

Practice Parameter: Evaluation of distal symmetric polyneuropathy: Role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review)

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INTRODUCTION

This parameter evaluates the role of autonomic testing, nerve biopsy, and skin biopsy for the assessment of polyneuropathy.

DESCRIPTION OF THE PROCESS

- To develop a guideline, the AAN poses a question, systematically identifies and evaluates all the published evidence on the topic, summarizes the evidence in answer to the clinical question, and makes specific recommendations for care.
- OVID MEDLINE (1966 to March 2007), OVID Excerpta Medica (EMBASE; 1980 to March 2007), and OVID Current Contents (2000 to March 2007) were searched for relevant, fully published, peer-reviewed articles. Panel members and subgroups of committee members also performed manual searches (see guideline for search terms).
- Of 1,045 article abstracts that were obtained, 106 articles were deemed relevant.
- At least three panel members reviewed each potentially relevant article and rated it according to the AAN classification of evidence system. Conclusions and recommendations were made according to the AAN criteria for translating the quality of the evidence to recommendations.
- Boards of the AAN, AANEM, and AAPM&R reviewed and approved the final version of the article.

CLASSIFICATION OF EVIDENCE FOR DIAGNOSTIC ACCURACY

Class I:	A cohort study with prospective data collection of a broad spectrum of persons with the suspected condition, using an acceptable reference standard for case definition. The diagnostic test is objective or performed and interpreted without knowledge of the patient’s clinical status. Study results allow calculation of measures of diagnostic accuracy.
Class II:	A case control study of a broad spectrum of persons with the condition established by an acceptable reference standard compared to a broad spectrum of controls or a cohort study where a broad spectrum of persons with the suspected condition where the data was collected retrospectively. The diagnostic test is objective or performed and interpreted without knowledge of disease status. Study results allow calculation of measures of diagnostic accuracy.
Class III:	A case control study or cohort study where either persons with the condition or controls are of a narrow spectrum. The condition is established by an acceptable reference standard. The reference standard and diagnostic test are objective or performed and interpreted by different observers. Study results allow calculation of measures of diagnostic accuracy.
Class IV:	Studies not meeting Class I, II or III criteria including consensus, expert opinion or a case report.

CLASSIFICATION OF RECOMMENDATIONS

The panel developed practice recommendations on the basis of the data, using the following definitions of strength of evidence:

Level A:	Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*
Level B:	Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)
Level C:	Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)
Level U:	Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

Note that recommendations can be positive or negative.

**In exceptional cases, one convincing Class I study may suffice for an “A” recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is > 2).*

ANALYSIS OF EVIDENCE

Clinical Question 1: What is the usefulness of clinical autonomic testing in the evaluation of polyneuropathy, and which tests have the highest sensitivity and specificity?

Evidence:

- Three studies found heart rate variability testing has high sensitivity and specificity for cardiovagal function.
- Three studies showed baroreflex function testing methods to be highly sensitive and specific but infrequently used.
- Four studies showed the quantitative sudomotor axon reflex test (QSART) can detect distal sudomotor loss with 75% to 90% sensitivity. Five studies found QSART can determine sudomotor abnormalities with relatively high sensitivity; three of these studies showed 75% sensitivity for detection of distal small fiber polyneuropathy.
- Studies show a combination of autonomic reflex-screening tests, such as the composite autonomic scoring scale (CASS), to be more useful than single-modality methods.

Evidence table for autonomic testing

Reference	Year	Target disorder	Predictor	Reference standard	Cases (Controls)	Design	Spectrum (Masked)	Class	Sens (Spec)
17	1992	Distal small fiber neuropathy	QSART, QST, HRV	Neurologic exam and EDx	40 (129)	Retrospective review	N (N)	III	80% (72%)
6	1992	Diabetic PN	QAE	EDx	380 (357*)	Concurrent comparative	B (Unmasked/Independent)	II	QAE: 97% (>90%)
7	1997	PN, Parkinson, multisystem atrophy	QSART	Older scale	18 (557)	Concurrent comparison	B (Unmasked/Independent)	II	>90% (>90%)
18	1999	Peripheral (small fiber) neuropathy	QSART, QST, clinical symptoms	EDx	138 (357*)	Concurrent comparative	B (Unmasked/Independent)	III	QSART: 80%; QST: 67% (93%)
19	2001	Painful neuropathy	QSART, ART, CASS	Clinical evaluation	126 (357*)	Noncomparative	N (N)	III	ART: 93%; QSART: 73% (94%)
9	1993	Diabetic PN	CASS	EDx and standard clinical exam	78 (350)	Concurrent comparative	N (Unmasked/Independent)	II	>90% (>90%)
13	2007	Adrenergic autonomic failure	BRSI	MSNA	84 (29)	Concurrent comparative	B (Unmasked/Independent)	II	86% (>90%)
12	2005	Multisystem atrophy, PN	PRT, CASS	Clinical exam	162 (32)	Concurrent comparative	B (Unmasked/Independent)	II	>90% (>90%)
5	2004	DSFN, PN, DN, IAN	CASS	Neurologic exam	11 (38)	Concurrent comparative	N (Unmasked/Independent)	III	95% (90%)

*QSART = quantitative sudomotor axon reflex testing; QST = quantitative sensory testing; HRV = heart rate variability; EDx = electrodiagnosis; PN = peripheral neuropathy; QAE = quantitative autonomic examination; ART = autonomic reflex testing; CASS = composite autonomic severity score; BRSI = baroreflex sensitivity index; MSNA = muscle sympathetic nerve activity; PRT = blood pressure recovery time; DSFN = distal small fiber neuropathy; DN = diabetic neuropathy; IAN = idiopathic autonomic neuropathy. * Per Dr. Low.*

Clinical Question 2: What is the usefulness of nerve biopsy in determining the etiology of distal symmetric polyneuropathy (DSP)?

Evidence:

- Several studies showed nerve biopsy to be useful in evaluation of related diseases but not in DSP.

Clinical Question 3: What is the usefulness and diagnostic accuracy of skin biopsy in the evaluation of polyneuropathy?

Evidence:

- Nine studies found patients with polyneuropathy had lower intraepidermal nerve fiber (IENF) density than patients without polyneuropathy; the absence of reduced IENF density does not rule out polyneuropathy, but the presence of reduced IENF density raises the likelihood of polyneuropathy.
- Three studies of IENF density testing in clinically suspected small fiber sensory polyneuropathy (SFSN) showed low to moderate sensitivity and high specificity; a fourth study showed relatively high sensitivity and specificity.

CONCLUSIONS

- Autonomic testing is probably useful in documenting autonomic nervous system involvement in polyneuropathy (Class II and Class III). The sensitivity and specificity vary with the particular test. The utilization of the combination of autonomic reflex screening tests in the CASS probably provides the highest sensitivity and specificity for documenting autonomic dysfunction (Class II).
- There is no evidence to support or refute a conclusion regarding the role of nerve biopsy in the evaluation of DSP (Class IV). IENF density assessment using protein-gene-product (PGP) 9.5 immunohistochemistry is a validated, reproducible marker of small fiber sensory pathology. Skin biopsy with IENF density assessment is possibly useful to identify DSP which includes SFSN in symptomatic patients with suspected polyneuropathy (Class III).

RECOMMENDATIONS

- Autonomic testing should be considered in the evaluation of patients with polyneuropathy to document autonomic nervous system involvement (**Level B**).
- Autonomic testing should be considered in the evaluation of patients with suspected autonomic neuropathies (**Level B**) and may be considered in the evaluation of patients with suspected distal SFSN (**Level C**).
- The combination of autonomic screening tests in the CASS should be considered to achieve the highest diagnostic accuracy (**Level B**).
- No recommendations can be made regarding the role of nerve biopsy in determining the etiology of DSP (**Level U**).
- For symptomatic patients with suspected polyneuropathy, skin biopsy may be considered to diagnose the presence of a polyneuropathy, particularly SFSN (**Level C**).

RECOMMENDATIONS FOR FUTURE RESEARCH

- Autonomic testing can with a high degree of accuracy document autonomic system dysfunction in polyneuropathy. This is particularly relevant to small fiber polyneuropathy and the autonomic neuropathies. Research is necessary to determine whether the documentation of autonomic abnormalities is important in modifying the evaluation and treatment of polyneuropathy. Specific tests such as QSART can document small fiber (i.e., sudomotor axon) loss with a high degree of sensitivity, making the test useful to confirm the diagnosis of small fiber polyneuropathy. Since skin biopsy with determination of IENF density can also document small fiber loss, there is a need for studies that compare and correlate the two techniques.
- There are no studies of nerve biopsy in the evaluation of DSP. Although it would be useful to know the outcome of well-designed prospective studies in this area, it is unlikely that such studies will be done.
- Skin biopsy with determination of IENF density is a technique that has come of age for the objective documentation of small fiber loss. This technique provides a unique opportunity for research in different varieties of neuropathy. Further studies are needed to characterize the diagnostic accuracy of skin biopsy in distinguishing patients with suspected polyneuropathy, particularly SFSN, from patients with sensory complaints or pain unrelated to peripheral neuropathy. Prospective studies with appropriate “other disease” controls should be done to assess the sensitivity, specificity, and predictive values of IENF density measurement to identify SFSN in patients with lower extremity pain or sensory complaints. A predetermined independent reference standard for the diagnosis of SFSN should be specifically stated in such studies. A case definition of SFSN should be developed. Investigators need to determine whether this case definition should be based upon clinical criteria, pathologic criteria (e.g., skin biopsy), or a combination of clinical, paraclinical, and pathologic criteria.
- The diagnostic accuracy of morphologic changes (e.g., axonal swellings) in the diagnosis of SFSN vs healthy controls and disease controls needs to be better defined.
- Studies exploring other uses for skin biopsy beyond identification and quantification of DSP and SFSN have been reported and should be further explored. Biopsies of glabrous skin and dermal skin include myelinated nerve fibers, and have been shown to have potential utility in the diagnosis of immune-mediated neuropathies, Charcot-Marie-Tooth, and related diseases. Other studies have employed skin biopsy for detection or monitoring of leprosy, hereditary amyloidosis, vasculitic neuropathy, and Fabry disease. Additional studies are required to determine the usefulness of skin biopsy in the diagnosis and monitoring of these and other varieties of neuropathy.
- Serial IENF density measurements and IENF regenerative capacity are being studied and used as outcome measures in therapeutic trials. Further studies are needed to validate and determine the value of skin biopsy for this purpose.

DISCLOSURE

J.D.E. holds financial interests in Pfizer and has received research support from Wyeth and Pfizer. G.S.G. has received speaker honoraria from Pfizer, GlaxoSmithKline, and Boehringer Ingelheim and served on the IDMC Committee of Ortho-McNeil. He estimates that < 2% of his clinical effort is spent on EMG and EEG. G.F., A.K.A., and K.S. have nothing to disclose. G.T.C estimates that 30% of his clinical effort is spent on EMG. J.A.C. has received speaker honoraria from Athena Diagnostics and estimates that 40% of his clinical effort is spent on EMG/NCS, 10% on autonomic testing, and 10% on botulinum toxin injections. L.J.K. has received speaker honoraria from American Medical Seminars, Cross Country Education, Therapath Laboratories and CME, LLC, and holds equity in Passnet Air Ambulance. He estimates 25% of his clinical effort is spent on NCS/EMG, 4% on skin biopsy for nerve fiber counting, and 8% on autonomic studies, and has received payment for expert testimony in legal proceedings. J.R.L. holds financial interests in Athena Diagnostics and has received research funding from NIH/NEI, NIH/NIDCR, Charcot-Marie-Tooth Association, and the March of Dimes. N.L. serves as a consultant for Talecris Biopharmaceuticals and Quest Diagnostics, receives royalties from Athena Diagnostics, and holds equity and is a partner in Therapath LLC. He is the Medical and Scientific Director for the Neuropathy Association, estimates that <1% of his clinical effort is spent on skin biopsy, and has received research support from Talecris Biotherapeutics. R.A.L. has consulted for Talecris and has received research funding from MDA, Baxter Pharmaceuticals, and CMTA. He estimates that 33% of his clinical effort is spent on electromyography. He has received payment for expert testimony regarding the use of IVIg in CIDP and neuropathic pain after breast reduction. P.A.L. estimates 25% of his clinical effort is spent on autonomic reflex screening. D.H. has received research funding from NIH, Astellas Pharmaceutical Company, and MDA/CMT Association. He estimates that 25% of his clinical effort is spent on EMG and 20% on skin biopsies. J.F.H. holds financial interests in FEMI, Johnson & Johnson, Pfizer, and General Electric. He estimates that 40% of his clinical effort is spent on EMG/NCS. G.L. holds financial interests in GlaxoSmithKline and Formenti-Grunenthal. In addition, he has received research funding from Pfizer, Formenti-Grunenthal, Italian Ministry of Health, and Regione Lombardia. He estimates that 25% of his clinical effort is spent in an outpatient pain center, 25% on out- and inpatient clinical examination, 25% on skin biopsy examination, and 25% on research. R.G.M. holds financial interests in Celgene, Knopp Neurosciences, Medivation, Teva Neuro, Taiji Biomedicals, and Translational Genomics. M.P. serves on the scientific advisory board of GSK, the editorial board of *Journal of the Peripheral Nervous System*, the speakers’ bureau of Pfizer and participated in the Joslin diabetes CME programs. He has received research funding from Astellas Pharma and Mitsubishi Pharma and reads clinical skin biopsies, runs an EMG lab, and cares for patients with peripheral nerve diseases. A.J.S. has received payment for expert testimony in the possible neurotoxic injury of the peripheral nerve.

CONFLICT OF INTEREST STATEMENT

The AAN, AANEM, and AAPM&R are committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN, AANEM, and AAPM&R keep separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN, AANEM, and AAPM&R limit the participation of authors with substantial conflicts of interest. The AAN, AANEM, and AAPM&R forbid commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least three AAN committees, AANEM and AAPM&R committees, a network of neurologists, *Neurology*[®] peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com.

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DISCLAIMER: The diagnosis and evaluation of polyneuropathy is complex. The practice parameter is not intended to replace the clinical judgment of experienced physicians in the evaluation of polyneuropathy. The particular kinds of tests utilized by a physician in the evaluation of polyneuropathy depend upon the specific clinical situation and the informed medical judgment of the treating physician. This statement is provided as an educational service of the AAN, AANEM, and AAPM&R. It is based upon an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific test or procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN, AANEM, and AAPM&R recognize that specific care decisions are the prerogative of the patient and physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.