



Peripheral Neuropathy

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
National Institutes of Health

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What is peripheral neuropathy?

Peripheral neuropathy refers to the many conditions that involve damage to the peripheral nervous system, the vast communication network that sends signals between the central nervous system (the brain and spinal cord) and all other parts of the body. Peripheral nerves send many types of sensory information to the central nervous system (CNS), such as a message that the feet are cold. They also carry signals from the CNS to the rest of the body. Best known are the signals to the muscles that tell them to contract, which is how we move, but there are different types of signals that help control everything from our heart and blood vessels, digestion, urination, sexual function, to our bones and immune system. The peripheral nerves are like the cables that connect the different parts of a computer or connect the Internet. When they malfunction, complex functions can grind to a halt.

Nerve signaling in neuropathy is disrupted in three ways:

- loss of signals normally sent (like a broken wire)
- inappropriate signaling when there shouldn't be any (like static on a telephone line)
- errors that distort the messages being sent (like a wavy television picture)

Symptoms can range from mild to disabling and are rarely life-threatening. The symptoms depend on the type of nerve fibers affected and the type and severity of damage. Symptoms may develop over days, weeks, or years. In some cases, the symptoms improve on their own and may not require advanced care. Unlike nerve cells in the central nervous system, peripheral nerve cells continue to grow throughout life.

Some forms of neuropathy involve damage to only one nerve (called *mononeuropathy*). Neuropathy affecting two or more nerves in different areas is called *multiple mononeuropathy* or *mononeuropathy multiplex*. More often, many or most of the nerves are affected (called *polyneuropathy*).

More than 20 million people in the United States have been estimated to have some form of peripheral neuropathy, but this figure may be significantly higher—not all people with symptoms of neuropathy are tested for the disease and tests currently don't look for all forms of neuropathy. Neuropathy is often misdiagnosed due to its complex array of symptoms.

How are the peripheral neuropathies classified?

More than 100 types of peripheral neuropathy have been identified, each with its own symptoms and prognosis. Symptoms vary depending on the type of nerves—motor, sensory, or autonomic—that are damaged.

- **Motor nerves** control the movement of all muscles under conscious control, such as those used for walking, grasping things, or talking.
- **Sensory nerves** transmit information such as the feeling of a light touch, temperature, or the pain from a cut.
- **Autonomic nerves** control organs to regulate activities that people do not control consciously, such as breathing, digesting food, and heart and gland functions.

Most neuropathies affect all three types of nerve fibers to varying degrees; others primarily affect one or two types. Doctors use terms such as predominantly motor neuropathy, predominantly sensory neuropathy, sensory-motor neuropathy, or autonomic neuropathy to describe different conditions.

About three-fourths of polyneuropathies are “length-dependent,” meaning the farthest nerve endings in the feet are where symptoms develop first or are worse. In severe cases, such neuropathies can spread upwards toward the central parts of the body. In non-length dependent polyneuropathies, the symptoms can start more toward the torso, or are patchy.

What are the symptoms of peripheral nerve damage?

Symptoms are related to the type of nerves affected.

Motor nerve damage is most commonly associated with muscle weakness. Other symptoms include painful cramps, fasciculations (uncontrolled muscle twitching visible under the skin), and muscle shrinking.

Sensory nerve damage causes various symptoms because sensory nerves have a broad range of functions.

- Damage to large sensory fibers harms the ability to feel vibrations and touch, especially in the hands and feet. You may feel as if you are wearing gloves and stockings even when you are not. This damage may contribute to the loss of reflexes (as can motor nerve damage). Loss of position sense often makes people unable to coordinate complex movements like walking or fastening buttons or maintaining their balance when their eyes are shut.
- The “small fibers” without myelin sheaths (protective coating, like insulation that normally surrounds a wire) include fiber extensions called axons that transmit pain and temperature sensations. Small-fiber polyneuropathy can interfere with the ability to feel pain or changes in temperature. It is often difficult for medical caregivers to control, which can seriously affect a patient’s emotional well-being and

overall quality of life. Neuropathic pain is sometimes worse at night, disrupting sleep. It can be caused by pain receptors firing spontaneously without any known trigger, or by difficulties with signal processing in the spinal cord that may cause you to feel severe pain (allodynia) from a light touch that is normally painless. For example, you might experience pain from the touch of your bedsheets, even when draped lightly over the body.

Autonomic nerve damage affects the axons in small-fiber neuropathies. Common symptoms include excess sweating, heat intolerance, inability to expand and contract the small blood vessels that regulate blood pressure, and gastrointestinal symptoms. Although rare, some people develop problems eating or swallowing if the nerves that control the esophagus are affected.

There are several types of peripheral neuropathies, the most common of which is linked to diabetes. Another serious polyneuropathy is Guillain-Barré syndrome, which occurs when the body's immune system mistakenly attacks the nerves in the body. Common types of focal (located to just one part of the body) mononeuropathy include carpal tunnel syndrome, which affects the hand and the wrist, and meralgia paresthetica, which causes numbness and tingling on one thigh. Complex regional pain syndrome is a class of lingering neuropathies where small-fibers are mostly damaged.

What are the causes of peripheral neuropathy?

Most instances of neuropathy are either *acquired*, meaning the neuropathy or the inevitability of getting it isn't present from the beginning of life, or *genetic*. Acquired neuropathies are either symptomatic (the result of another disorder or condition; see below) or idiopathic (meaning it has no known cause).

Causes of symptomatic acquired peripheral neuropathy include:

- *Physical injury (trauma)* is the most common cause of acquired single-nerve injury. Injury from automobile accidents, falls, sports, and medical procedures can stretch, crush, or compress nerves, or detach them from the spinal cord. Less severe traumas also can cause serious nerve damage. Broken or dislocated bones can exert damaging pressure on neighboring nerves and slipped disks between vertebrae can compress nerve fibers where they emerge from the spinal cord. Arthritis, prolonged pressure on a nerve (such as by a cast), or repetitive, forceful activities can cause ligaments or tendons to swell, which narrows slender nerve pathways. Ulnar neuropathy and carpal tunnel syndrome are common types of neuropathy from trapped or compressed nerves at the elbow or wrist. In some cases, there are underlying medical causes (such as diabetes) that prevent the nerves from tolerating the stresses of everyday living.

- *Diabetes* is the leading cause of polyneuropathy in the United States. About 60 - 70 percent of people with diabetes have mild to severe forms of damage to sensory, motor, and autonomic nerves that cause such symptoms as numb, tingling, or burning feet, one-sided bands or pain, and numbness and weakness on the trunk or pelvis.
- *Vascular and blood problems* that decrease oxygen supply to the peripheral nerves can lead to nerve tissue damage. Diabetes, smoking, and narrowing of the arteries from high blood pressure or atherosclerosis (fatty deposits on the inside of blood vessel walls) can lead to neuropathy. Blood vessel wall thickening and scarring from vasculitis can impede blood flow and cause patchy nerve damage in which isolated nerves in different areas are damaged—called mononeuropathy multiplex or multifocal mononeuropathy.
- *Systemic (body-wide) autoimmune diseases*, in which the immune system mistakenly attacks a number of the body's own tissues, can directly target nerves or cause problems when surrounding tissues compress or entrap nerves. Sjögren's syndrome, lupus, and rheumatoid arthritis are some systemic autoimmune diseases that cause neuropathic pain.
- *Autoimmune diseases that attack nerves only* are often triggered by recent infections. They can develop quickly or slowly, while others become chronic and fluctuate in

severity. Damage to the motor fibers that go to the muscle includes visible weakness and muscle shrinking seen in Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy. Multifocal motor neuropathy is a form of inflammatory neuropathy that affects motor nerves exclusively. In other autoimmune neuropathies the small fibers are attacked, leaving people with unexplained chronic pain and autonomic symptoms.

- *Hormonal imbalances* can disturb normal metabolic processes, leading to swollen tissues that can press on peripheral nerves.
- *Kidney and liver disorders* can lead to abnormally high amounts of toxic substances in the blood that can damage nerve tissue. Most individuals on dialysis because of kidney failure develop varying levels of polyneuropathy.
- *Nutritional or vitamin imbalances, alcoholism, and exposure to toxins* can damage nerves and cause neuropathy. Vitamin B12 deficiency and excess vitamin B6 are the best known vitamin-related causes. Several medications have been shown to occasionally cause neuropathy.
- *Certain cancers and benign tumors* cause neuropathy in various ways. Tumors sometimes infiltrate or press on nerve fibers. Paraneoplastic syndromes, a group of rare degenerative disorders that are triggered by a person's immune system response to a cancer, can indirectly cause widespread nerve damage.

- *Chemotherapy drugs* used to treat cancer cause polyneuropathy in an estimated 30 to 40 percent of users. Only certain chemotherapy drugs cause neuropathy and not all people get it. Chemotherapy-induced peripheral neuropathy may continue long after stopping chemotherapy. Radiation therapy also can cause nerve damage, sometimes starting months or years later.
- *Infections* can attack nerve tissues and cause neuropathy. Viruses such as varicella-zoster virus (which causes chicken pox and shingles), West Nile virus, cytomegalovirus, and herpes simplex target sensory fibers, causing attacks of sharp, lightning-like pain. Lyme disease, carried by tick bites, can cause a range of neuropathic symptoms, often within a few weeks of being infected. The human immunodeficiency virus (HIV), which causes AIDS, can extensively damage the central and peripheral nervous systems. An estimated 30 percent of people who are HIV-positive develop peripheral neuropathy; 20 percent develop distal (away from the center of the body) neuropathic pain.

Genetically-caused polyneuropathies are rare. Genetic mutations can either be inherited or arise *de novo*, meaning they are completely new mutations to an individual and are not present in either parent. Some genetic mutations lead to mild neuropathies with symptoms that begin in early adulthood and result in little, if any, significant impairment.

More severe hereditary neuropathies often appear in infancy or childhood. Charcot-Marie-Tooth disease, also known as hereditary motor and sensory neuropathy, is one of the most common inherited neurological disorders.

The small-fiber neuropathies that present with pain, itch, and autonomic symptoms also can be genetic. As our understanding of genetic disorders increases, many new genes are being associated with peripheral neuropathy.

How is peripheral neuropathy diagnosed?

The bewildering array and variability of symptoms that neuropathies can cause often makes diagnosis difficult. A diagnosis of neuropathy typically includes:

- *Medical history.* A doctor will ask questions about symptoms and any triggers or relieving factors throughout the day, work environment, social habits, exposure to toxins, alcohol use, risk of infectious diseases, and family history of neurological diseases.
- *Physical and neurological exams.* A doctor will look for any evidence of body-wide diseases that can cause nerve damage, such as diabetes. A neurological exam includes tests that may identify the cause of the neuropathic disorder as well as the extent and type of nerve damage.
- *Body fluid tests.* Various blood tests can detect diabetes, vitamin deficiencies, liver or kidney dysfunction, other metabolic disorders, infections, and signs of abnormal immune system activity. Less often other

body fluids are tested for abnormal proteins or the abnormal presence of immune cells or proteins associated with some immune-mediated neuropathies.

- *Genetic tests.* Gene tests are available for some inherited neuropathies.

Additional tests may be ordered to help determine the nature and extent of the neuropathy.

Physiologic tests of nerve function

- *Nerve conduction velocity (NCV)* tests measure signal strength and speed along specific large motor and sensory nerves. They can reveal nerves and nerve types affected and whether symptoms are caused by degeneration of the myelin sheath or the axon. During this test, a probe electrically stimulates a nerve fiber, which responds by generating its own electrical impulse. An electrode placed further along the nerve's pathway measures the speed of signal transmission along the axon. Slow transmission rates tend to indicate damage to the myelin sheath, while a reduction in the strength of impulses at normal speeds is a sign of axonal degeneration. Inability to elicit signals can indicate severe problems with either.
- *Electromyography (EMG)* involves inserting very fine needles into specific muscles to record their electrical activity at rest and during contraction. EMG tests irritability and responsiveness, detects abnormal muscular electrical activity in motor neuropathy, and can help differentiate between muscle and nerve disorders.

Neuropathology tests of nerve appearance

- *Nerve biopsy* involves removing and examining a sample of nerve tissue, usually a sensory nerve from the lower leg (called a sural nerve biopsy). Although a nerve biopsy can provide the most detailed information about the exact types of nerve cells and cell parts affected, it can further damage the nerve and leave chronic neuropathic pain and sensory loss.
- *Neurodiagnostic skin biopsy* allows specialists to examine nerve fiber endings following removal of only a tiny piece of skin (usually 3 mm diameter) under local anesthesia. Skin biopsies have become the gold standard for diagnosing small fiber neuropathies that don't affect standard nerve conduction studies and electromyography.

Autonomic testing

- Several different types of autonomic testing can evaluate peripheral neuropathies, one of which is a QSART test that measures the ability to sweat in several sites in the arm and leg. Abnormalities in QSART are associated with small fiber polyneuropathies.

Radiology imaging tests

- *Magnetic resonance imaging (MRI)* of the spine can reveal nerve root compression (“pinched nerve”), tumors, or other internal problems. MRI of the nerve (neurography) can show nerve compression.
- *Computed tomography (CT)* scans of the back can show herniated disks, spinal stenosis (narrowing of the spinal canal), tumors, and bone and vascular irregularities that may affect nerves.

- *Muscle and nerve ultrasound* is a noninvasive experimental technique for imaging nerves and muscles for injury such as a severed nerve or a compressed nerve. Ultrasound imaging of the muscles can detect abnormalities that may be related to a muscle or nerve disorder. Certain inherited muscle disorders have characteristic patterns on muscle ultrasound.

What treatments are available?

Treatments depend entirely on the type of nerve damage, symptoms, and location. Your doctor will explain how nerve damage is causing specific symptoms and how to minimize and manage them. With proper education, some people may be able to reduce their medication dose or manage their neuropathy without medications. Definitive treatment can permit functional recovery over time, as long as the nerve cell itself has not died.

Addressing neuropathy's causes. Correcting underlying causes can result in the neuropathy resolving on its own as the nerves recover or regenerate. Nerve health and resistance can be improved by healthy lifestyle habits such as maintaining optimal weight, avoiding toxic exposures, eating a balanced diet, and correcting vitamin deficiencies. Smoking cessation is particularly important because smoking constricts the blood vessels that supply nutrients to the peripheral nerves and can worsen neuropathic symptoms. Exercise can deliver more blood, oxygen, and nutrients to far-off nerve endings, improve muscle strength, and limit muscle atrophy. Self-care skills

in people with diabetes and others who have an impaired ability to feel pain can alleviate symptoms and often create conditions that encourage nerve regeneration. Strict control of blood glucose levels has been shown to reduce neuropathic symptoms and help people with diabetic neuropathy avoid further nerve damage.

Inflammatory and autoimmune conditions leading to neuropathy can be controlled using immunosuppressive drugs such as prednisone, cyclosporine, or azathioprine. Plasmapheresis—a procedure in which blood is removed, cleansed of immune system cells and antibodies, and then returned to the body—can help reduce inflammation or suppress immune system activity. Agents such as rituximab that target specific inflammatory cells, large intravenously administered doses of immunoglobulins, and antibodies that alter the immune system also can suppress abnormal immune system activity.

Specific symptoms can usually be improved

- For *motor symptoms*, mechanical aids such as hand or foot braces can help reduce physical disability and pain. Orthopedic shoes can improve gait disturbances and help prevent foot injuries. Splints for carpal tunnel problems can help position the wrist to reduce pressure of the compressed nerve and allow it to heal. Some people with severe weakness benefit from tendon transfers or bone fusions to hold their limbs in better position, or to release a nerve compression.

- *Autonomic symptoms* require detailed management depending on what they are. For example, people with orthostatic hypotension (significant drop in blood pressure when standing quickly) can learn to prevent drops by standing up slowly and taking medications to improve blood pressure swings. Many people use complementary methods and techniques such as acupuncture, massage, herbal medications, and cognitive behavioral or other psychotherapy approaches to cope with neuropathic pain.
- *Sensory symptoms*, such as neuropathic pain or itching caused by injury to a nerve or nerves, are more difficult to control without medication. Some people use behavioral strategies to cope with chronic pain as well as depression and anxiety that many may feel following nerve injury.

Medications recommended for chronic neuropathic pain are also used for other medical conditions. Among the most effective are a class of drugs first marketed to treat depression. Nortriptyline and newer serotonin-norepinephrine reuptake inhibitors such as duloxetine hydrochloride modulate pain by increasing the brain's ability to inhibit incoming pain signals. Another class of medications that quiets nerve cell electrical signaling is also used for epilepsy. Common drugs include gabapentin, pregabalin, and less often topiramate and lamotrigine. Carbamazepine

and oxcarbazepine are particularly effective for trigeminal neuralgia, a focal neuropathy of the face.

Local anesthetics and related drugs that block nerve conduction may help when other medications are ineffective or poorly tolerated. Medications put on the skin (topically administered) are generally appealing because they stay near the skin and have fewer unwanted side effects.

Lidocaine patches or creams applied to the skin can be helpful for small painful areas, such as localized chronic pain from mononeuropathies such as shingles. Another topical cream is capsaicin, a substance found in hot peppers that can desensitize peripheral pain nerve endings. Doctor-applied patches that contain higher concentrations of capsaicin offer longer term relief from neuropathic pain and itching, but they worsen small-fiber nerve damage. Weak over-the-counter formulations also are available. Lidocaine or longer acting bupivacaine are sometimes given using implanted pumps that deliver tiny quantities to the fluid that bathes the spinal cord, where they can quiet excess firing of pain cells without affecting the rest of the body. Other drugs treat chronic painful neuropathies by calming excess signaling.

Narcotics (opioids) can be used for pain that doesn't respond to other pain-control medications and if disease-improving

treatments aren't fully effective. Because pain relievers that contain opioids can lead to dependence and addiction, their use must be closely monitored by a physician. One of the newest drugs approved for treating diabetic neuropathy is tapentadol, which has both opioid activity and norepinephrine-reuptake inhibition activity of an antidepressant.

Surgery is the recommended treatment for some types of neuropathies. Protruding disks (“pinched nerve”) in the back or neck that compress nerve roots are commonly treated surgically to free the affected nerve root and allow it to heal. Trigeminal neuralgia on the face is also often treated with neurosurgical decompression. Injuries to a single nerve (mononeuropathy) caused by compression, entrapment, or rarely tumors or infections may require surgery to release the nerve compression. Polyneuropathies that involve more diffuse nerve damage, such as diabetic neuropathy, are not helped by surgical intervention. Surgeries or interventional procedures that attempt to reduce pain by cutting or injuring nerves are not often effective as they worsen nerve damage and the parts of the peripheral and central nervous system above the cut often continue to generate pain signals (“phantom pain”). More sophisticated and less damaging procedures such as electrically stimulating remaining peripheral nerve fibers or pain-processing areas of the spinal cord or brain have largely replaced these surgeries.

Transcutaneous electrical nerve stimulation

(TENS) is a noninvasive intervention used for pain relief in a range of conditions.

TENS involves attaching electrodes to the skin at the site of pain or near associated nerves and then administering a gentle electrical current. Although data from controlled clinical trials are not available to broadly establish its efficacy for peripheral neuropathies, in some studies TENS has been shown to improve neuropathic symptoms associated with diabetes.

How can I prevent neuropathy?

The best treatment is prevention, and strategies for reducing injuries are highly effective and well tested. Since medical procedures ranging from casting fractures to injuries from needles and surgery are another cause, unnecessary procedures should be avoided. The new adjuvanted vaccine against shingles prevents more than 95 percent of cases and is widely recommended for people over 50, including those who have had previous shingles or vaccination with the older, less effective vaccine. Diabetes and some other diseases are common preventable causes of neuropathy. People with neuropathy should ask their doctors to minimize use of medications that are known to cause or worsen neuropathy where alternatives exist. Some families with very severe genetic neuropathies use *in vitro* fertilization to prevent transmission to future generations.

What research is being done?

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to seek knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease. NINDS is a component of the National Institutes of Health (NIH), the leading supporter of biomedical research in the world.

NINDS-funded research ranges from clinical studies of the genetics and the natural history of hereditary neuropathies to discoveries of new cause and treatments for neuropathy, to basic science investigations of the biological mechanisms responsible for chronic neuropathic pain. Together, these diverse research areas will advance the development of new therapeutic and preventive strategies for peripheral neuropathies. Understanding the causes of neuropathy provides the foundation for finding effective prevention and treatment strategies.

Genetic mutations have been identified in more than 80 distinct hereditary neuropathies. NINDS supports studies to understand the disease mechanisms of these conditions and to identify other genetic defects that may play roles in causing or modifying the course of disease. The Inherited Neuropathies Consortium (INC)—a group of academic medical centers, patient support organizations, and clinical research resources dedicated to conducting clinical research in Charcot-Marie-Tooth disease and improving the care of people with the disease—seeks to better characterize the

natural history of several different forms of neuropathy and to identify genes that modify clinical features in these disorders. Knowing which genes are mutated, and what their normal function is, permits precise diagnosis and leads to new therapies that prevent or reduce nerve damage. INC is also developing and testing biomarkers (signs that can indicate the diagnosis or progression of a disease) and clinical outcome measures that will be needed in future clinical trials to determine whether individuals respond to candidate treatments.

Rapid communication between the peripheral nervous system and the central nervous system often depends on myelination, a process through which special cells called Schwann cells create an insulating coating around axons. Several NINDS-funded studies focus on understanding how myelin protein and membrane production and maintenance in Schwann cells is regulated and how mutations in genes involved in these processes cause peripheral neuropathies. Schwann cells play a critical role in the regeneration of nerve cell axons in the peripheral nervous system. By better understanding myelination and Schwann cell function, researchers hope to find targets for new therapies to treat or prevent nerve damage associated with neuropathy.

Other efforts focus on immune system peripheral nerve damage. In inflammatory peripheral neuropathies such as Guillain-Barré syndrome and chronic inflammatory

demyelinating polyneuropathy (CIDP), the body's immune system mistakenly attacks peripheral nerves, damaging myelin and weakening signaling along affected nerves. NINDS-supported researchers hope to better understand how antibodies to cell membrane components cause peripheral nerve damage and how the effects of these antibodies can be blocked. Researchers are also studying how mutations in the Autoimmune Regulator (AIRE) gene in a mouse model of CIDP cause the immune system to attack peripheral nerves. NINDS research has helped discover that some types of small-fiber polyneuropathy appear to be immune-caused, particularly in women and children.

NINDS-supported researchers are also exploring the use of tissue engineered from the cells of humans with peripheral neuropathy as models to identify specific defects in the transport of cellular components along axons and the interactions of nerves with muscles. Such tissue engineering approaches may eventually lead to new therapeutics for peripheral neuropathies.

In addition to efforts to treat or prevent underlying nerve damage, other NINDS-supported studies are informing new strategies for relieving neuropathic pain, fatigue, and other neuropathy symptoms. Researchers are investigating the pathways that carry pain signals to the brain and are working to identify substances that will block this signaling.

Where can I get more information?

For more information on neurological disorders or research programs funded by NINDS, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN

P.O. Box 5801
Bethesda, MD 20824
800-352-9424
www.ninds.nih.gov

Information also is available from the following organizations:

Foundation for Peripheral Neuropathy

485 Half Day Road
Suite 200
Buffalo Grove, IL 60089
877-883-9942
www.foundationforpn.org

Charcot-Marie-Tooth Association (CMTA)

P.O. Box 105
Glenolden, PA 19036
610-499-9264
800-606-2682
www.cmtausa.org

Muscular Dystrophy Association

2200 S. Riverside Plaza
Suite 1500
Chicago, IL 60606
520-529-2000
800-572-1717
www.mda.org

American Diabetes Association

2451 Crystal Drive

Suite 900

Arlington, VA 22202

703-549-1500

800-342-2383

www.diabetes.org

National Diabetes Information Clearinghouse (NDIC)

National Institute of Diabetes and

Digestive and Kidney Diseases

National Institutes of Health

1 Information Way

Bethesda, MD 20892-3560

800-860-8747

www.diabetes.niddk.nih.gov

NeuropathyCommons.org

(information for patients, professionals, and
researchers hosted by Harvard University)

<https://neuropathycommons.org>





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