

WALDENSTROM'S AND PERIPHERAL NEUROPATHY

by Todd Levine, MD



Todd Levine, M.D., at the 2009 IWMMF Ed Forum in Memphis.

What is PN and what causes its symptoms?

Peripheral neuropathy is a broad term used to describe any disease that damages nerves of the peripheral nervous system. The nervous system is divided into two parts. The central nervous system includes the brain and the spinal cord, while the nerves that travel between the spinal cord and the skin and muscles comprise the peripheral nervous system.

There are, literally, thousands of causes for peripheral neuropathies, and despite the most intensive investigations 50% percent of all cases of peripheral neuropathy have no clear cause. The term idiopathic describes such cases. Twenty-five percent of peripheral neuropathy cases are caused by diabetes. Five to 10% of peripheral neuropathy cases are caused by excessive alcohol use. This leaves a balance of 15 to 20% to other causes. Vitamin deficiencies, such as B12, and chemotherapies can also cause peripheral neuropathies. In rare cases a patient may have a cancer, such as WM, which can cause or be related to peripheral neuropathies. In our survey of 119 WM patients, 48% developed a peripheral neuropathy. This was in contrast to neuropathy being found in 19% of age-matched controls.

What are the signs and symptoms of PN?

Peripheral neuropathies can cause symptoms that are directly related to the type of nerve that is damaged. The most common type of nerve to be damaged is the sensory nerve. Patients with damage to their sensory nerves will experience numbness, tingling, pain, burning, stabbing, or shooting sensations. This is because the sensory nerves are designed to transmit this type of information, and, when damaged, they will give off abnormal electrical discharges mimicking these sensations even when nothing is stimulating them.

Alternatively, if the motor nerves are damaged, then patients will experience muscle weakness. And in many cases both the motor and sensory nerves are damaged together. This can also lead to problems with balance.

When damage occurs to peripheral nerves, the symptoms will relate directly to the damaged nerves. The most common place where these symptoms are first experienced is in the toes and feet. This is because the nerves located in the toes and feet are the longest nerves in our body. They begin in the spinal cord and extend all the way down to the toes.

If the neuropathy spreads from the feet, it then typically moves up the ankles and calves – and, if it becomes severe enough, neuropathy can begin to involve the hands. It is unusual to have symptoms that are worse in the hands or arms than in the feet. If the symptoms are more pronounced in the hands compared to the feet, it raises the possibility of another cause for the symptoms. There are many

other causes of numbness, pain, or weakness in addition to peripheral neuropathy. Other potential causes include pinched nerves around the spinal cord (called radiculopathy), pinched nerves in the arms such as carpal tunnel, orthopedic issues such as plantar fasciitis or spinal stenosis, or vascular insufficiency. All can cause symptoms that are similar to peripheral neuropathy. It is, therefore, important to see a doctor who understands how to diagnose and treat peripheral neuropathy because many of these mimics of peripheral neuropathy are actually more treatable than PN.

How is PN diagnosed?

If you have symptoms that are mentioned above, then you need to see a physician who can take your history, perform an examination, and determine if you have PN. However, because there are so many conditions that can have similar symptoms, there are only a few ways to determine for sure if you have peripheral neuropathy. The most common way is to do the test called Nerve Conduction Study (NCS).

This test uses electrical impulses to activate your nerves and study the way in which the nerves carry these impulses. For most patients, this test can detect whether there is damage to the peripheral nerves. If a neuropathy is suspected and the NCS is negative, then that result suggests that only the smallest nerves may be damaged. The nerves carrying information about sensations are too small to detect with NCS. In this case small, relatively painless punch biopsy of your skin can be done to actually look at these small nerves under a microscope and see if they appear damaged. The technique of examining these small fibers involves using an antibody to stain for the small fibers and then counting the number of nerve fibers per millimeter of skin. This technique is only available in a few specialized centers, but samples from any location can be shipped to the centers that perform Epidermal Nerve Fiber Counting.

Once you are diagnosed with PN, the focus switches to see if a cause can be determined. This is traditionally done through an extensive series of blood tests to look for the known treatable causes of peripheral neuropathy. If the blood tests do not give a specific answer and the neuropathy is aggressive, some patients will undergo a biopsy of a large nerve. In this way pathologists can study the nerve and see if the biopsy determines a specific cause for the neuropathy.

In many cases no specific test can answer the question as to what caused the neuropathy. In some of these cases the neuropathy can be attributed to other diseases or conditions that a person has, such as diabetes, heavy alcohol consumption, or a cancer known to be associated with PN. In the case of Waldenstrom's, we know that 48% of WM patients will develop neuropathy associated with WM. But keep in mind that neuropathy in a WM patient may be due to a number of reasons, including those listed above, and that it therefore can still be difficult to diagnose whether the PN is from WM. The only way to be certain is to test to see if the abnormal antibodies that directly attack the peripheral nerves are in your blood. There are several IgM antibodies that have been associated in this way, such as anti-MAG (Myelin Associated Glycoprotein) or sulfatide (a sulfur-containing lipid [fat] associated with the myelin layer). In our study of 119 patients with WM only 5% had antibodies to MAG and only 4% had antibodies to sulfatide. So it is important to rule out other causes of PN even if you have WM.

How is Peripheral Neuropathy treated?

The treatments for PN are directed at their underlying cause. So if the patient has diabetes, the best treatment is to control blood sugar, follow an appropriate diet, and exercise. If a patient has a vitamin deficiency then this can be corrected.

If the PN is caused by one of the abnormal proteins in the blood, then lowering the level of the antibody in the blood will treat the PN. The antibody level can be lowered using chemotherapy or by directly removing the antibodies through plasmapheresis. These treatments may lower the level of the IgM; however, plasmapheresis is both time consuming and expensive and its effect is of short duration. Moreover, most patients with peripheral neuropathies have relatively mild symptoms that do not progress to severe neuropathies, and there is not much evidence to show that starting therapy with chemotherapy or plasmapheresis for a mild neuropathy will delay the progression to a more severe neuropathy. Most cases of PN associated with abnormal antibodies are mild and remain that way. So it is rarely worth the risk of aggressive therapy early on. Such decisions should be discussed with a doctor familiar with these types of neuropathies, in other words with a neurologist who specializes in diseases of the peripheral nerves.

Even if there is no specific treatment for the underlying cause of the neuropathy, there are many treatments available that reduce the pain and the symptoms of PN. Such treatments are very commonly used in all forms of neuropathy and include amitriptyline, gabapentin, pregabalin and duloxetine. These agents can reduce the symptoms of PN by up to 50%. If the pain is uncontrollable even when these drugs are taken, then many patients will use narcotic medications such as oxycodone or methadone to reduce their pain. In these cases it is preferable to be followed by a pain specialist who can track the medications and their side effects. The key thing to keep in mind is that even without specific therapy for the cause of the neuropathy doctors should be able to improve your quality of life.

Which treatments for WM are known to cause PN?

This is a complicated subject since we know WM can cause PN, but we also know that some of the treatments for WM also cause or intensify PN symptoms. Several chemotherapy drugs including Vincristine, Velcade, Thalidomide, and Revlimid can cause PN. In most cases the likelihood that PN will develop during treatment is increased if there is even a mild PN before treatment. Further, if the drugs are the cause of the PN then the symptoms of PN tend to develop during the months of treatment. If symptoms of PN develop during chemotherapy it is important to notify your doctor immediately since stopping the chemotherapy can stop the progression of the PN or even reverse the symptoms. The decision to use the agents that cause PN has to be balanced against the need to treat Waldenstrom's and should be discussed with your doctor.

Peripheral neuropathy associated with Waldenstrom's is a complex disorder, and there are many people with WM who suffer from neuropathy. The following are steps that will help formulate a treatment plan for the WM patient with neuropathy. Note, however, that the same steps are recommended to the patient who is experiencing neuropathy but who does not have WM.

- 1) Establish that PN is the accurate cause of the symptoms.
- 2) Establish whether WM is the likely cause for the PN or if there are other causes.
- 3) Direct therapy based on the severity of symptoms, i.e. in cases of severe neuropathy related to WM patients need aggressive therapy to reduce antibody levels; in cases of mild PN symptomatic therapy may be all that is required.
- 4) Follow routinely with a neurologist familiar with disorders of the peripheral nervous system.

These steps will help ensure that everything that can be done will be done to treat your PN.

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