, confirming the length-dependent loss of cutaneous innervation.

Kennedy et al [11] evaluated the pharmacodynamic effects of a single 60-minute application of NGX-4010, a high-concentration (8% w/w) capsaicin patch, in healthy volunteers. "After 1 week, there was about an 80% reduction of ENF density compared to unexposed sites.

Wehrfritz et al [12] explored the ability of lidocaine patches (5%) to alter sensory function and epidermal nerve fiber density in skin of healthy volunteers. A moderate but significant decrease in epidermal nerve fiber density was observed in skin blister roofs obtained after 42days of treatment with lidocaine patches.

Limited yet sufficient evidence shows that ENFD had established normative reference range, predictive equation with respect to age and gender, low inter-measurement variability; and was correlated to quantitative sensory test measures, morphometry, pain-related evoked potentials and C-fiber axon reflex flare size; was used in HIV-related peripheral neuropathy, sensory ganglionopathies and Diabetic peripheral neuropathy; was influenced by topical treatments such as capsaicin and lidocaine patches. Thus ENFD is the one of earliest indicator of nerve function and dysfunction in peripheral nerve disorders.

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