

“DOC, MY FEET ARE NUMB”

EVALUATION AND MANAGEMENT OF PERIPHERAL NEUROPATHY

Lisa Sanders, MD

Week 15

Educational Objectives:

- 1. Identify the most common causes of symmetrical peripheral neuropathy*
- 2. Review components of the physical exam which may be useful in evaluating patients with a peripheral neuropathy*
- 3. Develop strategies for distinguishing between potential causes of peripheral neuropathy*
- 4. Describe therapeutic options and their efficacy in the treatment of this common disorder*

CASE ONE:

Ms. S. W. is a 65-year-old woman who has been your patient for many years. She's a very active woman, even after her retirement from an office job a couple of years ago. She comes in now with the titled complaint, "Doctor, my feet are numb." She has no past medical history. She quit smoking 20 years ago; she drinks socially; she lives with her husband and has two grown children and a handful of grandchildren. She has a strong family history of diabetes but tells you that she has been tested for diabetes many times and doesn't have it. On exam she is a woman of normal weight with no significant findings (including proprioception and vibration) except for diminished sensation to monofilament testing. You can't get an ankle jerk reflex, but you're not certain if that is due to a neurological deficit, or poor exam technique.

Questions:

1. What is on your differential? What other history would be useful to narrow this? Would any further physical exam findings be helpful?

What the patient is describing is a symmetrical peripheral neuropathy. Some patients describe the sensation as numbness; others focus more on the pins and needles like pain (like when your foot falls asleep). The numbness is often more prominent when patients are walking around, while the pain component is more prominent at rest. Some neuropathies are also associated with weakness, while others are strictly sensory. Thus in the history, it would be helpful to know if there is any weakness or other types of sensory symptoms - like burning or "pins and needles." The usual characteristics of a symptom would be helpful - when is it bothersome, what makes it worse or better, how it is affecting her life. You might also ask about symptoms of autonomic dysregulation – abdominal pain suggestive of gastroparesis, orthostatic hypotension, or palpitations. These symptoms often accompany a peripheral neuropathy because they both use the same class of small, unmyelinated fibers. A family history of peripheral neuropathy might suggest an inherited neuropathy. An occupational or recreational history of working in the lumber industry or other industries where exposure to arsenic is possible, or building with creosoted wood might suggest a toxic exposure. A review of the medications she takes as well as

any supplements would be important because several drugs and supplements can cause a peripheral neuropathy. Use of alcohol should be assessed. A review of systems should be performed looking for evidence of hypothyroidism, vitamin B12 deficiency, autoimmune disorders (Sjogren's, lupus, and RA) and neoplasms such as multiple myeloma.

On physical exam there are several dimensions of a peripheral neuropathy that may be useful: 1) reflexes (ankle jerk – consider reviewing this physical exam skill if appropriate), 2) vibratory sense, 3) proprioception, 4) strength, and 5) diminished or altered sensation as measured by monofilament test or pin prick. The first four findings suggest that larger myelinated A (alpha or beta) fibers are involved. Light touch is carried on small unmyelinated C fibers. Diabetes, chronic hyperglycemia, and some paraneoplastic syndromes can cause the neuropathies that involve only the small unmyelinated fibers. Finding that the neuropathy is limited to these fibers limits the differential. However, up to 90% of cases of this kind of exclusively unmyelinated nerve damage are idiopathic. Pain over the tarsal tunnel and tenderness to palpation over the flexor retinaculum (located just posterior to the medial malleolus) can suggest tarsal tunnel syndrome. Tinel's sign – elicited by percussing over the point of possible entrapment – has a sensitivity of 99% and specificity of 43%. (Gelber, 1996) The positive predictive value ranges from 74% to 88%.

In Ms. S.W.'s case the absence of an ankle jerk reflex makes this exam somewhat confusing because that deficit suggests spinal cord involvement or an S1 radiculopathy, and you have no suspicion of this entity. Poor technique makes this a less reliable test. (personal observation) In addition, according to at least one study, up to 10% of individuals over the age of 60 do not have an ankle jerk reflex even in the absence of known pathology. (Bowditch, 1996) The lack of other physical exam findings, beside the diminished sensation, suggests a neuropathy due to small unmyelinated fibers.

The patient denies any abdominal symptoms, dizziness, or palpitations but notes she sometimes feels that her feet are burning or tingling, especially at night. She remembers that her mother used to complain about her feet but doesn't recall anything more. On exam you still can't get an ankle jerk, but note that the patient does have mildly decreased vibratory sense, although proprioception and strength are normal. She has no pain over the tarsal tunnel or the flexor retinaculum.

2. What, if any, testing would you order?

Nerve conduction studies are recommended unless the cause of the neuropathy is obvious – long standing diabetes or known cryoglobulins from Hepatitis C. Nerve conduction studies measure the speed of nerve conduction while EMG's (electromyograms) assess the electrical potential generated by muscle cells and so evaluates nerve and muscle together; a nerve conduction velocity study measures the speed at which a signal is transmitted through the nerve. (Medline Plus) The nerve conduction study is done by placing a metal disk over the nerves being tested – one at a distal point near or at the affected area and the other more proximal. A mild electric charge is delivered to the distal disk and travels to the proximal disk. It's not painful but may be uncomfortable. An EMG involves the insertion of a needle into the affected muscle bed and a small charge sent from this distal needle to one more proximal. The amplitude and shape of the muscle potential is measured between these two points.

EMG is used when there is weakness involved. Nerve conduction velocity studies are used in cases where there is only pain and/or numbness and no weakness. NCV studies can confirm the neuropathic origin of the pain and help characterize the type of neuropathy. However, patients older than 75 will have a false positive rate of 20%. In addition, those with only small unmyelinated fiber involvement may have a false negative because the test primarily measures myelinated fibers.

Other recommended studies are fasting glucose and, if normal, a two-hour glucose tolerance test to look for diabetes and glucose intolerance. The GTT will detect those with abnormal insulin responses to a glucose challenge which may be helpful here because impaired glucose tolerance as well as frank diabetes can cause neuropathy. IGT accounts for up to one third of cases of peripheral neuropathy. Serum vitamin B12, TSH, SPEP are also suggested if the patient has a normal glucose tolerance. Her mother's history of painful feet might suggest an inherited neuropathy if all these tests are normal.

The patient has a two-hour glucose tolerance test consistent with glucose intolerance. The nerve conduction tests are normal. Based on this information, you conclude that the patient probably has a peripheral neuropathy caused by glucose intolerance.

3. After you share what you've learned, the patient asks, "Is there anything you can do for it? The burning at night is making it hard to sleep."

There are no great medicines here, but a few have been shown to be moderately effective. Amitriptyline (SP) and other tricyclics have been the most extensively studied and reduce symptoms by up to 50% in a third of patients. Effective doses are between 50-200 mg but to minimize the risk of side effects, Singleton recommends starting at 10mg and increasing by increments of 25mg to an effective dose. Gabapentin has been shown to be about as effective but required doses higher than 1600 mg per day (Mendell, NEJM 2003). SSRIs have been shown to be less effective than tricyclics. Paroxetine and citalopram have been shown to be better than placebo. Venlafaxine and bupropion were shown to be effective for 30% of patients in one small trial. Anti-seizure medications have been tried for a number of different neuropathies. Carbamazepine, lamotrigine (400-600mg qd) have been shown to be effective in some individuals. Opiates can work although there is concern about addiction. Tramadol has been shown to be just as effective with a lower risk of addiction. (Mendell, 2003) Capsaisin cream and lidoderm patches have also worked. However, a 2007 review of the treatment of diabetic neuropathy concludes that the older tricyclics and anticonvulsives were more effective than the newer ones. (Wong, 2007)

CASE TWO:

Ms. V. D. is a 30-year-old woman with no significant past medical history who presents with a complaint of numbness and tingling in her hands and feet. She takes only vitamins and the occasional ibuprofen, and doesn't smoke or use drugs, although she has used injection drugs in the past. She is a vegetarian. She drinks two to three glasses of wine several nights a week. Review of systems is positive only for severe menstrual cramps. On exam, she is overweight, but otherwise her exam is unremarkable.

Monofilament test shows some decrease in sensation and her ankle jerk (which you have mastered since your last patient) is present but reduced, as is her vibratory sense and proprioception.

4. What is your differential in this case? And what, if any, studies would you order at this point?

This patient is at risk for many causes of a peripheral neuropathy. She drinks more than is recommended for women and that puts her at risk for an alcohol-related peripheral neuropathy. She has used IV drugs in the past, which puts her at risk of Hepatitis C and HIV, both of which have associated peripheral neuropathies. She is a vegetarian and so is at risk for vitamin B12 deficiency.

All of her labs come back as normal.

5. Now what is on your differential, and how might you proceed?

She may still have an alcohol-related neuropathy, although some researchers think that this neuropathy is due to nutritional deficits. She also has no other stigmata of alcohol-related liver disease. This could be idiopathic peripheral neuropathy although this is most commonly seen in patients over the age of 50. With further questioning she tells you that she regularly takes vitamin E, vitamin C, and a multivitamin to keep her healthy, and vitamin B6 to help with her pre-menstrual syndrome. Vitamin B6 has been associated with the development of a reversible peripheral neuropathy. (Schaumburg, 1983) You suggest that she stop taking this vitamin and ask her to come back to see you in three weeks. At that point, she tells you that the symptoms are beginning to resolve.

Primary References:

1. Singleton JR. Evaluation and treatment of painful peripheral polyneuropathy. *Seminars in Neurology*. 2005; 25(2): 185-195. <http://dx.doi.org/10.1055/s-2005-871327>
2. Mendell JR, Sahenk Z. Painful sensory neuropathy. *New England Journal of Medicine*. 2003; 348(13): 1243-1255. <http://content.nejm.org/cgi/content/full/348/13/1243>

Additional References:

1. Amato AA, Oaklander AL. Case 16-2004: A 76-year-old woman with numbness and pain in the feet and legs. *New England Journal of Medicine*. 2004; 350:2181-2189.
2. Bowditch MG, et al. The significance of an absent ankle reflex. *Journal of Bone and Joint Surgery*. 1996; 78-B: 276-279.
3. Gelber DA, et al. Clinical features that distinguish tarsal tunnel syndrome from non-neuropathic causes of foot pain. *Electrophysiology and Clinical Neurophysiology*. 1996; 98(3): 22.
4. Schaumburg H, et al. Sensory neuropathy from pyridoxine abuse. A new megavitamin syndrome. *New England Journal of Medicine*. 1983; 309: 445-448.
5. Wong MC, Chung JW, Wong TK. Effects of treatments for symptoms of painful diabetic neuropathy: systematic review. *British Medical Journal*. 2007; 335: 87.

Lisa Sanders received her M.D. from Yale School of Medicine and completed her training at Yale's Primary Care Internal Medicine Residency Program. Her clinical and academic interests include obesity, nutrition, the physical exam, and diagnostic errors. She is the author of *The Perfect Fit Diet: How to Lose Weight, Keep it Off and Still Eat the Foods You Love*. Before entering medical school, Sanders was a producer for CBS News, where she covered medicine and health.