

Explaining Peripheral Neuropathy



Living Well with Neuropathy

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My Diagnosis

My Treatment Plan

1. What is Peripheral Neuropathy?

Peripheral Neuropathy or *Neuropathy* is the term used to describe disorders resulting from injury to the peripheral nerves. Peripheral nerves are outside the brain and spinal cord and carry information back and forth from your brain and spinal cord to the rest of the body. Neuropathy can be caused by diseases that affect only the peripheral nerves or by conditions that affect other parts of the body as well. And symptoms almost always involve weakness, numbness, or pain – usually in the arms and legs. The Peripheral Nervous System is one of the two main divisions of the body’s nervous system. (The other is the Central Nervous System, which includes the brain and spinal cord.) “Peripheral” means away from the center: and this system contains the nerves that connect the Central Nervous System to the muscles, skin, and internal organs.

2. What are the symptoms?

Some neuropathies come on suddenly, others gradually over many years. The symptoms depend on the types of nerves affected and their location, but the problem usually starts with weakness, numbness, or pain. Here are some of the telltale signs people describe.

- **Weakness in the arms or legs.**

Usually caused by damage to the motor nerves, leg symptoms include difficulty walking or running, “heaviness” – it takes most of your strength just to climb the stairs – and stumbling or tiring easily. Muscle cramps may be common.

In the arms, difficulties with carrying a load of groceries, opening jars, turning door knobs, or combing your hair. Or you may be frustrated to

find you keep dropping things you thought you had a good grip on.

- **Numbness, tingling, and pain.**

The sensory nerves, when damaged, can cause many different symptoms. Early on, you may have spontaneous sensations, called *paresthesias* which include numbness, tingling, pins and needles, prickling, burning, cold, pinching, sharp, deep stabs, electric shocks, or buzzing. They are usually worse at night, often painful and severe. Unpleasant abnormal sensations brought on by touching or other stimuli are called *dysesthesias*. Or instead, you may have *anesthesia*, a lessening or absence of sensation, which can cause you to burn or cut yourself and not know it.

- **Absence of position sense.**

When you have this symptom, you're probably not sure just where your feet are and may thus be uncoordinated and unsteady when you walk. Or you may realize that the way you walk has changed, but not be sure exactly how or why. Chances are you have widened your gait in an unconscious effort to keep your balance, or that you tend to drag your feet.

- **“Glove and Stocking Sensation”.**

This is what doctors call the odd feeling you may have that you're wearing stockings or gloves or slippers when, in fact, your hands and feet are completely bare.

- **Symptoms of Autonomic Damage**

Damage to the autonomic nerves can cause dizziness when standing up, constipation,

diarrhea, sexual dysfunction, and thinning of the skin, with easy bruising and poor healing.

3. How is Neuropathy diagnosed?

While many healthcare providers such as podiatrists, endocrinologists, pain management physicians, primary care physicians, podiatrists or acupuncturists can most likely determine that a patient has a type of neuropathy, usually a neurologist trained in neuromuscular disease is the most qualified practitioner to definitively diagnose neuropathy. Depending on the cause, treatment can slow, halt, or reverse the neuropathy. Once the damage is stopped, the nerves can then regenerate. The extent of the recovery depends on how much damage was done, so the less the damage, the better the recovery. *Therefore, it is very important to diagnose the disease as early as possible and begin treatment.*

Complete health history: The neurologist first takes a careful history of the symptoms including onset, duration and location as well as a complete list of medications taken.

Neurological exam: this examines reflexes, strength and the ability to feel sensations.

Blood and urine tests: the physician will order a number of lab tests to help identify the cause of the neuropathy. This may include tests for vitamin levels, immune response, blood sugar levels, presence of toxins or infections and underlying diseases or genetic defects.

Electromyography (EMG) and nerve conduction studies: these are used to measure the electrical properties of the nerves. These tests can identify the abnormal nerves and their distribution, and determine

whether the myelin sheaths or the axons are primarily affected.

Nerve and muscle biopsy can provide important information about the type and cause of the neuropathy. You can see the nerve and examine it for evidence of vasculitis, infection, inflammation, or abnormal deposits.

MRI: This may be performed to rule out other causes of the neuropathy such as trauma or nerve entrapment and sometimes shows inflammation along the nerves.

A lumbar puncture (spinal tap) is often useful for identifying infection or inflammation.

4. What are the treatments?

There are two goals for treatment:

- a. eliminate the cause of the disease (if known)
- b. relieve its symptoms

a. Treatments aimed at eliminating causes:

Vitamin deficiency can be corrected by the oral supplementation or injection of the deficient vitamin.

Infections are treated with antibiotics or antiviral agents.

Autoimmune diseases are treated by IVIG (intravenous immune globulin), plasmapheresis or immunosuppression or using corticosteroids.

Paraneoplastic neuropathies are treated by eliminating the underlying tumor.

Toxic or drug-induced neuropathies are treated by removing the offending agent.

Diabetic neuropathy is treated by close control of the hyperglycemia, healthy diet and exercise.

b. Treatments to relieve symptoms:

Medications - Although medication cannot reverse neuropathy nor relieve numbness, it may relieve the pain. The most common medications used to treat neuropathic pain are anti-depressant and anti-seizure medications.

Anti-seizure medications: Gabapentin (Neurontin), Pregabalin (Lyrica), Topiramate (Topamax)

Anti-depressants: Duloxetine (Cymbalta), Nortriptyline (Pamelor), Amitriptyline (Elavil)

Topical agents: Lidocaine patch (Lidoderm), Capsaicin cream

NSAIDS - Advil, Naproxen

Opiates - Hydrocodone, Oxycodone

Complementary Treatments - Acupuncture, massage and relaxation techniques may decrease pain and increase sensation where numbness occurs.

Physical and/or Occupational Therapy - Therapy can keep muscles strong and improve coordination and balance. Therapists can recommend assistive devices to help complete daily activities.

Decrease Inflammation in the Body - Our daily living causes a certain amount of inflammation, but too much irritates the body and this leads to illness and disease. Ways to decrease inflammation include:

Better nutrition - Eating a diet rich in B vitamins (especially B12), folic acid and anti-oxidants helps the body repair damage. Avoid too much sugar and eat a balanced diet full of colors from the rainbow. Avoid or drink very little alcohol.

Vitamins/Supplements - Many people take multivitamins and other supplements that may help with symptoms and improve overall health:

B12

Alpha Lipoic Acid

Vitamin D

Fish Oils

Acetyl-L-Carnitine

Metanx - FDA approved for diabetic neuropathy

Neuro-V

Exercise - Four types of exercise are important for overall good health and to improve strength and balance. Of course, talk with your physician before starting any new exercise program.

Aerobic conditioning - swim, elliptical or stationary bike

Strength training - progressive strengthening or weights

Balance training

Flexibility/stretching - Tai Chi or yoga

Handle Emotional Stress and Get Good Sleep - many people with neuropathy find their symptoms worsen during times of stress or when they don't get good sleep. Unfortunately, neuropathy symptoms often appear strongest at night and make it difficult to sleep. Find a way to handle stress and treat depression with counseling and get help finding ways to get your best night's sleep.

Supportive Care - Comfortable, good supportive shoes are critical to manage symptoms, Orthotics, leg braces, or a cane or other assistive walking device may help as

well. Good foot care is critical as neuropathy makes it difficult to know if you have a cut or injury to your feet.

Other Treatments - A pain management physician can provide a nerve block by injecting a nerve with medication that blocks or removes pain or symptoms. Other treatments include a TENS (transcutaneous electrical nerve stimulator) unit or insertion of a Spinal Cord Stimulator to intercept or mask the signal that goes from the brain and spine to the nerves.

5. More detail on the peripheral nerves

The basic unit of the peripheral nervous system is the “neuron” or nerve cell. Its job is to carry information by electrical impulse from one part of the body to another. Each nerve is made up of a cell body and a long projection or process called an “axon”. The axon carries impulses between the cell body and nerve terminals called “receptors” in the muscles, skin, or internal organs. Many axons are wrapped with a membrane, known as the “myelin sheath”, which insulates the axon so that it can conduct electrical impulses faster and more efficiently. Myelin, which can renew itself, is produced by another cell type called the “Schwann Cell” that lies alongside it.

Axons travel together in bundles called “nerve trunks”, in a special compartment, the “endoneurium”, which also contains blood vessels supplying nutrients to the nerves. These bundles span the body like wires in an intricate electrical network.

a. Three kinds of nerves

Within these bundles, there are three distinct kinds of nerves: motor; sensory; and autonomic.

Motor nerves are responsible for voluntary movement. Their cell bodies lie within the spinal cord, and their processes transmit signals outward to specialized motor receptors on the skeletal muscles. When you reach to open a door or run to catch a train, for instance, your motor nerves are at work.

Sensory nerves allow us to feel pain, vibrations or touch, recognize shapes by feel and sense where our limbs are positioned in space. Their cell bodies are grouped in specialized structures called sensory “ganglia” next to the spinal cord. And they transmit signals from sensory receptors in the skin and other organs inward to the Central Nervous System.

Autonomic nerves control involuntary functions like breathing, heartbeat, blood pressure, digestion, and sexual function. They work automatically when we’re awake or asleep and are not under our control. Their cell bodies, clustered in autonomic ganglia, are spread throughout the body. Although most neuropathies affect all three types of nerve fibers, to varying degrees, some diseases involve only one or two, and are thus said to be purely or predominantly motor, sensory, or autonomic neuropathies.

b. Is it Mono or Polyneuropathy?

Mononeuropathy is a disorder of a single peripheral nerve. It is usually caused by trauma, local compression – the nerve is being squeezed – or inflammation.

Examples include Carpal Tunnel Syndrome, a wrist and hand disorder, and Bell's Palsy, a facial nerve disorder. They affect single nerve trunks in distinct areas. If there is a problem in two or more nerve trunks in separate areas and it is caused by a generalized disorder like diabetes, for instance, the neuropathy is then called *Mononeuritis Multiplex*.

Polyneuropathy, the umbrella name for the greatest number of Peripheral Neuropathies, means that the disorder is diffuse and symmetric – relatively the same on both sides of the body. When motor and sensory fibers are affected, the neuropathy is called “sensorimotor”. It usually begins in the hands and feet – the “distal” ends of the longest nerves.

Neuritis is an inflammation of the nerves caused by infection or the immune system.

Plexitis refers to an inflammation of a nerve plexus – a place where many nerves come together and interconnect. Two common spots are the brachial plexus under the shoulder, which causes arm weakness, and the lumbosacral plexus in the pelvis, causing weakness in the legs.

6. Types of Peripheral Neuropathy

Since anything that damages the peripheral nerves can cause neuropathy, there are over one hundred different identifiable causes or types. Some diseases and causes affect only the peripheral nerves; others also affect other parts of the body. Neuropathies are usually classified as Acquired or Inherited with most types being acquired. They are then further classified according to their causes or manifestations. For a few, the cause is only partly understood, and for many it cannot yet be identified. In

these cases, the neuropathy is called “Idiopathic”. It is estimated that about one-third of all neuropathies are idiopathic. In Section 8, you will find some detail on each of the major causes.

7. Getting Help

People who notice signs and symptoms that we have listed here should not wait to see what develops. Much as one may wish it, chances are that if the neuropathy is chronic, it is not going to go away by itself. Instead, the longer it takes for diagnosis and treatment, the worse it is apt to get and the harder it will be to treat successfully.

Some neuropathies develop quickly, but most develop slowly over the years. So get busy now – even if you don’t feel too badly. Nerve damage can be mild initially, but then if untreated, can spread and become much more serious, even irreversible. Find a good doctor. And don’t be a passive patient. You don’t have to accept a diagnosis that says nothing can be done about it. Instead, get other opinions. Read. Inform yourself. Find a support group and talk to others. Help raise money for research to find a cure. Over twenty million people in this country have neuropathy in one form or another. Yet it has been called the silent disease because too few people, both patients and doctors, are aware of it.

Local Help:

Neuropathy Alliance of Texas

www.neuropathyalliancetx.org is a Central Texas non-profit organization with a mission to provide hope and support to Texans with neuropathy. Their website lists local resources, physicians and a calendar of support group meetings to attend.

National Help:

The Foundation for Peripheral Neuropathy

www.foundationforpn.org focuses on all neuropathies

The Hereditary Neuropathy Foundation

www.hnf-cure.org focuses on all hereditary neuropathies

The Neuropathy Action Foundation

www.neuropathyaction.org focuses on multifocal motor neuropathies and access to IVIg

The Charcot-Marie Tooth Foundation

www.cmtausa.org focuses on helping those with CMT

National Center for Complementary and Alternative Medicine

nccih.nih.gov supports research on complimentary and alternative medicine (CAM).

8. The Many Causes of Peripheral Neuropathy

a. ACQUIRED NEUROPATHIES

Diabetic

Diabetes is the most common known cause of neuropathy and accounts for about one-third of all neuropathies. About half of all people with diabetes will develop neuropathy at some point. In most cases, the neuropathy is predominantly sensory, with pain and sensory loss in the hands and feet. But some diabetics have mononeuritis or mononeuritis multiplex which causes weakness in one or more nerves, or lumbosacral plexopathy or amyotrophy which causes weakness in the legs.

Immune-Mediated

The main function of the immune system is to protect the body against infectious organisms which enter from

outside. In some cases, however, the immune system turns against the body and causes autoimmune disease. The immune system consists of several types of white blood cells, including T-lymphocytes, which also regulate the immune response; and B-lymphocytes or plasma cells, which secrete specialized proteins called “antibodies”. Sometimes, for unknown reasons, the immune system mistakenly attacks parts of the body such as the peripheral nerves. This is “autoimmune” Peripheral Neuropathy. There are several different types, depending on the part of the peripheral nerve which is attacked and the type of the immune reaction. The following are brief descriptions of the neuropathies which are mediated by the immune system.

a. Guillain-Barré Syndrome (GBS) and Variants

Guillain-Barré is an acute neuropathy because it comes on suddenly or rapidly and can progress to paralysis and respiratory failure within days or weeks after onset. The neuropathy is caused when the immune system destroys the myelin sheath of the motor and sensory nerves. It is often preceded by infection, vaccination or trauma, which triggers the autoimmune reaction. The disease is self-limiting, with spontaneous recovery within six to eight weeks. But the recovery is often incomplete.

Other acute neuropathies include Acute Motor Neuropathy, Acute Sensory Neuropathy, and Acute Autonomic Neuropathy, in which there is an immune attack against the motor, sensory, or autonomic nerves, respectively. The Miller-Fisher Syndrome is another variant in which there is paralysis of the eye gaze, incoordination, and unsteady gait.

b. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

CIDP is thought to be a chronic and more indolent form of the Guillain-Barré Syndrome. The disease progresses either with repeated attacks, called relapses, or in a stepwise or steady fashion. As in GBS, there appears to be destruction of the myelin sheath by antibodies and T-lymphocytes. The diagnosis is based on the clinical and laboratory characteristics as well as a lumbar puncture (spinal tap).

c. Chronic Polyneuropathies with antibodies to Peripheral Nerves

In some types of chronic neuropathies, antibodies to specific components of nerve have been identified. These include demyelinating neuropathy associated with antibodies to the Myelin Associated Glycoprotein (MAG), motor neuropathy associated with antibodies to the gangliosides GM1 or GD1a, and sensory neuropathy associated with anti-sulfatide or GD1b ganglioside antibodies. The antibodies in these cases bind to oligosaccharide or sugar-like molecules, which are linked to proteins (glycoproteins) or lipids (glycolipids or gangliosides) in the nerves. It is suspected that these antibodies may be responsible for the neuropathies.

d. Neuropathy Associated with Vasculitis or Inflammation of Blood Vessels in Peripheral Nerves

Neuropathy can also be caused by Vasculitis – an inflammation of the blood vessels in the peripheral nerve. It produces small “strokes” along the

course of the peripheral nerves, and may be restricted to the nerves or it may be generalized, include a skin rash, or involve other organs.

Several rheumatological diseases like Rheumatoid Arthritis, Lupus, Periarteritis Nodosa, or Sjogren's Syndrome, are associated with generalized Vasculitis, which can also involve the peripheral nerves. Vasculitis can cause Polyneuritis, Mononeuritis, or Mononeuritis Multiplex, depending on the distribution and severity of the lesions.

e. Brachial or Lumbosacral Plexitis

The brachial plexus, which lies under the armpit, contains the nerves to the arm and hand. And when it's inflamed, you have what's called Brachial Plexitis, which produces weakness and pain in one or both arms. Lumbosacral Plexitis, which occurs in the pelvis, causes weakness and pain in the legs. These are usually self-limiting conditions, which may improve after the acute phase of the disease.

f. Neuropathies associated with Monoclonal Gammopathy

In Monoclonal Gammopathy, single clones of B-cells or plasma cells in the bone marrow or lymphoid organs expand to form benign or malignant tumors and secrete antibodies. "Monoclonal" is because there are single clones of antibodies. And "Gammopathy" stands for gammaglobulins, which is another name for antibodies. In some cases, (see "2c" above), the antibodies react with nerve components; in others, fragments of the antibodies form amyloid deposits (see Section "4").

Neuropathy Associated with Cancer

Neuropathy is a relatively common side effect of cancer and its treatment. Anyone diagnosed with cancer is at risk, but the following factors can increase the risk:

Location of tumor: a tumor pressing or growing on a nerve may damage it.

Chemotherapy: certain types of chemotherapy, especially in high doses may damage nerves

- Bortzomib (Velcade)
- Platinums including cisplatin (Platinol), oxaliplatin (Eloxatin) and carboplatin (Paraplatin)
- Taxanes including docetaxel (Docefrez, Taxotere) and paclitaxel (Taxol)
- Thalidomide (Synovir, Thalomid)
- Vinca alkaloids, including vincristine (Vincasar), vinorelbine (Navelbine) and vinblastine (Velban)

Radiation: radiation therapy may injure nerves and it may take several years for symptoms to appear

Cancer-related disorders: paraneoplastic disorders are rare and caused by the immune system's response to cancer cells in the body. Several types have been described.

- Sensory Neuropathy associated with Lung Cancer - This neuropathy is associated with antibodies to a protein called Hu, which is present in the sensory neurons of the peripheral nerves.
- Neuropathy Associated with Multiple Myeloma - Some people with Multiple Myeloma develop a Sensorimotor Polyneuropathy with degeneration of axons in the peripheral nerves.
- Neuropathy Associated with Waldenstrom's Macroglobulinemia, Chronic Lymphocytic Leukemia,

or B-cell Lymphoma -These are tumors caused by antibody-secreting B-lymphocytes in the spleen, bone marrow, or lymph nodes. These antibodies are monoclonal and frequently react with peripheral nerve components such as MAG, GM1, or sulfatide.

Neuropathy Associated with Amyloidosis

Amyloid is a substance which is deposited in the peripheral nerves and interferes with their operation: the disorder is Amyloidosis. There are two main types: Primary Amyloidosis, in which the deposits contain fragments of monoclonal antibodies (see the Monoclonal Gammopathy paragraph above); and Hereditary Amyloidosis, in which the deposits contain a mutated protein called Transthyretin. Primary Amyloidosis is usually associated with Monoclonal Gammopathies or myeloma. (See above.)

Neuropathy Caused by Infections

Neuropathy can be caused by infection of the peripheral nerves. Viruses causing Neuropathy include:

- AIDS virus HIV-1, which causes slowly progressive sensory neuropathy,
- Cytomegalovirus which causes a rapidly progressive paralytic neuropathy,
- Herpes Zoster which causes Shingles, and
- Poliovirus which causes a motor neuropathy.
- Hepatitis B or C infections are sometimes associated with vasculitic neuropathy.
- Leprosy which causes a patchy sensory neuropathy, and
- Bacterial infections that cause neuropathy include:
 - Diphtheria which can cause a rapidly progressive paralytic neuropathy.

- Lyme disease which is caused by a spirochete
- Trypanosomiasis which is caused by a parasite.

Neuropathy Caused by Nutritional Imbalance

Deficiencies of Vitamins B12, B1 (thiamine), B6 (pyridoxine), or E can produce polyneuropathies with degeneration of peripheral nerve axons. This can be due to poor diet, or inability to absorb the nutrients from the stomach or gut. Mega doses of Vitamin B6 can also cause a peripheral neuropathy.

Neuropathy Caused by Kidney Disease

Chronic renal failure can cause a predominantly sensory Peripheral Neuropathy with degeneration of the peripheral nerve axons.

Hypothyroid Neuropathy

Hypothyroidism is sometimes associated with a painful sensory polyneuropathy with axonal degeneration. Mononeuropathy or Mononeuropathy Multiplex can also occur due to compression of the peripheral nerves by swollen tissues.

Neuropathy caused by Alcohol and Toxins

Certain toxins can cause Peripheral Neuropathy. Lead toxicity is associated with a motor neuropathy; arsenic or mercury cause a sensory neuropathy, Thallium can cause a sensory and autonomic neuropathy. Several of the organic solvents and insecticides can also cause polyneuropathy. Alcohol is directly toxic to nerves and alcohol abuse is a major cause of neuropathy.

Neuropathy caused by Drugs

Several drugs are known to cause neuropathy in addition to the ones listed about for cancer treatment. Others include nitrofurantoin, which is used in pyelonephritis, amiodarone in cardiac arrhythmias, disulfiram in alcoholism, ddC and ddI in AIDS, and dapsone for Leprosy.

Neuropathy caused by trauma or compression

Localized neuropathies can result from compression of nerves by external pressure or overlying tendons and other tissues. The best known of these are the Carpal Tunnel Syndrome which results from compression at the wrist, and cervical or lumbar radiculopathies (Sciatica) which result from compression of nerve roots as they exit the spine. Other common areas of nerve compression include the elbows, armpits, and the back of the knees.

Idiopathic Neuropathy

About one-third of all neuropathies are idiopathic. The term “idiopathic” is used whenever the cause of the neuropathy cannot be found. In these cases, the neuropathy is classified according to its manifestations, i.e., sensory, motor, or sensorimotor idiopathic polyneuropathy.

B. HEREDITARY NEUROPATHIES

Hereditary neuropathies are caused by genetic abnormalities which are transmitted from generation to generation. For several of these, the genetic defect is known, and tests are available for diagnosis and prenatal counseling.

Charcot-Marie Tooth Disease (CMT)

This is a general term given to the hereditary sensorimotor neuropathies. CMT type 1 (CMT 1) is associated with demyelination or breakdown of the myelin sheaths. Several different abnormalities have been identified. CMT Type 1A is most commonly caused by duplication of a gene encoding a myelin protein called PMP-22, and CMT type 1B is caused by a mutation in a myelin protein called the Po glycoprotein. Hereditary neuropathy with liability to pressure palsies (HNPP) frequently results from deletion of the gene encoding pmp-22. CMTX is a hereditary sensorimotor neuropathy which is caused by a mutation in a gene encoding a protein called Connexin 32 on the X-chromosome.

Familial Amyloidotic Neuropathy and other Hereditary Neuropathies.

Familial Amyloidotic Neuropathy usually presents with pain, sensory loss, and autonomic dysfunction. It is caused by a mutation in a protein called Transthyretin, resulting in deposition of the protein as amyloid in the peripheral nerves.

Hereditary Porphyria is also associated with a Peripheral Neuropathy. There are other hereditary neuropathies in which the genetic defect has not yet been identified.

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