

Expert Opinion #1

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Case:

A 60 year-old woman has a 1 year history of fairly constant numbness and tingling of the entirety of both feet at times going up to the ankles. At night, she may have a mild burning sensation in the feet. She has a past medical history of only hypertension on amlodipine. Neurological examination is normal except for distally diminished pin prick and vibration in both lower extremities. Deep tendon reflexes including ankle jerks are 2+ and symmetric.

Questions:

What diagnostic testing would you recommend? What is the yield? If the blood tests are normal, what is the most likely diagnosis? How often are the deep tendon reflexes normal? How often do the hands become symptomatic and when might spread occur?

Discussion:

The patient presents with symptoms typical of chronic distal symmetric polyneuropathy. After excluding a mimicking CNS disorder, evaluation turns to ascertaining the etiology of the polyneuropathy. Neurologists well know that the list of potential causes -- many of which are treatable -- is extensive, and includes nutritional, metabolic, toxic, infectious, autoimmune, and genetic illnesses. The work-up therefore can be both daunting and expensive. The American Academy of Neurology recently released a practice parameter which utilizes available evidence to help guide this process (England et al, 2009).

Following a detailed history (including extensive family history) and neurologic examination, patients should undergo nerve conduction studies and blood tests. The following blood tests are recommended for all patients: complete blood count, erythrocyte sedimentation rate, complete metabolic panel (including glucose, renal, and liver tests), thyroid function tests, vitamin B12 level (including the metabolites methylmalonic acid and homocysteine), and serum protein electrophoresis with immunofixation (SPEP/IFE). Of these, the highest yield according to the AAN practice parameter are glucose, vitamin

B12, and SPEP/IFE. When vitamin B12 levels are in the low-normal range (200-500 pg/ml), elevated methylmalonic acid or homocysteine can indicate a functional deficiency of vitamin B12. The most sensitive test for identifying prediabetes or diabetes is the 2-hour oral glucose tolerance test, which may detect impaired glucose tolerance even when hemoglobin A1c is normal (Smith and Singleton, 2004).

Should these results prove unrevealing, further testing for less-common etiologies may be performed according to the judgment of the clinician. Investigation may be directed, for example, toward identifying connective tissue disorders or other autoimmune illnesses, celiac disease, heavy metal toxicity, malignancy, or infectious diseases such as Lyme or hepatitis. Copper deficiency could be considered, although typical features of myeloneuropathy are not evident.

DNA testing, which is both highly sensitive and specific, should be pursued if a genetic origin is suspected from the presentation, family history, or nerve conduction study. The clinical presentation of hereditary neuropathies is highly variable: family members with a common mutation may manifest very differently, while mutations in distinct genes can cause similar-appearing phenotypes. Detailed investigation of family history and evaluation of relatives can contribute significantly to diagnosis of previously-unclassified neuropathies (Dyck et al, 1981). Of course, assessment is further complicated since some 30% of patients with genetic neuropathies have sporadic mutations.

Because genetic testing is expensive, a directed approach is recommended based on the inheritance pattern and the finding of demyelinating versus axonal polyneuropathy on nerve conduction testing (England et al). For demyelinating polyneuropathies, the most common inherited and sporadic form is autosomal dominant and is caused by duplication of the PMP22 gene; an X-linked form may be caused by mutation of GJB1. Axonal neuropathy, when auto-

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somal dominant, is most likely due to mutation of MFN2. Here too, mutation of GJB1 can result in an X-linked axonal form.

The patient in our case had preserved ankle jerks, which may seem unusual in peripheral neuropathy. Wolfe et al (1999) noted, however, that in patients with polyneuropathy of unknown etiology, deep tendon reflexes were present at the ankles in half of the cases. For the great majority of patients in that study, symptoms began in the lower extremities, as with our patient. Progression occurred slowly over years, with spread to the hands in 42% of patients. In diabetic peripheral neuropathy, hand symptoms typically are seen after sensory loss has ascended to the level of the knees (Said, 2007).

In about 25% of neuropathy patients, all laboratory testing is normal despite clear clinical and electrodiagnostic indications of neuropathy. These patients are classified as having cryptogenic or idiopathic neuropathy. While that outcome is frustrating to patients and clinicians alike, the extent of progression tends to be slow, and virtually all such patients remain ambulatory (Wolfe et al, 1999). Cryptogenic polyneuropathy is an active area of research in our neuromuscular clinic at UT Southwestern Medical Center.

References:

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