SPECIAL ARTICLE

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

Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation

J.D. England, MD
G.S. Gronseth, MD, FAAN
G. Franklin, MD
G.T. Carter, MD
L.J. Kinsella, MD
J.A. Cohen, MD
A.K. Asbury, MD
K. Szigeti, MD, PhD
J.R. Lupski, MD, PhD
N. Latov, MD
R.A. Lewis, MD
P.A. Low, MD
M.A. Fisher, MD
D.N. Herrmann, MD
J.F. Howard, Jr., MD
G. Lauria, MD
R.G. Miller, MD
M. Polydefkis, MD, MHS
A.J. Sumner, MD

Address correspondence and reprint requests to the American Academy of Neurology, 1080 Montreal Avenue, St. Paul, MN 55116
guidelines@aan.com

ABSTRACT

Background: Distal symmetric polyneuropathy (DSP) is the most common variety of neuropathy. Since the evaluation of this disorder is not standardized, the available literature was reviewed to provide evidence-based guidelines regarding the role of autonomic testing, nerve biopsy, and skin biopsy for the assessment of polyneuropathy.

Methods: A literature review using MEDLINE, EMBASE, and Current Contents was performed to identify the best evidence regarding the evaluation of polyneuropathy published between 1980 and March 2007. Articles were classified according to a four-tiered level of evidence scheme and recommendations were based upon the level of evidence.

Results and Recommendations: 1) Autonomic testing should be considered in the evaluation of patients with polyneuropathy to document autonomic nervous system dysfunction (Level B). Such testing should be considered especially for the evaluation of suspected autonomic neuropathy (Level B) and distal small fiber sensory polyneuropathy (SFSN) (Level C). A battery of validated tests is recommended to achieve the highest diagnostic accuracy (Level B). 2) Nerve biopsy is generally accepted as useful in the evaluation of certain neuropathies as in patients with suspected amyloid neuropathy, mononeuropathy multiplex due to vasculitis, or with atypical forms of chronic inflammatory demyelinating polyneuropathy (CIDP). However, the literature is insufficient to provide a recommendation regarding when a nerve biopsy may be useful in the evaluation of DSP (Level U). 3) Skin biopsy is a validated technique for determining intraepidermal nerve fiber density and may be considered for the diagnosis of DSP, particularly SFSN (Level C). There is a need for additional prospective studies to define more exact guidelines for the evaluation of polyneuropathy. *Neurology*® 2009;72:177–184

GLOSSARY

AAN = American Academy of Neurology; **AANEM** = American Academy of Neuromuscular and Electrodiagnostic Medicine; **AAPM&R** = American Academy of Physical Medicine and Rehabilitation; **ART** = autonomic reflex testing; **BRSI** = baroreflex sensitivity index; **CASS** = composite autonomic scoring scale; **CIDP** = chronic inflammatory demyelinating polyneuropathy; **DSFN** = distal small fiber neuropathy; **DSP** = distal symmetric polyneuropathy; **EDx** = electrodiagnosis; **EFNS** = European Federation of Neurological Societies; **HRV** = heart rate variability; **IAN** = idiopathic autonomic neuropathy; **IENF** = intraepidermal nerve fibers; **MSNA** = muscle sympathetic nerve activity; **NCSs** = nerve conduction studies; **PGP 9.5** = protein-gene-product 9.5; **PN** = peripheral neuropathy; **PRT** = blood pressure recovery time; **QAE** = quantitative autonomic examination; **QSART** = quantitative sudomotor axon reflex test; **QSS** = Quality Standards Subcommittee; **QST** = quantitative sensory testing; **SFSN** = small fiber sensory polyneuropathy; **TST** = thermoregulatory sweat testing.

Polyneuropathy is a relatively common neurologic disorder.[1] The overall prevalence is approximately 2,400 (2.4%) per 100,000 population, but in individuals older than 55 years, the prevalence rises to approximately 8,000 (8%) per 100,000.[2,3] Since there are many etiologies of polyneuropathy, a logical clinical approach is needed for evaluation and management.

This practice parameter provides recommendations for the evaluation of distal symmetric polyneu-

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Authors' affiliations are listed at the end of the article.

The AAN Mission Statement, Classification of evidence, Classification of recommendations, and Conflict of Interest Statement (appendices e-1 through e-4), as well as references e1–e16, are available as supplemental data on the *Neurology*® Web site at www.neurology.org.

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Disclosure: Author disclosures are provided at the end of the article.

ropathy (DSP) based upon a prescribed review and analysis of the peer-reviewed literature. The parameter was developed to provide physicians with evidence-based guidelines regarding the role of autonomic testing, nerve biopsy, and skin biopsy for the assessment of polyneuropathy. The diagnosis of DSP should be based upon a combination of clinical symptoms, signs, and electrodiagnostic criteria as outlined in the previous case definition.[1] See Mission statement (appendix e-1 on the *Neurology*® Web site at www.neurology.org) for details.

FORMATION OF EXPERT PANEL The Polyneuropathy Task Force included 19 physicians with representatives from the American Academy of Neurology (AAN), the American Academy of Neuromuscular and Electrodiagnostic Medicine (AANEM), and the American Academy of Physical Medicine and Rehabilitation (AAPM&R). All of the task force members had extensive experience and expertise in the area of polyneuropathy. Additionally, four members had expertise in evidence-based methodology and practice parameter development. Two are current members (J.D.E., G.F.), and two are former members (G.S.G, R.G.M.) of the Quality Standards Subcommittee (QSS) of the AAN. The task force developed a set of clinical questions relevant to the evaluation of DSP, and subcommittees were formed to address each of these questions.

DESCRIPTION OF THE ANALYTIC PROCESS The literature search included OVID MEDLINE (1966 to March 2007), OVID Excerpta Medica (EMBASE; 1980 to March 2007), and OVID Current Contents (2000 to March 2007). The search included articles on humans only and in all languages. The search terms selected were peripheral neuropathy, polyneuropathy, and distal symmetric polyneuropathy. These terms were cross-referenced with the terms diagnosis, electrophysiology, autonomic testing, nerve biopsy, and skin biopsy.

Panel experts were asked to identify additional articles missed by the initial search strategy. Further, the bibliographies of the selected articles were reviewed for potentially relevant articles.

Subgroups of committee members reviewed the titles and abstracts of citations identified from the original searches and selected those that were potentially relevant to the evaluation of polyneuropathy. Articles deemed potentially relevant by any panel member were also obtained.

Each potentially relevant article was subsequently reviewed in entirety by at least three panel members. Each reviewer graded the risk of bias in each article by using the diagnostic test classification-of-evidence scheme (appendix e-2). In this scheme, articles attaining a grade of Class I are judged to have the lowest risk of bias, and articles attaining a grade of Class IV are judged to have the highest risk of bias. Disagreements among reviewers regarding an article's grade were resolved through discussion. Final approval was determined by the entire panel. The AAN's method for determining the strength of recommendation was used (appendix e-3).

The QSS (AAN; appendix 1), the Practice Issues Review Panel (AANEM; appendix 2), and the Practice Guidelines Committee (AAPM&R; appendix 3) reviewed and approved a draft of the article. The draft was next sent to members of the AAN, AANEM, and AAPM&R for further review and then to *Neurology*® for peer review. Boards of the AAN, AANEM, and AAPM&R reviewed and approved the final version of the article. At each step of the review process, external reviewers' suggestions were explicitly considered. When appropriate, the expert panel made changes to the document.

ANALYSIS OF EVIDENCE The search yielded 1,045 references with abstracts. After reviewing titles and abstracts, 106 articles were reviewed and classified.

Role of clinical autonomic testing in the evaluation of polyneuropathy. Autonomic nervous system dysfunction occurs in several phenotypes. It may occur as one component of a generalized polyneuropathy such as DSP of diabetes. Such polyneuropathies are usually diagnosed by a combination of neuropathic symptoms, decreased or absent ankle reflexes, decreased distal sensation, distal muscle weakness or atrophy, and abnormal nerve conduction studies (NCSs).[1] The majority of these features constitute evidence of "large fiber" sensory and motor involvement. However, signs of autonomic nervous system involvement may also constitute findings indicative of DSP. In DSP with autonomic involvement, the most common clinical findings are abnormalities of sweating and circulatory instability in the feet.[1,3]

A second phenotype is that of an autonomic neuropathy such as in amyloidosis and autoimmune autonomic neuropathy, where autonomic nerves are affected disproportionately relative to somatic nerves.[4] In these neuropathies, autonomic fibers can be affected in isolation and their involvement may precede somatic fiber involvement.[5]

A third relatively common phenotype is distal small fiber sensory polyneuropathy (SFSN), which can manifest as burning pain affecting the feet, often with allodynia and sometimes with erythromelalgia (red hot and painful skin). Involvement of autonomic and somatic C fibers usually occurs concurrently in small fiber polyneuropathy.[5]

Table 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* (per Dr. Low)	Concurrent comparative	B	Unmasked/ independent	III	QSART: 80%; QST: 67%	93%
19	2001	Painful neuropathy	QSART, ART, CASS	Clinical evaluation	126	357* (per Dr. Low)	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.

What is the usefulness of clinical autonomic testing in the evaluation of polyneuropathy, and which tests have the highest sensitivity and specificity? Currently available autonomic tests can provide indices of cardiovagal, adrenergic, and postganglionic sudomotor function. As such, they provide indices for both parasympathetic and sympathetic autonomic function. Heart rate variability testing is a simple and reliable test of cardiovagal function. It detects the presence of diabetic polyneuropathy with nearly the same sensitivity as NCSs (Class II).[6] Specificity is high (97.5%) for identifying parasympathetic deficits if the recommended age-controlled values are used (Class II).[7] Intrinsic cardiac disease can affect the results of this test, and this possibility must be considered in the interpretation.

Cardiovagal function can be evaluated using different indices in the time and frequency domains.[8] There is no compelling evidence that one method is better than another or that the use of multiple indices confers any advantage. Heart rate variability to deep breathing is the most widely used test of cardiovagal function and has a specificity of approximately 80% (Class II).[9]

The vagal component of the baroreflex can be evaluated by quantitating the heart period response to induced changes in BP. A well-studied test is the modified Oxford method.[10] The test consists of an evaluation of heart period responses to induced increases and decreases in arterial BP. The increase is evoked by IV phenylephrine and decrease by nitroprusside in incremental doses. Baroreflex sensitivity is defined by the slope of the heart period to BP relationship. Linearity is required ($R > 0.85$). The advantage of this test is that it evaluates vagal baroreflex sensitivity; however, the disadvantage is that the test is invasive and not widely performed. Approximation of this method is possible by relating heart period alterations to changes in BP induced by the Valsalva maneuver.[11] The sensitivity and specificity of invasive and noninvasive tests of baroreflex function are high, but these tests are not generally used in the study of neuropathy since their value is considered only additive to current tests of cardiovagal function (Class II).[4,9,12,13]

Thermoregulatory sweat testing (TST) is a sensitive test of sudomotor function that utilizes an indicator substance whose color changes upon exposure to sweat.[14,15] The test results can be semiquantitated by estimating the percentage of skin surface that is anhidrotic. Since the test is tedious, messy, and time-consuming, it is not routinely done. Additionally, TST is not able to distinguish between postganglionic, preganglionic, and central lesions.[14,15] The most quantitative test of sudomotor function is the

quantitative sudomotor axon reflex test (QSART).[16] QSART is mediated by impulses traveling antidromically then orthodromically along the postganglionic sympathetic sudomotor axon. QSART can detect distal sudomotor loss with a sensitivity of 75–90% (Class III).[7,17-19] Several studies have demonstrated that QSART can determine sudomotor abnormalities with relatively high sensitivity and specificity in many types of polyneuropathies (Class II and III).[4-7,16,17,19-21] In three Class III studies, QSART was shown capable of detecting distal small fiber polyneuropathy with a sensitivity of >75%.[17-19]

Skin vasomotor reflexes assessed by monitoring skin blood flow using laser Doppler flowmeter have not been well studied. Limited data from one Class III study using this technique demonstrated an unacceptably large coefficient of variation.[22]

Analysis of the available Class II and III studies on autonomic testing indicates that a combination of autonomic reflex screening tests provides distinct advantages over single modality methods (table). The composite autonomic scoring scale (CASS), which includes QSART, orthostatic blood pressure, heart rate response to tilt, heart rate response to deep breathing, the Valsalva ratio, and beat-to-beat blood pressure measurements during phases II and IV of the Valsalva maneuver, tilt, and deep breathing, provides a useful 10-point scale of autonomic function (Class II).[4,9] In a study of 78 patients with graded autonomic failure obtained by selecting approximately equal numbers of patients with multiple system atrophy, Parkinson disease, autonomic neuropathies, and idiopathic peripheral neuropathies, this combination of tests provided a noninvasive, sensitive, specific, and reproducible methodology for grading the degree of autonomic dysfunction (Class II).[9]

Conclusions. Autonomic testing is probably useful in documenting autonomic nervous system involvement in polyneuropathy (Class II and 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).

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).

Role of nerve biopsy in the evaluation of polyneuropathy. Nerve biopsy is generally accepted as useful in the diagnosis of inflammatory diseases of nerve such as vasculitis, sarcoidosis, CIDP, infectious diseases such as leprosy, or infiltrative disorders such as tumor or amyloidosis.[3] Nerve biopsy is most valuable in mononeuropathy multiplex or suspected vasculitic neuropathy. There are no studies regarding the role of nerve biopsy in the evaluation of DSP although on occasion the above noted diseases may present in that fashion.

What is the usefulness of nerve biopsy in determining the etiology of distal symmetric polyneuropathy? Out of 50 articles judged to be relevant, no article attained a grade greater than Class IV. Most of the articles discussed the nerve biopsy findings in specific diseases, the clinical suspicion of which had prompted the biopsy.[23-34] No article provided guidance regarding when to perform a nerve biopsy in the evaluation of DSP.

Conclusions. There is no evidence to support or refute a conclusion regarding the role of nerve biopsy in the evaluation of DSP (Class IV).

Recommendations. No recommendations can be made regarding the role of nerve biopsy in determining the etiology of DSP (Level U).

Role of skin biopsy in the evaluation of polyneuropathy. Skin biopsy is being increasingly used to evaluate patients with polyneuropathy. The most common technique involves a 3 mm punch biopsy of skin from the leg. After sectioning by microtome, the tissue is immunostained with anti-protein-gene-product 9.5 (PGP 9.5) antibodies and examined with immunohistochemical or immunofluorescent methods. This staining allows for the identification and counting of intraepidermal nerve fibers (IENF). PGP 9.5 immunohistochemistry has been validated as a reliable method for IENF density determination with good intra- and interobserver reliability in normal controls and patients with DSP.[35-38]

In March 2005, the European Federation of Neurological Societies (EFNS) published a guideline on the use of skin biopsy in peripheral neuropathy.[35] This comprehensive review focused on the technical aspects of skin biopsy as well as normative data and correlations with other clinical, physiologic, and pathologic tools. The EFNS concluded that skin biopsy is a safe, validated, and reliable technique for the determination of IENF density. The major conclusion was that skin biopsy (IENF density) was diagnostically efficient at distinguishing polyneuropathy patients (including small fiber neuropathy) from normal controls. The EFNS guideline also reviewed

the literature on IENF morphologic changes such as axonal swellings as a measure of distal symmetric polyneuropathy.[35,39,40] The EFNS concluded that axonal swellings may be predictive of progression of polyneuropathy but further studies were needed to determine their diagnostic accuracy.[35]

What is the usefulness and diagnostic accuracy of skin biopsy in the evaluation of polyneuropathy? Beyond distinguishing asymptomatic normal controls from polyneuropathy patients, one clinical question not addressed by the EFNS guideline was the diagnostic accuracy of skin biopsy in distinguishing symptomatic patients with polyneuropathy from symptomatic patients without polyneuropathy. For example, in patients with painful feet, would skin biopsy accurately distinguish patients with polyneuropathy from patients with other conditions causing painful feet?

To address this separate question, a subgroup of the Polyneuropathy Task Force (J.D.E., R.A.L., D.H., G.L., M.P., and G.S.G.) independently reviewed the literature regarding the diagnostic accuracy of skin biopsy in DSP and in the SFSN form of DSP. To be considered for review, studies needed to determine IENF density in patients with and without polyneuropathy. Furthermore, the data from studies had to be presented in such a way as to allow calculation of the sensitivity and specificity of skin biopsy for polyneuropathy.

Nine studies met inclusion criteria.[36,39–40,e1-e6] One was a prospective cohort survey of patients presenting with bilateral painful feet and normal strength, but skin biopsy was done only in those with normal NCS.[e1] Patients with reduced IENF density and normal NCS were assumed to have painful small fiber neuropathies. However, the study did not compare the results of the IENF density to an independent reference standard to confirm the presence of small fiber neuropathy. Thus, for the purposes of determining the diagnostic accuracy of skin biopsy for polyneuropathy, this study was graded Class IV.

The remaining studies employed a case-control design.[36,39,40,e2-e6] In these studies, the investigators performed skin biopsies on patients with established polyneuropathy and normal controls. No study included patients with conditions causing lower extremity pain or sensory complaints that might be confused with polyneuropathy. Thus, all studies had potential spectrum bias. Following the evidence classification scheme for studies of diagnostic accuracy, all of these studies were graded Class III.

All of the case control studies showed a significant reduction in IENF density in polyneuropathy patients as compared to controls.[36,39,40,e2-e6] The sensitivity of decreased IENF density for the diagnosis of polyneuropathy was moderate to good (range 45 to 90%). The specificity of normal IENF density for the absence of polyneuropathy was very good (range 95 to 97%). Thus, the absence of reduced IENF density (using the clinical impression as the diagnostic reference standard) would not "rule out" polyneuropathy, but the presence of reduced IENF density would importantly raise the likelihood of polyneuropathy.

The form of DSP for which IENF assessment is particularly diagnostically attractive is SFSN for the following reasons: 1) IENF are the nerve terminals of somatic unmyelinated C fibers, which are hypothesized to be predominantly affected in SFSN. 2) There has been a lack of a direct objective measure of small fiber sensory nerves since objective measures of large fiber function (e.g., NCS) are by most definitions normal in SFSN.[e7] 3) Patients in whom SFSN is clinically suspected manifest with symptoms of small fiber sensory dysfunction (e.g., tingling, numbness, and neuropathic pain) but few objective signs, making it difficult to diagnose and to distinguish SFSN from non-neurologic causes of sensory complaints.[e7]

Since no validated objective gold standard exists for the diagnosis of SFSN, the authors considered whether demonstration of a pathologic lesion (small sensory fiber pathology on skin biopsy) should be the de facto diagnostic standard or whether a clinical impression of SFSN should be the independent reference standard. For the purposes of this parameter, a clinical impression of SFSN was adopted as the independent reference standard for calculation of sensitivity and specificity of IENF density in the detection of SFSN.

In order to assess the diagnostic accuracy of IENF density assessment for SFSN, the literature was surveyed for studies assessing IENF density in subjects with clinically suspected SFSN (symptoms or symptoms and signs of DSP but with normal NCS) and controls where the diagnostic accuracy of IENF density for clinically defined SFSN could be determined. Four Class III studies met these criteria.[e6,e8-e10] The sensitivity of IENF density assessment at the ankle for DSP with normal NCS was 58% (20% for subjects with symptoms but no signs of SFSN; 100% for subjects with symptoms and signs of SFSN),[e8] 90%,[e6] and 24%.[e9] In these studies, the specificity of the test ranged from 95% to 97.5%.[e6,e8,e9] The other case control study found that among patients with symptoms of SFSN and an abnormal pinprick examination in the feet, but normal ankle reflexes, normal vibration sensibility, and normal NCS, an IENF density of <8 fibers/mm at the dorsal foot provided a sensitivity of 88%, a specificity of 91%, a positive predictive value of 0.9, and a negative predictive value of 0.83 for the diagnosis of SFSN.[e10]

Conclusions. IENF density assessment using PGP 9.5 immunohistochemistry is a validated, reproduc-

ible 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. 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

This comprehensive review reveals several weaknesses in the current approach to the evaluation of polyneuropathy and highlights opportunities for research.

- Autonomic testing. 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.
- Nerve biopsy. 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. 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.[e2] Other studies have employed skin biopsy for detection or monitoring of leprosy, hereditary amyloidosis, vasculitic neuropathy, and Fabry disease.[e11-e14] 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.[e15,e16] Further studies are needed to validate and determine the value of skin biopsy for this purpose.

AUTHORS' AFFILIATIONS

From the Louisiana State University Health Sciences Center (J.D.E., A.J.S.), New Orleans; University of Kansas (G.S.G.), Kansas City; University of Washington (G.F.), Seattle; Providence Health System (G.T.C.), Southwest Washington; St. Louis University School of Medicine (L.J.K.), St. Louis, MO; Dartmouth Hitchcock Medical Center (J.A.C.), Lebanon, NH; University of Pennsylvania School of Medicine (A.K.A.), Philadelphia; Baylor College of Medicine (K.S., J.R.L.), Houston, TX; Weill Medical College of Cornell (N.L.), New York, NY; Wayne State University School of Medicine (R.A.L.), Detroit, MI; Mayo Clinic (P.A.L.), Rochester, MN; Loyola University Chicago Stritch School of Medicine and the Hines VAH (M.A.F.), IL; University of Rochester Medical Center (D.H.), NY; University of North Carolina (J.F.H.), Chapel Hill; Fondazione IRCCS National Neurological Institute "Carlo Besta" (G.L.), Milan, Italy; California Pacific Medical Center (R.G.M.), San Francisco; and Johns Hopkins Medical Institutions (M.P.), Baltimore, MD.

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.

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.

APPENDIX 1

Quality Standards Subcommittee (AAN): Jacqueline French, MD, FAAN (chair); Charles E. Argoff, MD; Eric Ashman, MD; Stephen Ashwal, MD, FAAN (ex-officio); Christopher Bever, Jr., MD, MBA, FAAN; John D. England, MD, FAAN (QSS facilitator); Gary M. Franklin, MD, MPH, FAAN (ex-officio); Deborah Hirtz, MD (ex-officio); Robert G. Holloway, MD, MPH, FAAN; Donald J. Iverson, MD, FAAN; Steven R. Messé, MD; Leslie A. Morrison, MD; Pushpa Narayanaswami, MD, MBBS; James C. Stevens, MD, FAAN (ex-officio); David J. Thurman, MD, MPH (ex-officio); Dean M. Wingerchuk, MD, MSc, FRCP(C); and Theresa A. Zesiewicz, MD, FAAN.

APPENDIX 2

Practice Issues Review Panel (AANEM): Yuen T. So, MD, PhD (chair); Michael T. Andary, MD; Atul Patel, MD; Carmel Armon, MD; David del Toro, MD; Earl J. Craig, MD; James F. Howard, Jr, MD; Joseph V. Campellone Jr., MD; Kenneth James Gaines, MD; Robert Werner, MD; and Richard Dubinsky, MD.

APPENDIX 3

Practice Guidelines Committee (AAPM&R): Dexanne B. Clohan, MD (chair); William L. Bockenek, MD; Lynn Gerber, MD; Edwin Hanada, MD; Ariz R. Mehta, MD; Frank J. Salvi, MD, MS; and Richard D. Zorowitz, MD.

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