Peripheral neuropathy (PN) is a common disease in the general population and in the Waldenstrom community. It is defined as a diseased or degenerative state of the peripheral nerves in which nerve fibers are damaged. Peripheral nerves are all the nerves in the body that are not in the brain or spinal cord. They are divided into three categories: sensory, motor, and autonomic. Sensory nerves carry information from the body to the spinal cord and brain by an electrochemical signal. These signals are perceived as taste, smell, touch, sight, and hearing. Special sensors in the skin and deep inside the body help people identify if an object is sharp, rough, or smooth, if it's hot or cold, or if a body part is still or in motion. Sensory nerve damage can result in tingling, numbness, pain, and extreme sensitivity to touch. Motor nerves carry information from the brain and spinal cord to muscle fibers throughout the body to enable movement. Autonomic nerves regulate bodily functions such as temperature, heart rate, blood pressure, digestion, respiration, urination, and many others.

Peripheral neuropathy affects 3-4% of the general US population, increasing to 8% with advancing age, and affects at least thirty million people. A myriad of diseases, cancers, and medications can attack nerves, resulting in a neuropathy. This makes it very difficult to determine the cause.
Monoclonal gammopathy of unknown significance (MGUS) is present in 3.2% of the general population over fifty years old and increases to 9% by age 90. The major immunoglobulins present in MGUS patients and their incidence are IgA (12%), IgM (15%), and IgG (70%). PN is reported in 30-50% of IgM MGUS patients and up to 47% of WM patients. PN is reported by 25% of newly diagnosed WM patients as their presenting symptom at diagnosis. The clinical spectrum spans from distal paresthesias (abnormal skin sensations in the extremities) and mild gait imbalance to more severe sensory ataxia (loss of coordination), with falls and a varying degree of both sensory and motor deficits in the extremities.

**IgM MGUS and WM Neuropathy Etiology**

Myelin composes the peripheral nerve cell sheath, which is the insulation covering that protects the nerve, and is made by Schwann cells. Patients with PN caused by IgM MGUS or WM typically manifest symptoms associated with dysfunction or loss of large myelinated nerve fibers. This occurs because of specific IgM monoclonal proteins that attack peripheral nerves, causing demyelination of the nerves and neuropathy that ultimately lead to nerve death. If you have PN caused by monoclonal IgM, you have one of these anti-myelin IgMs, although not all of them have been delineated yet. Anti-MAG is the most prevalent in WM PN patients. Myelin associated glycoprotein (MAG) is a special type of glycoprotein that plays a role in a signaling cascade that “turns on” the Schwann cells, leading to normal myelin production and healthy peripheral nerve activity. Anti-MAG IgM blocks MAG, resulting in loss of myelin production and destruction of the nerve sheath. Patients with anti-MAG can develop a neuropathic tremor that may respond to currently approved WM therapies. Anti-MAG and anti-sulfoglucuronyl paragloboside (SGPG) are the major two glycoproteins that induce PN (50% and 25%, respectively). GM1, GM2, GD1A, GT1B, and GQ1B are other targets that result in PN—GM1 and GM2 induce motor neuropathy. All of these can be tested by a blood sample.

Polyneuropathies are rarely a presenting feature in WM, as anti-MAG or anti-SGPG are seen in 75% of neuropathy cases. Polyneuropathies can attack both sensory and motor nerves. Polyneuropathy can be associated with an anti-MAG antibody, and it is a demyelinating, slowly progressing, sensory or sensorimotor ataxic neuropathy. Other rare polyneuropathies are POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes); anti-GM1; anti-GM2; amyloidosis; CIDP (Chronic Inflammatory Demyelinating Polyneuropathy); cryoglobulinemia; and CANOMAD (Chronic Ataxic Neuropathy with Ophthalmoplegia, M protein, cold Agglutinins, and Disialosyl antibodies).

**IgM MGUS and WM Neuropathy Symptoms**

These include one or more of the following:
- Paresthesias, including numbness; burning, stabbing, lancing, boring, shooting pains; and pins and needles or tingling sensations. Many of these are worse at night.
- Sensitivity to touch or temperature.
• Loss of reflexes.
• Sensory neuropathy that is symmetrical and begins in the toes.
• Progression of symptoms up the legs, then the arms.
• Feeling like a sock is rolled up under your foot, or a feeling that you are wearing a tight, invisible glove or sock.
• Impaired balance, particularly in the dark.
• Distal extremity weakness.
• Motor damage – muscle weakness, cramps, spasms, twitching, muscle shrinking.
• Dizziness, especially when getting up from a bed or a chair.
• Loss of co-ordination and proprioception (the ability to sense stimuli arising within the body regarding position, motion, and equilibrium).
• Fatigue.
• Ataxia and tremors.

**Nerve Destruction**

As discussed previously, the IgM associated with anti-MAG and similar antibodies destroys the myelin covering of the nerve. Think of the myelin as the insulation covering of an electric cord. As the myelin insulation is destroyed, the nerve is exposed and dies. This is similar to the copper wire in an electrical cord that shorts out when the insulated wall has been stripped away. Which nerve in the body becomes demyelinated first? Of course, it would be the longest nerve in the body, as it has more myelin for the anti-MAG IgM to attack. That nerve is the one that goes from the spinal column to the toe. It is approximately four feet long, depending on your height. Breaks in the sheath will happen more quickly in that nerve. The neuropathy creeps up your leg as the disease progresses. The other leg will show symptoms at that same time because it is the same length. Once the PN is far enough up the legs, it begins to cause symptoms in the second longest nerves, in the arms. This type of PN is also called DADS (Distal Acquired Demyelinating Symmetric).

Some WM PN patients state that their PN began in the wrist, or the arm, or a rib, and so on. In order for that to happen, the patient has to have two diseases. Any nerve in the body that has had damage or is being damaged by a second disease will deteriorate faster into PN than a normal nerve. In the examples above, those patients must have had asymptomatic carpal tunnel syndrome, nerve impingement in the neck, or shingles in an intercostal nerve, previously or concurrently.

**PN Workup**

Determination of the cause of PN can be long and tedious. There are many other diseases, cancers, and drugs, more prevalent than IgM-MGUS or WM, which can cause PN:

• Diseases – diabetes, degenerative joint disease, infections in nerves, shingles, spinal cord injuries, poor circulation, hypothyroidism, surgery, radiation therapy, amyloidosis, renal
failure, inflammatory disease, heavy metal poisoning, prior chemotherapy, physical injury, alcohol abuse, low vitamin B-12, some autoimmune diseases, HIV, sarcoidosis, Lyme disease, hepatitis, cryoglobulinemia, and cold agglutinins.

- Common cancers – breast, lung, other B-cell lymphomas, ovarian, testicular, multiple myeloma, any cancer that presses on a nerve.
- Chemotherapy drugs – cisplatin, carboplatin, cytosine, tacrolimus, Taxol, Taxotere, Jevtana.
- WM therapy drugs – immunomodulatory drugs (IMiDs) such as Thalomid, Revlimid, Pomalyset; proteasome inhibitors such as Velcade, Kyprolis, Ninlaro.
- Other drugs – amiodarone, Flagyl, HIV medications, Antabuse, interferon, and others.

Considerable testing may be required to make the diagnosis.

Neurological tests may be used to help determine the nerve problem. Nerve conduction studies (NCS) and electromyography (EMG) are used to help define the neuropathy. Negative testing may not mean that you don’t have PN, since early in the disease these tests cannot pick it up. CT and MRI scans can discern nerve impingement, Bing-Neel syndrome, and masses that compress nerves.

Many people may have more than one disease, drug, or cancer that results in PN. That makes it difficult to come to a conclusion.

**More Specific Tests for PN from IgM MGUS and WM**

- Cerebrospinal fluid shows an elevated protein level (IgM) in 80% of demyelinating PN (>1 g/L).
- Anti-MAG IgM antibody testing.
- Anti-SGPG IgM antibody testing.
- WM neuropathy is mostly associated with IgM kappa light chains.
- If the diagnosis is unclear after a peripheral PN workup, multiple plasmaphereses should be considered. Plasmapheresis can be diagnostic and therapeutic. It will lower the IgM level considerably, although temporarily. Having three or four of these at two-to-three week intervals should temporarily improve the PN. If so, one has PN from IgM MGUS or WM.
- A sural nerve biopsy is also a definitive test. This is performed at the ankle. Sural nerve biopsies will cause a permanent sensory deficit on the lateral side of the foot and a 10-20% risk of post-biopsy pain. The biopsy will show IgM and an immune system protein called complement deposited on the myelin sheath and delamination (separation) of the sheath.
- Fat and skin biopsies are usually non-diagnostic, except, for example, in the case of fat pad biopsies and amyloidosis.
PN Medications
PN is a quality of life issue. Medications are used to allow the patient to remain functional, mobile, free of pain, and enjoy life. Over-the-counter medications are used to treat the minor symptoms of neuropathy. Escalation to prescription drugs is tailored by one’s doctor to fit each patient’s situation. Some of the drugs may also help with depression, hypertension, and degenerative joint disease.
  • Non-narcotic pain relievers – Tylenol, Motrin, Mobic
  • COX-2 inhibitors – Celebrex
  • Narcotics for pain
  • Ultram/ tramadol
  • Tricyclic antidepressants – Pamelor (nortriptyline), Elavil (amitriptyline), Cymbalta (duloxetine)
  • Topical medications and/or lidocaine patches
  • Alpha 2 adrenergic agonists – Clonidine (blood pressure medication)
  • Anti-seizure medications – Neurontin (gabapentin), Lyrica (pregabalin)

Waldenstrom Treatment for PN
The only way to decrease the progression of PN due to monoclonal IgM in WM patients relies on lowering the IgM level. If the PN becomes a quality of life issue, consideration should be given to WM treatment. Early treatment intervention may prevent debilitating neuropathy. Nerve regrowth after treatment may take up to two years to resolve neuropathy. Neuropathy is permanent after two years if not treated, but treatment may still prevent its worsening.

Local treatments with nerve blocks or a transcutaneous electrical nerve stimulation (TENS unit) may be of value. Steroids are used only in those with inflammatory or autoimmune neuropathy like CIDP. IVIG is rarely used now as it is only 15-20% effective, has only short term benefit, and costs approximately $10,000 per course.

The first drug tested to lower IgM for WM PN was Rituxan in the early 2000s. It has been the mainstay treatment for WM PN when there are no other WM problems, due to its safety profile. However, it only has a 30-50% improvement rate. Combination therapies of other drugs with Rituxan are now the preferred first-line treatment of many indolent lymphomas, including Waldenstrom. It is logical to extrapolate conclusions from WM treatment results when treating WM PN. Many times those drugs are used with Rituxan for its synergy.

Mantras for PN from IgM MGUS and WM
  • Quality of life is paramount.
  • The presence of mild neuropathy alone is not a justification for WM treatment, but steady progression with accumulating disability or loss of quality of life should prompt action.
• Most WMers with neuropathy have relatively low IgM levels and predominant IgM kappa light chains.
• Drugs that induce neuropathy should not be used.
• The treatment goal for WM PN should be to use standardized treatment protocols. Perhaps those with non-improving WM PN after treatment, or those with anti-MAG, cryoglobulin, or amyloidosis should continue on treatment to lower the IgM as much as possible. Even if the IgM does not go back to normal, a significant improvement can be gained. Rituxan maintenance may help. Newer drugs, such as ibrutinib and venetoclax, lower the IgM considerably and may end up becoming the best therapies for PN.
• Rituxan alone may not give adequate relief.
• Nerve regrowth and function may take up to two years to return to normal.
• Stability, rather than improvement, is the likely outcome of treatment in someone with chronic neuropathy (> two years).
• Supportive treatment is helpful – orthotics, balance training, occupational and physical rehab.
• Medication usage and exercise help maintain quality of life.

Peripheral neuropathy can be a daunting problem and a huge quality of life issue. All patients with IgM-MGUS or WM should be aware of the symptoms of PN and report them to their physicians. If symptoms progress, their severity and effect on daily activities should be discussed at each visit. Your physician may not be aware of the fact that PN is a complication of WM. If so, provide a printed copy of this article or other medical information on PN related to WM to increase his or her knowledge on the subject. Ask for (insist upon) a neurology consult or a second opinion when the symptoms have become more than just a minor nuisance.