

Intraepidermal Nerve Fiber Density Analysis

TO ASSESS THE EXTENT OF SMALL-CALIBER SENSORY FIBER PATHOLOGY IN PATIENTS WITH PERIPHERAL NEUROPATHIES

Test Highlights

This test qualitatively and quantitatively assesses unmyelinated intraepidermal nerve fibers from skin punch biopsies.

Clinical Background

- The diagnosis of small-fiber neuropathy may be difficult to confirm with standard electromyographic and nerve conduction studies that mainly measure large nerve fiber function, which are usually normal in this disorder.
- Standard light microscopic analysis of peripheral nerve biopsies, such as sural and peroneal nerve biopsies, do not address pathology of the small unmyelinated nerve fibers.

Pathophysiology

- Although there are many documented causes of small-fiber neuropathy, a specific etiology is unidentified for a majority of clinically encountered cases.
- The most common cause is diabetes mellitus or glucose intolerance.
- Other reported causes include: chronic inflammatory autoimmune diseases, sarcoidosis, inflammatory bowel disease, celiac disease, demyelinating disorders, hereditary and metabolic disorders, amyloidosis, human immunodeficiency virus infection, and toxin exposures.

Indications for Ordering

- To confirm the clinical suspicion that a patient has a sensory neuropathy.
- To use as an indicator of neuropathy progression and/or as a measure of therapeutic response.

Interpretation

- The analysis includes qualitative light microscopic assessment for histopathologic changes and quantitative assessment of nerve fiber density within the epidermis.
- Published normative values are used as standards. Values below or equal to the fifth percentile of that reported for normal populations is considered abnormal and consistent with a diagnosis of peripheral neuropathy.

Limitations

This test is intended to assess the presence of small-caliber sensory fiber pathology only. It is not intended to substitute for peripheral nerve biopsies in cases of suspected neuropathies that involve large myelinated nerve fibers.

Methodology

- Two 3-mm skin punch biopsies from a lower extremity: one obtained from a distal site (such as 10 cm above the lateral malleolus or from the calf) and from a proximal site (such as the lateral thigh); immediately fixed in cold paraformaldehyde-lysine-periodate fixative for 24 hours.
- Thick 50 micron sections are prepared and immunohistochemically stained with anti-PGP9.5 (ubiquitin carboxyl-terminal hydrolase) antibodies.
- Linear intraepidermal nerve fiber density is calculated after counting stained nerve fibers and measuring the length of the sections.

References

1. Holland NR, Crawford TO, Hauer P, et al. Small-fiber sensory neuropathies: Clinical course and neuropathology of idiopathic cases. *Ann Neurol* 1998;44:47-59.
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3. McArthur JC, Stocks EA, Hauer P, et al. Epidermal nerve fiber density: Normative reference range and diagnostic efficiency. *Arch Neurol* 1998;55:1513-1520.
4. Smith AG, Ramachandran P, Tripp S, Singleton JR. Epidermal nerve innervation in impaired glucose tolerance and diabetes-associated neuropathy. *Neurology* 2001;57:1701-1704.

Test Information

For specific collection, transport, and testing information, please call ARUP Client Services at (800) 522-2787.

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Steven Chin, M.D., Ph.D., received his medical degree from New York University School of Medicine and his Ph.D. from New York University, Department of Pharmacology. He performed his residency at Columbia-Presbyterian Medical Center where he also completed a fellowship in Neuropathology. Before coming to the University of Utah, as an associate professor and the director of Neuropathology, he was an assistant professor and pathologist at Columbia University. While at Columbia University, Dr. Chin had numerous neuropathology teaching responsibilities. He was also the associate director of the Columbia University Brain Bank and the Columbia University Alzheimer's Disease Research Center Neuropathology Core. His research has been in the area of neurodegenerative diseases, with a special interest in taupathies.

Dr. Chin currently serves on two grant review panels: The Parkinson Study Group, Scientific Review Committee and the Alzheimer's Association. In the past, he has also participated on the NIH-NIA, Scientific Review Panel. He has published over 50 original research publications and abstracts.

Dr. Chin performs the Intraepidermal Nerve Fiber Density Analysis test for ARUP Clients.