



# Diagnosing and Treating Peripheral Neuropathy

By Todd Levine, MD

The only way to effectively treat neuropathies is to identify which of the many different diseases is the underlying cause and then make the proper diagnosis.

**M**ore than 20 million Americans have peripheral neuropathy. People who suffer from peripheral neuropathy are experiencing a malfunction in the way in which the nerves of the peripheral nervous system send signals from the brain to the arms and legs and vice versa. Their symptoms can present in many ways, from numbness to painful sensations, balance difficulties and weakness.

## Localizing a Peripheral Neuropathy

Identifying the cause of peripheral neuropathy can be difficult. This is because the symptoms of peripheral neuropathy can be due to dysfunction in the parts of the peripheral nervous system or even diseases that affect organs other than peripheral nerves. A good analogy for patients experiencing symptoms would be to imagine they are placing a call from New York (their brain) to Los

Angeles (their foot). During the call, the patients hear static, or in other words, they feel numbness or pain. But that static (the pain and numbness) is in fact abnormal nerve sensations. Unfortunately, these patients can't tell if the problem is originating in New York, Los Angeles or in between. Identifying where the pain and numbness are originating is the first issue that needs to be addressed. Is there a chance the symptoms are coming from a problem with the brain, the spine, blood circulation, or even a problem in the bones or ligaments? Diseases in any of these parts of the body can mimic peripheral neuropathy.

The process of localization can involve several different tests. Typically, a neurologist will take a history of patients' symptoms, perform a neurologic exam, and then order electromyography (EMG) and nerve conduction studies. These steps are crucial to understanding if the peripheral

nerves are involved. It also identifies several other important issues: how badly the nerves are damaged, which nerves are damaged and which parts of the nerves are damaged. In this way, localization goes from identifying the peripheral nerve as the problem to understanding how the disease process is affecting the nerves. One of the most important things to understand from this stage of the evaluation is how quickly the disease has damaged the nerves; for instance, has it developed over days, weeks or years?

The inner workings of a nerve can be broken down into three parts. The first part is the cell body, which sits in or near the spinal cord and is the machinery that keeps the cells working. If nerves of the peripheral nervous system are damaged, they can regrow as long as the cell body is alive. Once the cell body dies, the nerve can never regenerate. The second part is the axon, which is the long part of the nerve that extends from the spinal cord to the skin and muscles that the nerve supplies. Unlike all other cells in the body that are microscopic in all three dimensions, the peripheral nerve cells can be three feet long. These axons convey all the signals to move and to feel back and forth from the brain. The third part is the insulation around the nerves (myelin), which allows the nerves to quickly conduct the electrical signals. The more myelin wrapped around each axon, the bigger the nerve is and the faster the nerve conducts electricity — in some cases as fast as 350 miles per hour. By localizing the neuropathy, a neurologist can tell whether the damage is to the cell body, the axon or the myelin. And this is crucial because there are vastly different diseases that affect each part.

### **Diagnosing and Treating the Types of Peripheral Neuropathy Diseases**

Once a neurologist understands the what (neuropathy) and the where (the cell body, the axon or the myelin), the next step is to figure out the why. This is the part that is still somewhat discouraging. Despite an ever-growing number of blood tests, spinal taps, nerve biopsies, genetic tests, etc., at least 50 percent of neuropathies remain undiagnosed. These types of neuropathies are called idiopathic (meaning, we are too idiotic to figure it out). One group of diseases that commonly affect peripheral nerves are: disorders of glucose metabolism such as diabetes, vitamin B12 deficiency, alcohol use and drugs such as chemotherapies. These diseases comprise about 30 percent of the other types of neuropathies, and tend to damage the axon. Approximately 10 percent to 15 percent of neuropathies may be inherited. These patients often have

multiple family members with neuropathy and, unfortunately, inherited neuropathies are not treatable at the present time. The final group of diseases that affect the nerves are related to problems with patients' immune systems. The immune system, which is supposed to fight bacteria and viruses, can start to work incorrectly and damage the nerves. These immune-mediated neuropathies are the most treatable.

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Immune-mediated neuropathies can be subdivided into different groups based on the type of nerve that is damaged: motor, sensory, motor and sensory, or autonomic. They are diagnosed based on characteristic changes on nerve conduction studies, or abnormalities in blood tests, spinal taps or nerve biopsies. At times, it can be difficult to be certain that a neuropathy is caused by the immune system. In these cases, doctors may opt for a short trial of a therapy designed to treat immune neuropathies. If patients respond, then it is likely their neuropathy is immune-mediated. Should patients fail to respond to the first trial of therapy, it is still possible they have an immune-mediated neuropathy. However, repeated failures may indicate the neuropathy is untreatable. One final point is that even if patients have diabetes, they may have a superimposed immune-mediated neuropathy that is treatable. So for diabetics, if a neuropathy starts to rapidly get worse or to involve a lot of motor weakness, a more aggressive evaluation should be undertaken; the neuropathy should not simply be blamed on the diabetes.

Immune-mediated motor neuropathies are relatively rare. The most common is multifocal motor neuropathy. These patients have weakness, typically beginning in their arms, and have no numbness or pain. They respond very well to intravenous immune globulin (IVIG) and often can fully recover. The IVIG usually has to be continued indefinitely.

Although not classically a neuropathy, one disease that presents as pure weakness (no numbness or pain) is myasthenia gravis (MG). MG is caused by specific autoantibodies that inhibit a part of the muscle fiber to react to the nerve stimuli to move. As the disease worsens, patients experience weakness that can be in their arms or legs, in their eyes (which can cause double vision or droopy eyes), or even in their muscles that allow them to swallow, talk or breathe. Untreated, this can be a fatal disease. MG can be diagnosed by nerve conduction studies, but in almost all cases, an abnormal antibody can be identified in the blood of these patients. When the symptoms are severe, resulting in talking, swallowing and breathing problems, patients are typically treated acutely with either IVIG or plasmapheresis. Over the long run, most patients can be transitioned to oral drugs such as corticosteroids or one of several organ transplant rejection drugs to lower the level of the antibodies.

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The immune-mediated pure sensory neuropathies are very rare and present as numbness and pain without weakness. In some cases, only the smallest nerves (those nerves with no myelin) are damaged. In these cases, the nerve conduction studies and exam may be normal. However, these neuropathies can be diagnosed with a skin biopsy that allows the pathologist to examine the small nerves to see if they are healthy. If these so-called small-fiber neuropathies, or pure sensory neuropathies, are related to an immune disorder such as Sjögren's disease, they can respond to drugs that modulate the immune system such as IVIG, steroids or plasmapheresis. Tying the pure sensory neuropathies to an immune system disorder can be very challenging, and physicians often rely on abnormal blood tests and a strong clinical suspicion. In the right setting, a short course of IVIG (three months or so) to see if the symptoms can improve is very warranted and has little long-term risk.

There are many different types of motor and sensory neuropathies caused by the immune system. If they present very rapidly, causing weakness and sensory loss over a two-week period or so, it is called acute inflammatory demyelinating polyneuropathy, or Guillain-Barré syndrome. These patients may have severe weakness and may even require a ventilator to breathe. They are treated with one dose of IVIG or plasmapheresis, which allows their nerves to slowly recover and, in most cases, fully recover. If the disease presents more slowly (over more than six weeks), it is called chronic inflammatory demyelinating polyneuropathy (CIDP). These patients can be subdivided further in some cases based on the identification of certain specific blood tests or patterns on the nerve conduction studies. There are many treatment options available for CIDP patients, including IVIG, corticosteroids, chemotherapy drugs, drugs to prevent organ transplant rejection, etc. The key is to find drugs that the patients respond to and that they can tolerate. In most cases, patients will require the therapy indefinitely or at least for several to many years. Therefore, tolerability, expense and convenience all need to be considered by the patients and the neurologist.

#### **The Importance of Proper Diagnosis**

It is important to properly evaluate the symptoms of weakness, numbness and pain to identify what is causing the problem. Once patients have been definitively diagnosed with peripheral neuropathy, a neurologist familiar with nerve diseases should tailor the evaluation to the type of neuropathy and see if they can uncover the cause. If the cause is believed to be the immune system, there are several treatment options, depending on the type of neuropathy. Finally, and perhaps most importantly, patients need to be their own advocates. They should ask their doctor what type of neuropathy they have and what he or she believes is causing it. If their neuropathy is rapidly getting worse and the neurologist is not conducting additional tests to uncover the reason, then they should get another opinion. However, while this is unfortunate, patients must remember that even in the best hands, 50 percent of neuropathies will have no identifiable cause. ■

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