The Diagnostic Yield of a Standardized Approach to Idiopathic Sensory-Predominant Neuropathy

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Background: Peripheral neuropathy is a common problem that often prompts a lengthy and expensive diagnostic evaluation. A rational, evidence-based diagnostic approach to peripheral neuropathy is desirable. Prior studies have focused on all patients presenting to a tertiary referral center with a diagnosis of unclassified neuropathy. However, most patients with peripheral neuropathy have primarily sensory symptoms. This study focuses on patients with sensory-predominant neuropathy. The goal was to develop a focused diagnostic algorithm that can be easily applied in a general medical setting.

Methods: Patients referred with predominantly sensory symptoms and no previously defined cause were included and evaluated using a standard diagnostic approach.

Results: Among 138 patients, 25% had at least 1 first-degree relative with symptoms suggestive of neuropathy. Among laboratory studies, a 2-hour oral glucose tolerance test had the highest diagnostic yield (61%) and was more sensitive than other measures of glucose metabolism. Vitamin B12 deficiency was identified in 2 patients. Results of serum protein electrophoresis, immunofixation, and antinuclear antibody testing were abnormal in less than 5% of patients, and these rates are similar to those found in the general population. Using this approach, only 31% of patients completing the recommended evaluation were found to have an idiopathic neuropathy.

Conclusions: Patients with sensory-predominant neuropathy should be tested for glucose tolerance and vitamin B12 concentration. The significance of abnormalities of serum protein electrophoresis and antinuclear antibodies is uncertain. Other tests should be performed only when the clinical scenario is suggestive. Patients with atypical features may benefit from referral to a peripheral neuropathy center.

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Peripheral neuropathy is one of the most common neurologic disorders encountered in general medical practice. Population-based estimates suggest that at least 2% to 7% of individuals may have neuropathy. Although peripheral neuropathy is common, its evaluation frequently provokes feelings of diagnostic nihilism. Patients often undergo an extensive and expensive evaluation that frequently fails to reveal a definitive cause, and up to 50% of patients are left with a diagnosis of idiopathic neuropathy. Several investigators have demonstrated an improved diagnostic yield with thorough evaluation of peripheral neuropathy and several rational diagnostic algorithms have been suggested. These algorithms are largely based on identification of atypical features such as prominent weakness, asymmetry, proximal involvement, or autonomic failure, and accurate diagnosis often requires experience and expertise in peripheral nerve disease. Development of an algorithm that can be easily used in the primary care setting is desirable to minimize unnecessary laboratory testing and increase diagnostic yield prior to referral to a specialty peripheral neuropathy clinic. Most patients with peripheral neuropathy have a distal sensory-predominant axonal neuropathy that is symmetric, often painful, and associated with minimal weakness, if any. We hypothesize that patients with this common neuropathy pattern only require a limited diagnostic evaluation. In this study, we evaluated a simple and minimal diagnostic approach to this common problem.
on family history of neuropathy, numbness, and foot pain or deformity, and a complete general and neurologic examination was performed. Patients thought on clinical grounds to have idiopathic peripheral neuropathy were included if no etiology was identified from the history, physical examination, and electrodiagnostic study. Those with a known history of diabetes mellitus or an exclusively motor neuropathy were excluded.

Nerve conduction studies were performed in 103 patients using standard technique and maintaining skin temperature above 32°C. All patients underwent sural sensory, peroneal motor, and tibial motor examinations with measurement of conduction velocity and minimal F-wave latencies. Needle electromyography of the anterior tibialis muscle was performed in 90 patients. Other nerve conduction studies or electromyography were performed if thought necessary.

Following previously described methods, 3-mm punch biopsy specimens were taken from the distal leg and proximal thigh. Analysis was performed using light microscopy. Epidermal length was measured using imaging software (Image-Pro Plus; Media Cybernetics, Baltimore, Md) and fiber density was calculated.

We recommended for each patient a standard laboratory evaluation that included serum protein electrophoresis and immunofixation, evaluation of serum levels of vitamin B12, and thyrotropin, and a 2-hour fasting oral glucose tolerance test (OGTT). If the vitamin B12 level was between 200 and 300 pg/mL, selenium, and a 2-hour fasting oral glucose tolerance test (OGTT).

<table>
<thead>
<tr>
<th>Test</th>
<th>No. (%) of Patients With a Positive Result</th>
<th>No. (%) of 138 Patients Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>OGTT</td>
<td>53 (61)</td>
<td>87 (63)</td>
</tr>
<tr>
<td>HbA1c</td>
<td>16 (26)</td>
<td>61 (44)</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>12 (11)</td>
<td>106 (77)</td>
</tr>
<tr>
<td>ANA</td>
<td>2 (3)</td>
<td>65 (47)</td>
</tr>
<tr>
<td>SPEP/IFIX</td>
<td>3 (3)</td>
<td>104 (75)</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>2 (2)</td>
<td>120 (87)</td>
</tr>
<tr>
<td>WESR</td>
<td>0</td>
<td>65 (47)</td>
</tr>
<tr>
<td>Folate</td>
<td>0</td>
<td>51 (37)</td>
</tr>
<tr>
<td>TSH</td>
<td>0</td>
<td>112 (81)</td>
</tr>
</tbody>
</table>

Abbreviations: ANA, antinuclear antibody; HbA1c, hemoglobin A1c; OGTT, oral glucose tolerance test; SPEP/IFIX, serum protein electrophoresis pattern and immunofixation; TSH, thyrotropin; WESR, Westergren erythrocyte sedimentation rate.

A total of 138 consecutive patients (72 men and 66 women) fulfilled all study criteria. Their mean age was 63 years (range, 43-92 years), and at symptom onset it was 57.6 years (range, 34-91 years). Most patients (80%) complained of pain, and 84% had exclusively sensory symptoms with clinical findings of sensory loss without weakness. All patients had reduced sensation to pinprick or vibratory stimuli (a 128-Hz tuning fork).

One or 2 first-degree relatives of 25% of patients had symptoms suggestive of peripheral neuropathy (eg, foot numbness, pain, or high arches) and for 2 patients, 1 of whom with diabetes, 3 family members had suggestive symptoms.

The Table displays the diagnostic yield of the recommended diagnostic tests, ie, those for oral glucose tolerance, fasting glucose levels, serum protein electrophoresis pattern and immunofixation, vitamin B12 concentration, and thyrotropin levels. The results for other commonly ordered tests are also displayed, including those for HbA1c and fasting plasma glucose levels. Not every patient had every recommended test performed, as those who traveled a long distance had fasting blood work performed locally. However, 67 patients underwent every recommended test and the 21 patients (31%) who had no abnormal test results were diagnosed as having idiopathic neuropathy.

The most common abnormal laboratory test results were related to glucose metabolism. Plasma fasting glucose levels were measured in 106 patients and found abnormal in 12 (11%). Impaired fasting glucose levels were found in 8 (7.5%) of these patients and diabetes in 4 (3.7%). Among the various tests, the most sensitive measure of abnormal glucose metabolism was the OGTT. An abnormal result was found in 53 (61%) of the 87 patients who had an OGTT. Of these 53 patients, 2 (2%) had impaired fasting glucose, 39 (45%) had IGT, and 12 (13%) had diabetes. Levels of HbA1c were evaluated for 61 patients and found abnormal in 16 (26%). However, HbA1c levels were normal in 59 (68%) of those who had an abnormal OGTT. Conversely, all but 1 patient with an abnormal HbA1c also had an abnormal OGTT result. The clinical characteristics of most of the patients with IGT are reported elsewhere.
a mildly elevated anti-GM1 ganglioside antibody titer of 75 enzyme immunoassay units (normal level <10 U) in a patient with a painful sensory neuropathy.

Electrodiagnostic testing was abnormal in 72 (70%) of 103 patients. The most sensitive electrophysiologic attribute was sural sensory amplitude, which was abnormal in 65 (63%). Needle electromyography of the anterior tibialis muscle revealed denervation changes in 25 (28%) of 90 patients, and the results of nerve conduction studies for all but 2 of these were abnormal. Four patients who had normal electrophysiologic studies findings and underwent skin biopsy had reduced density of intraepidermal nerve fibers.

Several diagnostic approaches to peripheral neuropathy have been proposed that focus on the identification of atypical features such as prominent weakness, proximal involvement, or asymmetry. However, most of the patients with peripheral neuropathy present with distal sensory-predominant features and often with pain. This pattern is easily recognized by the primary care provider. Our objective was to determine which diagnostic tests needed to be routinely performed in this common subset of patients with peripheral neuropathy.

We identified 138 consecutive patients with sensory-predominant peripheral neuropathy. Most (84%) had exclusively sensory symptoms and signs, and 80% presented with pain. No patient had significant ankle dorsiflexor or hand muscle weakness, and evidence of motor nerve involvement on needle electromyography was scant. These findings emphasize that the presence of significant motor nerve involvement on clinical or electrodiagnostic examination should prompt a more detailed evaluation.

A careful family history should be taken of each patient. In our study, nearly one quarter of patients had at least 1 first-degree relative with symptoms suspicious for neuropathy. However, because most of these had only 1 or 2 potentially affected relatives, it is not clear that their neuropathy was hereditary and the positive family history may only indicate a hereditary predisposition to neuropathy. Charcot-Marie-Tooth disease, the most common type of hereditary neuropathy, is motor predominant. While none of our patients met criteria for this disorder, hereditary sensory neuropathies, including familial, are in agreement with those of other investigators and suggest that MGUS and neuropathy may not be related, or that MGUS may be a risk factor for the development of a few neuropathies. Given that 20% of patients with MGUS progress to a more malignant lymphoproliferative disease over 20 years, screening patients who have peripheral neuropathy with serum protein electrophoresis pattern and immunofixation studies may be reasonable, but these tests have a low diagnostic yield with respect to an underlying cause of sensory axonal peripheral neuropathy.

Abnormalities of glucose regulation were the most common laboratory findings, and the OGTT was significantly more sensitive than other measures of glucose metabolism. Diabetes was found in 12 (13%) and IGT in 39 (45%) of the patients who underwent an OGTT. The prevalence of IGT among patients with neuropathy was hereditary and the positive family history was similar despite its slightly younger age. Our findings are in agreement with those of other investigators and suggest that MGUS and neuropathy may not be related, or that MGUS may be a risk factor for the development of a few neuropathies. Given that 20% of patients with MGUS progress to a more malignant lymphoproliferative disease over 20 years, screening patients who have peripheral neuropathy with serum protein electrophoresis pattern and immunofixation studies may be reasonable, but these tests have a low diagnostic yield with respect to an underlying cause of sensory axonal peripheral neuropathy. Furthermore, there is no evidence that screening improves long-term outcome or is cost-effective. We prefer to selectively screen patients who have a demyelinating neuropathy. Patients with a painful neuropathy and autonomic dysfunction require an aggressive evaluation for amyloidosis.

The prevalence of low-level ANA titers (<1:160) was 4.6%, within the range of 4.2% to 12.7% reported for normal individuals. An abnormal ANA titer was not associated with any clinical features of connective tissue disease and did not alter the management of any of our
patients. Our recommendation is to check abnormal ANA titers only in patients who, on clinical grounds, are suspected of having a connective tissue disease.

Commercial laboratory companies are exerting growing pressure on clinicians to order neuropathy antibody panels, including antiganglioside and paraneoplastic antibodies. These panels, which were most often administered prior to referral to our clinic, were not useful tests in this population. The only abnormality they detected was a low-level–positive anti-GM1 antibody test that was not clinically relevant. This resulted in the inappropriate treatment of this patient with intravenous immunoglobulin and prednisone for presumed multifocal motor neuropathy prior to referral. While testing for individual antibodies is useful in specific clinical situations (eg, for anti-GM1 antibody in motor neuropathy), routine screening of patients with distal sensory neuropathy is not warranted.

Serum vitamin B6 levels were mildly elevated in several patients who were taking dietary supplements containing pyridoxine. The clinical significance of this finding is uncertain. Acute pyridoxine toxicity may cause a severe sensory neuropathy and long-term ingestion may cause a painful axonal sensory peripheral neuropathy.23,24 We recommended discontinuation of pyridoxine supplementation in all patients with an elevated serum level of vitamin B6.

No patient had abnormal results for thyroid function studies. While thyroid disease often causes neuromuscular complaints, thyroid disease is uncommon among patients presenting with neuropathy. Each patient should be carefully questioned regarding symptoms of thyroid dysfunction, and only those with a suspicious history or physical examination should undergo further testing. No patient was found to have an abnormal serum folate level or blood sedimentation rate, and these tests need not be routinely performed.

Approximately 30% of patients (31/103) had normal nerve conduction study findings. Nerve conduction studies primarily reflect large myelinated fiber integrity. Our findings suggest that many individuals with painful sensory neuropathy have preferential small fiber involvement. Other investigators have also demonstrated that up to 40% of patients with idiopathic sensory neuropathy have normal nerve conduction study findings.10-25 Skin biopsy showed that 4 patients with normal nerve conduction had reduced density of intraepidermal nerve fibers. Intraepidermal nerve fiber density is abnormal in most patients with both idiopathic and IGT-associated neuropathy whose nerve conduction study results are normal.26 Sudomotor and quantitative sensory testing are complementary to skin biopsy and may also be useful in this patient population.

Our findings are similar to those of other investigators. Periquet et al19 identified 117 consecutive patients with painful neuropathy and normal strength without a diagnosis at the time of referral. Each patient underwent extensive laboratory testing including thyroid and immunofixation studies; a random evaluation of blood glucose; evaluation of serum levels of vitamin B12 (with methylmalonic acid for patients with a level <250 mg/dL) and vitamin E; evaluation of serum titers of ANA, extractable nuclear antigen, antinerve antibodies (sulfatide, Hu, and MAG), and rheumatoid factor; and testing for fluorescent treponemal antibodies and human immunodeficiency virus. The only laboratory abnormality found was an elevated antisympathetic antibody titer in 1 patient. Hypertriglyceridemia and hypercholesterolemia were present in 34% and 28% of patients, respectively. No patients were identified with diabetes, but fasting blood glucose evaluation and OGTT were not performed. Because patients with IGT often have dyslipidemia, the high frequency of lipid disorders in the study suggests many patients, if tested, might have been found to have IGT.

Our study has several limitations. First, it is representative of patients seen in a tertiary care setting and the prevalence of laboratory abnormalities may be biased against common disorders. For example, primary care physicians would be less likely to refer patients with recognized vitamin B12 deficiency. Because of the distances many patients traveled, the recommended evaluation had to be pursued by their local physician and, consequently, not every patient had every recommended test. Despite these limitations, our data suggest that the evaluation of sensory-predominant axonal neuropathy may be focused. All patients should be questioned carefully about family history. All patients should have an OGTT and a serum vitamin B12 level evaluation. Those found to have IGT should undergo diet and exercise counseling to prevent the development of diabetes or large-vessel atherosclerotic complications. Other serologic tests should be performed in selected patients. For example, inquiry into dietary supplements that may contain pyridoxine may be useful. Because the sensory-predominant axonal neuropathy pattern is common and easily recognized, this diagnostic approach may be particularly useful in the primary care setting. Patients with atypical clinical presentations, or those with suspected idiopathic neuropathy, may benefit from referral to a tertiary care peripheral neuropathy clinic for diagnostic confirmation and further diagnostic testing.

Since the manuscript was accepted for publication the American Diabetes Association has revised its criterion for impaired fasting glucose.27 It is now defined as a fasting plasma glucose concentration of 100 to 125 mg/dL (5.6-6.9 mmol/L). Using the new criterion, an additional 12 patients had impaired fasting glucose. However, of these, 7 had IGT and 2 had diabetes on the basis of the 2-hour plasma glucose test during an OGTT. Therefore, only 3 patients were previously considered healthy using the old criterion. The revised criterion has not substantially altered the diagnostic yield of the fasting plasma glucose test (either alone or as part of the OGTT) in this patient population.

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REFERENCES


