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Use of Skin Biopsy: Diagnosis of Peripheral Neuropathy

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Description

Skin biopsy has become a standard method for evaluating small diameter sensory nerves, such as somatic unmyelinated Intraepidermal Nerve Fibres (IENF), dermal myelinated nerve fibres, and autonomic nerve fibres, in peripheral neuropathies and other illnesses. Different approaches of tissue processing and nerve fibre evaluation have been employed. The European Federation of Neurological Societies (EFNS) formed a Task Force in March 2004 with the purpose of developing guidelines for using skin biopsy in the diagnosis of peripheral neuropathies.

Using bright-field immunohistochemistry or immunofluorescence with anti-PGP 9.5 antibodies to quantify the linear density of IENF in at least three 50-m thick sections per biopsy, fixed in 2% PLP or Zamboni's solution, for diagnostic purposes in peripheral neuropathies (level a recommendation). IENF density was found to be more sensitive than sensory nerve conduction studies and sural nerve biopsies in predicting warm and heat pain thresholds in the diagnosis of small-fibre sensory neuropathy.

This method has a high diagnostic efficiency as well as a high prediction value (level A recommendation). Myelinated nerve fibres, dermal receptors, and dermal annex innervation could all benefit from confocal imaging. The diagnostic yield of dermal myelinated nerve fibre measurement and sweat gland innervation should be the focus of future research.

Longitudinal studies of IENF density and regeneration rate are needed to assess the value of skin biopsy as a peripheral neuropathy trial outcome metric and to correlate neuropathological changes with neuropathy progression (level B recommendation). Finally, punch skin biopsy is a treatment that is both safe and dependable (level a recommendation). It is recommended that you undergo training in a well-established cutaneous nerve laboratory before using skin biopsy as a diagnostic tool in peripheral neuropathies. At all levels, quality control is necessary.

Peripheral neuropathy affects about 2% of the overall population, but it affects between 12% and 17% of people who have one or two identified risk factors. A number of risk factors contribute to peripheral neuropathy, the most common of which is diabetes. Peripheral neuropathy affects almost half of persons who have had diabetes for longer than 25 years.

Diabetic neuropathy and other peripheral neuropathies are caused by the degeneration of small somatic nerve fibres, which are sometimes the only nerves affected. On the other hand, traditional physical, neurophysiological, and neuro-pathological exams may miss "small fibre neuropathy." Skin biopsy has been a prominent procedure for examining tiny nerve fibres in the last decade. It enables non-experts and general practitioners, such as diabetologists and orthopaedic specialists, to diagnose neuropathy (avoiding delayed or erroneous diagnosis), investigate the reason, and target treatment, particularly for neuropathic pain.

Over the last three decades, the study of cutaneous innervation utilising 3 mm-punch-biopsy has contributed significantly to our understanding of tiny fibre somatic and autonomic neuropathies, as well as large fibre neuropathies. Unlike sural nerve biopsy, skin biopsy is a less invasive treatment that may be performed on any area of the body, is repeatable throughout time, and allows for the identification of each population of nerve fibre through its target.

The gold standard for verifying the diagnosis in individuals with symptoms and signs of small fibre neuropathy is intraepidermal nerve fibre density evaluation, while the quantification of sudomotor, pilomotor, and vasomotor nerve fibres allows evaluating and characterising the autonomic involvement. All of these traits can be re-evaluated over time to follow the disease's course and evaluate the efficacy of treatments. Myelinated fibres and their receptors can be examined when nerve conduction investigations are normal to detect a "dying back" neuropathy early.

Furthermore, cutaneous myelinated fibre morphometry has revealed new information on the pathophysiology of numerous types of inherited and acquired large fibre neuropathies. Skin biopsy has become a proxy for sural nerve biopsy, which is no longer required in the diagnosis procedure, to investigate genotype–phenotype relationships in hereditary neuropathies.

A skin biopsy for epidermal nerve fibre analysis is an important objective test for peripheral neuropathy diagnosis, particularly in the case of Small Fiber Sensory Neuropathy (SFSN). The assessment of Epidermal Nerve Fibre Density (ENFD) is precise and has a good diagnostic specificity and sensitivity. Due to the risk of false negatives, biopsy results must be interpreted in conjunction with neurologic symptoms and laboratory data, particularly objective sensory and autonomic function testing.

SFSN is usually length dependent, with about half of the cases being idiopathic. In biopsies taken from the proximal (thigh) and distal (calf), ENFD anomalies are more prevalent distally than proximally. A more severe ENFD abnormality in the thigh than in the calf increases the chance of a non–length–dependent SFSN. This type of neuropathy can be caused by Sjogren's syndrome, sarcoidosis, or celiac disease.