SPECIAL ARTICLE

Practice Parameter: Evaluation of distal symmetric polyneuropathy: Role of laboratory and genetic testing (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

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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 laboratory and genetic tests for the assessment of DSP.

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) Screening laboratory tests may be considered for all patients with polyneuropathy (Level C). Those tests that provide the highest yield of abnormality are blood glucose, serum B12 with metabolites (methylmalonic acid with or without homocysteine), and serum protein immunofixation electrophoresis (Level C). If there is no definite evidence of diabetes mellitus by routine testing of blood glucose, testing for impaired glucose tolerance may be considered in distal symmetric sensory polyneuropathy (Level C). 2) Genetic testing should be conducted for the accurate diagnosis and classification of hereditary neuropathies (Level A). Genetic testing may be considered in patients with cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype (Level C). Initial genetic testing should be guided by the clinical phenotype, inheritance pattern, and electrodiagnostic features and should focus on the most common abnormalities which are CMT1A duplication/HNPP deletion, Cx32 (GJB1), and MFN2 mutation screening. There is insufficient evidence to determine the usefulness of routine genetic testing in patients with cryptogenic polyneuropathy who do not exhibit a hereditary neuropathy phenotype (Level U). *Neurology*® 2009;72:185–192

GLOSSARY

AAN = American Academy of Neurology; **AANEM** = American Academy of Neuromuscular and Electrodiagnostic Medicine; **AAPM&R** = American Academy of Physical Medicine and Rehabilitation; **CMT** = Charcot-Marie-Tooth; **DSP** = distal symmetric polyneuropathy; **EDX** = electrodiagnostic; **GTT** = glucose tolerance testing; **IFE** = immunofixation electrophoresis; **QSS** = Quality Standards Subcommittee; **SPEP** = serum protein electrophoresis.

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 role of laboratory and genetic tests in the evaluation of distal symmetric polyneuropathy (DSP) based upon a prescribed review and analysis of

Supplemental data at www.neurology.org

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The AAN Mission Statement, Classification of evidence, Classification of recommendations, and Conflict of Interest Statement (appendices e-1 through e-4), as well as tables e-1, e-2, and e-3, 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.

the peer-reviewed literature. The parameter was developed to provide physicians with evidence-based guidelines regarding the role of laboratory and genetic tests 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 laboratory test, diagnosis, electrophysiology, and genetic testing.

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 4,500 references with abstracts. After reviewing titles and abstracts, 450 articles were reviewed and classified.

Role of laboratory testing in the evaluation of polyneuropathy. With the exception of electrodiagnostic (EDX) studies, laboratory tests are not utilized to diagnose polyneuropathy; however, laboratory tests are routinely utilized in patients with a diagnosis of polyneuropathy as a screening test for specific etiologies. Several questions regarding the use of laboratory testing as a screening tool in the evaluation of polyneuropathy were assessed.

What is the yield of screening laboratory tests in the evaluation of DSP, and which tests should be performed? The cause of most polyneuropathies is evident when the information obtained from the medical history, neurologic examination, and EDX studies are combined with simple screening laboratory tests. Such a comprehensive investigation yields an etiologic diagnosis in 74 to 82% of patients with polyneuropathy.[4-13] Laboratory test results must be interpreted in the context of other clinical information since the etiologic yield of laboratory testing alone is limited by the low specificity of many of the tests. For example, one study of idiopathic polyneuropathy found that laboratory tests alone had only a 37% diagnostic yield (Class III).[6] In another study, laboratory abnormalities were documented in 58% of 91 patients with chronic cryptogenic polyneuropathy, but only 9% were etiologically diagnostic (Class III).[10] The majority of studies indicated that screening laboratory tests comprised of a complete blood count, erythrocyte sedimentation rate, comprehensive metabolic panel (blood glucose, renal function, liver function), thyroid function tests, serum B12, and serum protein immunofixation electrophoresis are indicated for most patients with polyneuropathy.[4-13] Five Class III studies indicated that the highest yield of abnormality was seen with screening for blood glucose,

serum B12, and serum protein immunofixation electrophoresis.[4,6,10,13,14] The test with the highest yield was the blood glucose, consistent with the well-known fact that diabetes mellitus is the most common cause of DSP. In patients with DSP, blood glucose was elevated in approximately 11%, serum protein electrophoresis or immunofixation was abnormal in 9%, and serum B12 was low in approximately 3.6%. Two Class III studies showed that routine CSF analysis had a low diagnostic yield except in demyelinating polyneuropathies, which usually showed an increased CSF protein level.[5,8]

Vitamin B12 deficiency was relatively frequent in patients with polyneuropathy, and the yield was greater when the metabolites of cobalamin (methylmalonic acid and homocysteine) were tested (Class II and III).[4,14-17] Serum methylmalonic acid and homocysteine were elevated in 5–10% of patients whose serum B12 levels were in the low normal range of 200–500 pg/dL.[16,17] In large series of patients with polyneuropathy, between 2.2 and 8% of patients had evidence of B12 deficiency as indicated by elevations of these metabolites.[4,14] In one Class III study involving 27 patients with polyneuropathy and B12 deficiency, 12 (44%) had B12 deficiency based upon the finding of abnormal metabolites alone.[14] Thus, serum B12 assays with metabolites (methylmalonic acid and homocysteine) are useful in documenting B12 deficiency.

Although both methylmalonic acid and homocysteine are sensitive for B12 deficiency, methylmalonic acid is more specific. In a large Class III study involving 434 patients with vitamin B12 deficiency, serum methylmalonic acid was elevated in 98.4% and serum homocysteine was elevated in 95.9%.[17] In the same study, serum methylmalonic acid was elevated in 12.2%, but serum homocysteine was elevated in 91% of 123 patients with isolated folate deficiency.[17] Homocysteine may also be elevated in pyridoxine deficiency and heterozygous homocystinemia. Both homocysteine and methylmalonic acid may be elevated in hypothyroidism, renal insufficiency, and hypovolemia.

Several studies highlight the relatively high prevalence of prediabetes (impaired glucose tolerance) in patients with DSP who do not fulfill the criteria for definite diabetes mellitus (Class III).[18-20] In these studies, glucose tolerance testing (GTT) was performed in patients with idiopathic DSP. Impaired glucose tolerance was documented in 25–36% of patients compared to approximately 15% of controls. Additionally, patients with painful sensory polyneuropathies were more likely to have impaired glucose tolerance than those with painless sensory polyneuropathies. Only one major study has not found an increased prevalence of impaired glucose tolerance in chronic idiopathic axonal polyneuropathy (Class III).[21]

Monoclonal gammopathies are more common in patients with polyneuropathy than in the normal population. IgM monoclonal gammopathies may be associated with autoantibody activity, type I or II cryoglobulinemia, macroglobulinemia, or chronic lymphocytic leukemia. IgG or IgA monoclonal gammopathies may be associated with myeloma, POEMS syndrome, primary amyloidosis, or chronic inflammatory conditions. In one Class III study of 279 consecutive patients with polyneuropathy of otherwise unknown etiology seen at a referral center, 10% had monoclonal gammopathy, a significant increase over that reported in community studies.[22] Serum protein immunofixation electrophoresis (IFE) is more sensitive than serum protein electrophoresis (SPEP), especially for detecting small or nonmalignant monoclonal gammopathies. Ten of 58 (17%) monoclonal gammopathies, including 10 of 36 (30%) with IgM <5 g/L, were identified by IFE but not by SPEP.[23]

Conclusions. Screening laboratory tests are possibly useful in determining the cause of DSP, but the yield varies depending upon the particular test (Class III). The tests with the highest yield of abnormality are blood glucose, serum B12 with metabolites (methylmalonic acid with or without homocysteine), and serum protein immunofixation electrophoresis (Class III). Patients with distal symmetric sensory polyneuropathy have a relatively high prevalence of diabetes or prediabetes (impaired glucose tolerance), which can be documented by blood glucose or GTT (Class III).

Recommendations. Screening laboratory tests may be considered for all patients with DSP (Level C). Although routine screening with a panel of basic tests is often performed (table e-1), those tests with the highest yield of abnormality are blood glucose, serum B12 with metabolites (methylmalonic acid with or without homocysteine), and serum protein immunofixation electrophoresis (Level C). When routine blood glucose testing is not clearly abnormal, other tests for prediabetes (impaired glucose tolerance) such as a GTT may be considered in patients with distal symmetric sensory polyneuropathy, especially if it is accompanied by pain (Level C).

Although there are no control studies (Level U) regarding when to recommend the use of other specific laboratory tests, clinical judgment correlated with the clinical picture will determine which additional laboratory investigations (table e-2) are necessary.

Role of genetic testing in the evaluation of polyneuropathy. Hereditary neuropathies are an important subtype of polyneuropathy with a prevalence of approximately 1:2,500 people. DSP is the predominant phenotype, but phenotypic heterogeneity may be present even within the same family; therefore, when

Table 1 Evidence table for genetic testing

Reference	Data collection	Setting*	Sampling	Completeness gene dependent	Masking	Class
26	Prospective	Referral center	NA	PMP22 dup	Waived	II
27	Prospective	Referral center	Consecutive	PMP22 dup	Waived	II
28	Prospective	Referral center	Consecutive	PMP22 mut, Cx32, MPZ	Waived	I
29	Prospective	Referral center	Consecutive	PMP22 dup, del, mut, Cx32, MPZ	Waived	I
30	Prospective	Referral center	Consecutive	PMP22 dup, del, Cx32	Waived	II
31	Prospective	NA	NA	PMP22 dup	Waived	III
32	Prospective	Referral center	Consecutive	PMP22 dup, del	Waived	I
33	Prospective	Referral center	Consecutive	PMP22 dup, mut, Cx32, MPZ	Waived	II
34	Prospective	Referral center	Consecutive	PMP22 dup, del, mut, Cx32, MPZ	Waived	II
35	Prospective	Referral center	Consecutive	PMP22 dup, mut, Cx32, MPZ	Waived	I
24	Prospective	Referral center	Consecutive	PMP22 dup, mut, Cx32, MPZ	Waived	I
36	Prospective	Referral center	Consecutive	PMP22 dup, mut, Cx32, MPZ	Waived	I
37	Prospective	Referral center	Selected	MFN2	Waived	II

*Referral center for test, not for patient; patients come from general neurology clinics.

genetic testing is contemplated all neuropathy phenotypes need to be considered. In the evaluation of polyneuropathy, a comprehensive family history should always be elicited. A high index of suspicion for a hereditary neuropathy phenotype is essential. Since molecular diagnostic techniques are available, guidelines for their usefulness in the evaluation of polyneuropathy are needed.

The majority of genetically determined polyneuropathies are variants of Charcot-Marie-Tooth (CMT) disease, and genetic testing is available for an increasing number of these neuropathies. The clinical phenotype of CMT is extremely variable, ranging from a severe polyneuropathy with respiratory failure through the classic picture with pes cavus and "stork legs" to minimal neurologic findings.[24,25] Since a substantial proportion of CMT patients have de novo mutations, a family history of neuropathy may be lacking.[24-26] Additionally, different genetic mutations can cause a similar phenotype (genetic heterogeneity) and different phenotypes can result from the same genotype (phenotypic heterogeneity).

How accurate is genetic testing for identifying patients with genetically determined neuropathies? The CMT phenotype has been linked to 36 loci and mutations have been identified in 28 different genes, several of which can be identified by commercially available genetic testing. Previous segregation studies followed by several prospective cohort studies have documented that the results of currently available genetic testing are unequivocal for diagnosis of established pathogenic mutations, providing a specificity of 100% (i.e., no false positives) and high sensitivity (Class I and II).[27-36] The interpretation of novel mutations may require further characterization available in specialized centers. Data from six Class I, six Class II, and one Class III study indicate that genetic testing is useful for the accurate classification of hereditary polyneuropathies.[24,26-37] See table 1 for details.

Which patients with polyneuropathy should be screened for hereditary neuropathies? Genetic studies of hereditary neuropathies have tested the prevalence of various mutations in selected patients with the classic CMT phenotype with and without a family history of polyneuropathy[27,31-36] (Class III evidence for screening). For these patients, the yield of genetic tests has been relatively high.

Data from seven studies indicate that the demyelinating form of Charcot-Marie-Tooth (CMT1) is the most prevalent, and about 70% of these patients have a duplication of *PMP22* gene (CMT1A).[27,31-36] CMT1A is also the most common variety of sporadic CMT1, accounting for 76–90% of cases.[26,32] Six studies showed that when the test for CMT1A duplication is restricted to patients with clinically probable CMT1 (i.e., autosomal dominant, primary demyelinating polyneuropathy), the yield is 54–80% as compared to testing a cohort of patients suspected of having any variety of hereditary peripheral neuropathy where the yield is only 25–59% (average of 43%).[27,29,30,32,34,36]

Axonal forms of Charcot-Marie-Tooth (CMT2) are most commonly caused by *MFN2* mutations, which account for approximately 33% of the cases.[37] *MFN2* mutations have not occurred in the CMT1 group.

Data from eight studies indicate that *Cx32(GJB1)* mutations cause an X-linked neuropathy (CMTX), which may present with either a predominantly demyelinating or axonal phenotype and account for approximately 12% of all cases of CMT.[27-30,33-36] If the pedigree is uninformative as to whether the inheri-

tance is autosomal dominant or X-linked (lack of father to son transmission), *Cx32(GJB1)* mutation is in the differential diagnosis for both predominantly demyelinating and axonal neuropathies.

Data from seven studies have established average mutation frequencies of 2.5% for *PMP22* point mutations, and 5% for *MPZ* mutations in the CMT population.[27-29,34-36] CMT caused by other genes is much less frequent (figure).

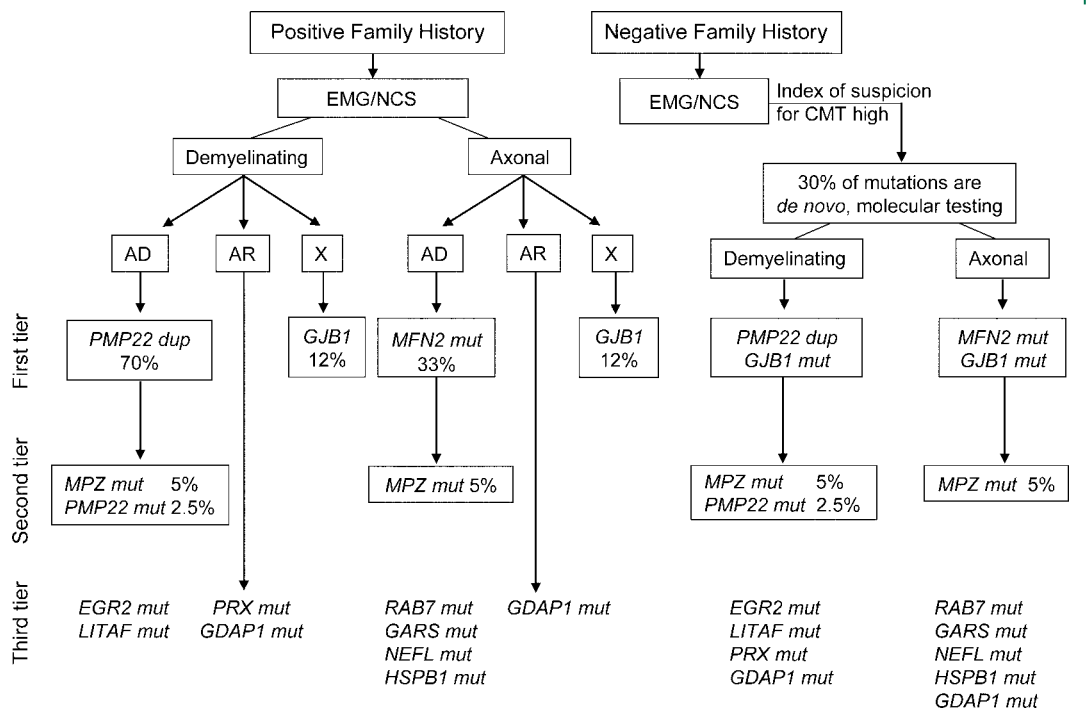
Given the relationships between pattern of inheritance, EDX results, and specific mutations, the efficiency of genetic testing can be improved by following a stepwise evaluation of patients with possible hereditary neuropathy. First, a clinical classification that includes EDX studies should be performed to determine whether the neuropathy is primarily demyelinating or primarily axonal in type. Since EDX studies are sometimes problematic in children, some physicians may opt to proceed directly to genetic testing of symptomatic children suspected of having CMT. Secondly, the inheritance pattern (autosomal dominant, autosomal recessive, or X-linked) should be ascertained. Based upon this information, the most appropriate genetic profile testing can then be performed.

The figure indicates an evidence-based, tiered approach for the evaluation of suspected hereditary neuropathies, and table 2 shows the relative frequency of the most common genetic abnormalities accounting for the CMT phenotype from population studies.

The previous discussion applies to patients with polyneuropathy and a classic hereditary neuropathy phenotype with or without a family history. The authors were not able to find studies of the yield of genetic screening in polyneuropathy patients without a classic hereditary neuropathy phenotype. Some patients with CMT genetic mutations have minimal neurologic findings and do not have the classic CMT phenotype.[24,25] Thus, some patients with cryptogenic polyneuropathies without the classic CMT phenotype may also have hereditary neuropathies. The prevalence of mutations in this population is unknown.

Conclusions. Genetic testing is established as useful for the accurate diagnosis and classification of hereditary polyneuropathies (Class I). For patients with a cryptogenic polyneuropathy who exhibit a classic hereditary neuropathy phenotype, routine genetic screening may be useful for CMT1A duplication/deletion and *Cx32* mutations in the appropriate phenotype (Class III). Further genetic testing may be considered guided by the clinical question. There is

Figure **Evaluation of suspected hereditary neuropathies**



Decision algorithm for use in the diagnosis of suspected hereditary polyneuropathies using family history and NCSs. **PMP22* denotes peripheral myelin protein 22; *MPZ* myelin protein zero; *PRX* periaxin; *GDAP1* ganglioside-induced differentiation-associated protein 1; *GJB1* gap-junction beta-1 protein (connexin 32); *MFN2* mitofusin 2; *EGR2* early growth response 2; *LITAF* lipopolysaccharide-induced tumor necrosis factor α; *RAB7* small guanosine triphosphatase late endosomal protein; *GARS* glycyl-transfer RNA synthetase; *NEFL* neurofilament light chain; *HSPB1* heat shock protein beta-1.

Table 2 Mutation frequencies for Charcot-Marie-Tooth (CMT) and related neuropathies in various populations

Population	Cohort (no. of patients), total/CMT1/HNPP	CMT1A duplication (%), total/CMT1	HNPP deletion (%), total/HNPP	PMP22 mutation (%), total/CMT1	Cx32 mutation (%), total/CMT1	MPZ mutation (%), total/CMT1
American[27]	75/**63**	56/**68**	ND	3.9	7.2	3.3
Spanish[28]	52	Excluded	Excluded	3.8	19.2	9.6
				0.8*	7.7*	3.8*
Belgian[29]	443	24.6	10.6	2.7	5.4	0.7
Finnish[30]	157	40.7	26.1	ND	7.6	ND
Slovene[31]	**71**	**81**	ND	ND	ND	ND
European[32]	975/**819**/*156*	59.4/**70.7**	13.4/***84***	ND	ND	ND
Australian[33]	**224**	**61**	ND	**1.3**	**12**	**3.1**
Russian[34]	174 /**108**/*3*	33.9 /**53.7**	***100***	1.1/**1.9**	6.8/**7.4**	3.4, 5.6
Italian[35]	**172**	**57.6**	ND	**1.2**	**6.9**	**2.3**
Korean[36]	57	26/**54**	ND	1.7	5.3	5.3
Average		43/**70**	11/92	2.50	12	5

The mutation frequencies are given in the total CMT cohort and in the clinical phenotypes (CMT1 and HNPP) when available. Bold = CMT1 subpopulation; italics = HNPP subpopulation.
*Extrapolated total number and mutation frequencies recalculated for the total number. For the estimation of the total number, we calculated with the average frequencies for CMT1A duplication and HNPP deletion derived from the other studies.

insufficient evidence to determine the usefulness of routine genetic screening in cryptogenic polyneuropathy patients without a classic hereditary neuropathy phenotype.

Recommendations. Genetic testing should be conducted for the accurate diagnosis and classification of hereditary neuropathies (Level A). Genetic testing may be considered in patients with a cryptogenic polyneuropathy and classic hereditary neuropathy phenotype (Level C). There is insufficient evidence to support or refute the usefulness of routine genetic testing in cryptogenic polyneuropathy patients without a classic hereditary phenotype (Level U).

Clinical context. To achieve the highest yield, the genetic testing profile should be guided by the clinical phenotype, inheritance pattern (if available), and EDX features (demyelinating vs axonal). See the figure for guidance.

RECOMMENDATIONS FOR FUTURE RESEARCH

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

- Laboratory testing. The finding of a laboratory abnormality does not necessarily mean that the abnormality is etiologically significant. For instance, there is a relatively high prevalence of impaired glucose tolerance in patients with DSP; however, whether this is etiologically diagnostic is not known. This and other such examples point to the need for more research into the basic pathobiology of the peripheral nervous system. As an extension of this area of research, there is a need to determine whether aggressive treatment or reversal of specific laboratory abnormalities improves or alters the course of polyneuropathy.
- Genetic testing. The genetic revolution has provided great insights into the mechanisms of hereditary neuropathies. Genetically determined neuropathies are more common and clinically diverse than previously appreciated. Further research to identify genotype–phenotype correlation is needed to improve the evaluation process for patients with suspected hereditary neuropathies. The issue of cost/benefit ratio of genetic testing is important since an ever-increasing number of genetic tests are commercially available. More clearly defined guidelines for genetic testing are needed to maximize yield and to curtail the costs of such evaluations. Continued exploration into the genetic basis of neuropathies has tremendous potential for the understanding of basic pathophysiology and treatment of neuropathies.

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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. 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.

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

Clinical Quality Improvement 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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