

GBS | CIDP

Foundation International

**Guillain-Barré Syndrome and
Chronic Inflammatory
Demyelinating Polyneuropathy**

*Serving patients of GBS, CIDP and Variants
with support, education and research*

***CIDP
Chronic Inflammatory
Demyelinating
Polyneuropathy***

*A publication of the
GBS/CIDP Foundation International*

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INTRODUCTION

This publication is an overview of a chronic but treatable disorder of peripheral nerves called Chronic Inflammatory Demyelinating Polyneuropathy or CIDP. It is primarily meant for use by patients and their families in whom the diagnosis of CIDP has been made or proposed. The symptoms, causes of nerve damage, tests to confirm the diagnosis and the variety of treatments available will be discussed. By doing so it is hoped that it might help the reader to better understand the disorder and the reasons one treatment might be selected over another.

What are peripheral nerves?



Peripheral nerves are bundles of nerve fibers called axons that connect the brain and spinal cord with the arms and legs. They carry electric-like impulses to muscles causing them to shorten or contract and relay sensations from skin and other organs such as pain, hot and cold back to the brain. Damage to these nerves produces weakness, muscle wasting, poor balance and numbness. Some of the causes of nerve damage include trauma, pressure on nerves, blood vessel blockage and inflammation. Immune or inflammatory mechanisms are implicated in a

number of chronic disorders affecting the peripheral nerve.

How common is CIDP and what type of person can develop it?

CIDP is one of the treatable but rare disorders caused by peripheral nerve inflammation. If left untreated, it results in progressive loss of strength and sensation in the legs and arms. Though more people develop CIDP when they are between the ages of 50 and 60 more than at any other time, people of all ages can get this disorder, from children to the elderly. Some studies suggest that CIDP affects men twice as often as women. The number of new cases of CIDP that occur each year in the United States and throughout the world is small. Only one and half to three and half people per million develop CIDP each year. The ongoing peripheral nerve damage from CIDP can extend over many years and even decades. At any one time, between 5,000 and 10,000 people in the United States are affected by it.

What are the symptoms of CIDP?

A patient with CIDP will usually report loss of strength and sensation equally in both legs and arms.. Most patients complain of difficulty climbing stairs or lifting their arms up to carry a bag of groceries, shave or blow dry their hair. These symptoms indicate muscle weakness. Signs of sensory nerve involvement are numbness, pins and needles sensation, unsteadiness or poor

balance, shaking of your hand while reaching for objects, or pain. The development of symptoms can occur in steady or stepwise fashion over a period of at least eight weeks. The slower and prolonged progression over two months distinguishes it from more acute neuropathies such as the Guillain Barré syndrome also known as GBS, where most patients develop their peak weakness within 1 to 4 weeks. This is an important difference, since many patients are mistakenly told they have GBS or chronic GBS. This confusion may lead to delayed or incorrect treatment. During the recovery that follows, most patients with Guillain Barré syndrome walk without help within three months. Unlike Guillain Barré syndrome, CIDP does not automatically go away. Although patients in the past could, over time, become very weak to the point where they required a wheel chair, currently available treatment insures that 90% of patients are able to walk without aid and enjoy an active life. CIDP develops differently in individual patients. Some forms progress gradually over several years. Others consist of multiple episodes that may be separated by months or even years. A third type is more limited and extends from one to, perhaps, three years.

What causes CIDP?

The factors that cause patients to develop CIDP as opposed to the more limited course of GBS are not known. Some investigators suspect that certain patients may inherit a gene that makes them more at risk to develop CIDP, but at this time, there is no strong evidence to support this theory. Rarely, CIDP can affect more than one family member, brothers or sisters or a parent and child, but it does not normally occur in later generations.

The way in which the nerve is damaged in CIDP is not fully understood. Most evidence suggests that this is a condition caused by our own immune system. Each of our bodies has an immune system that includes antibodies, certain plasma proteins and white blood cells. It normally fights off viruses and other infections. In some disorders, the immune system, by mistake, reacts against parts of our bodies causing disease. This may be the case with CIDP. With CIDP, drugs that regulate a patient's immune system can be used to treat and prevent peripheral nerve damage in CIDP patients.

Figure 1 shows healthy peripheral nerve consisting of a bundle of nerve fibers surrounded by a connective tissue sheath. Certain fibers carry impulses to muscle while others carry sensory information back to the brain and spinal cord.

Figure 2 shows a single fiber known as an axon that is surrounded by a casing, or sheath, covering the fibers. This fat-rich tissue called myelin is produced by a special cell called a Schwann cell. Myelin works like insulating material that wraps around an electrical wire. If it is stripped, it can cause the wire to short out.

In the nerves of CIDP patients, the myelin surrounding the motor and sensory nerves is attacked and stripped from the nerve by invading white blood cells called macrophages (Figure 3). This loss of myelin makes it difficult for the nerve to conduct electrical messages from the brain and is the reason patients become weak or lose the ability to detect certain sensations. In patients with prolonged or severe cases, the nerve fiber or axon can be damaged, contributing to prolonged and

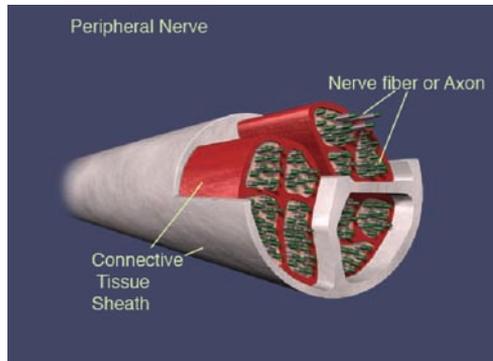


Figure 1: Peripheral nerve diagram

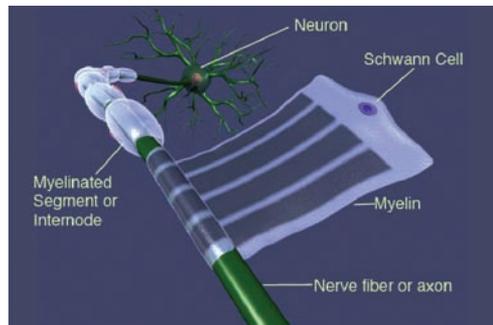


Figure 2: Myelinated nerve fiber

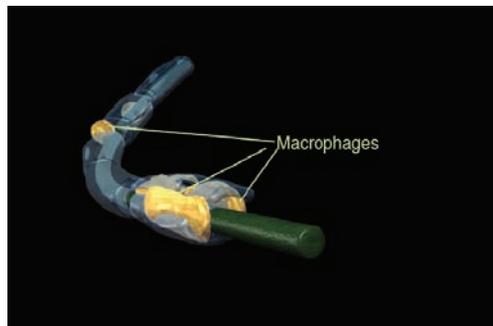


Figure 3: Nerve Fiber demyelination

prolonged and severe cases, the nerve fiber or axon can be damaged, contributing to prolonged and

poor recovery even with adequate treatment.

During CIDP, the peripheral nerve continually repairs itself, re-growing damaged nerve fibers and replacing the myelin. This repair process may be slower with older people than with younger people, causing them to have a poorer recovery.

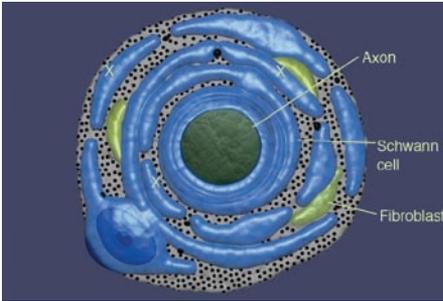


Figure 4: Onion bulb formation

Over time with repeated episodes of myelin damage and attempted repair, layers of the myelin producing-

Schwann and other cells produce a swelling around the nerve fiber called an “onion bulb”. Normal myelin formation is prevented which further limits the nerve’s ability to function.

How is CIDP diagnosed?

One of the critical issues facing the patient and the practicing neurologist is early recognition and treatment of CIDP patients when they are more likely to respond and in some cases go into remission. Unfortunately, there is no definitive diagnostic test for this disorder. The diagnosis instead is based on a combination of the clinical history provided by the patient, the examination performed by a neurologist and supporting diagnostic studies including nerve conduction velocities and a cerebrospinal fluid examination. Studies on the patient’s blood samples are also done to exclude other conditions such as diabetes, infections, toxin exposure and inflammatory disease of blood vessels. Infrequently a nerve biopsy will be done to either confirm the diagnosis of CIDP or rule out other disease entities.

The symptoms the patient experiences and the neurologist confirms by examination include:

- Muscle weakness
- Loss of deep tendon reflexes
- Poor balance
- Distal loss (feet or hands > calves or forearms) of sensation including the ability to feel pain, light touch, vibration
- Decreased perception of the position of a body part relative to the

space around the patient which is otherwise known as proprioception.

Although most patients manifest weakness early in their disease, a predominantly sensory form can occur that results in poor balance, clumsiness, and falling. Seventy percent of these primarily sensory patients develop muscle weakness within two to three years.

CIDP is clinically distinct from a variety of other inflammatory neuropathies which include:

- Multifocal Motor Neuropathy (MMN)
- Multifocal Sensory Neuropathy,
- Distal Acquired Demyelinating Sensory and Motor Neuropathy (DADS)
- Multifocal Acquired Demyelinating Sensory and Motor Neuropathy (MADSAM), or the Lewis Sumner syndrome.

MMN and the Lewis Sumner syndrome are distinguished from CIDP in that they have persistently asymmetrical weakness throughout their clinical course. In the case of MMN the symptoms are primarily motor with little or no sensory involvement. The importance in distinguishing these presentations from CIDP is that not all of them respond to the same treatments.

What Tests are used to diagnose CIDP?

After the history and physical examination, one of the most important tests that help to support the diagnosis of CIDP is a study that measures the ability of nerves to transmit an electrical signal. This test is otherwise known as a nerve conduction velocity and is performed by trained physicians or technicians under the supervision of a physician. At least three different nerves in the arms and legs are directly stimulated by a brief electrical impulse in two more places along the path of each nerve. Stimulation of the nerve is detected by contraction of a muscle that the nerve controls or innervates. Contraction of the muscle is measured with flat electrodes applied to the surface of the muscle. If there is significant myelin loss, reflecting peripheral nerve demyelination, the ability of the nerve to conduct the electrical impulse is either slowed or blocked. In addition to the nerve conduction velocities, the examiner will use a thin, acupuncture-like needle, placed into a poorly functioning or weak muscle, to look for evidence of

muscle fibers that are no longer innervated by the nerve, as a measure of nerve damage.

A spinal fluid examination can also be helpful in supporting the diagnosis of CIDP. During a lumbar puncture, the patient either lies on his or her side or sits upright. After the back is cleaned with an antiseptic solution, a local anesthetic medicine, similar to that used in a dentist's office, is injected into the skin and the tissue beneath it. When the skin is numb, a thin needle is inserted in between two spinal vertebrae in the middle of your back at the level of the hip bones below the bottom of the spinal cord which ends at about the level of the waist. The needle is pushed forward gently until the spinal fluid is found. Two to three teaspoonfuls of fluid are removed for testing and put into special sterile tubes. Spinal fluid from CIDP patients frequently shows increased protein content but no significant numbers of white blood cells. The presence of large numbers of white blood cells could indicate that infection or other diseases are causing the patient's symptoms.

Nerve biopsy is usually not required but may be considered in cases where the diagnosis is in question; for example, with pure sensory syndromes or where other conditions such as inflammation of blood vessels are suspected.

There is no specific blood test for CIDP, but blood is studied to look for other diseases that can also cause nerve damage that can clinically look like CIDP. Some of these diseases include Diabetes Mellitus Type II, inflammation of blood vessels such as Systemic Lupus Erythematosus, infections such as Lyme disease, and forms of hereditary neuropathy. In MMN, 30-60% of cases have antibodies to certain lipids called gangliosides including GM1 and GD1a. Elevated titers or levels of these antibodies are not specific for MMN but help to support the diagnosis. Blood tests are also used to determine any abnormal function in organs such as kidney or liver that might impact therapy selection.

How is CIDP treated?

Although the cause of CIDP is not well understood, up to eighty percent of CIDP patients respond to one or more therapies that modulate the immune system. Treatments shown to work in

clinical trials include prescribing corticosteroids, blood plasma exchange or plasmapheresis, and intravenous immunoglobulin or IVIG. All three treatments are highly effective and lead to improved strength and function in CIDP patients. Each treatment has its advantages and disadvantages that should be discussed with the physician.

A steroid such as Prednisone (60-100mg/ day) can be taken by mouth and given in doses that decrease over time. Other regimens include the use of larger oral doses or intravenous preparations given monthly. Corticosteroids may take five to eight weeks to see significant benefit but are effective and inexpensive. It can result in better muscle strength, improved coordination, speed and strength of the signal being transmitted by nerve fibers. Side effects of treatment are usually mild and include irritability and weight gain. Less frequently some patients may become depressed, experience elevated blood sugar, calcium loss from the bone or osteoporosis, and high blood pressure. Side effects are reduced by use of the smallest possible steroid dose that is effective in each patient. Patients should anticipate being on this drug for one year or more. Additional drugs may be used to further decrease the steroid dose. Such agents include azathioprine and mycophenolate mofetil, among others.

Plasmapheresis or plasma exchange is a procedure that removes plasma from the blood and replaces it with a new fluid. This procedure is done through a rigid tube or catheter that is inserted into a large vein in the neck or under the collarbone. At first, the procedure is repeated five times, every other day over a ten day period. Plasma exchange is safe when done by an experienced center and causes rapid improvement in many patients. If the procedure is not repeated, the benefit is lost usually within three to four weeks. Rare complications during exchange can include abnormal heart beat, salt imbalances in the blood, low blood calcium, red blood cell damage, infection, and bleeding. Because the use of this treatment is limited by the need for repeated catheter placement, most patients, over time, will require other treatments to manage their condition.

Intravenous immunoglobulin (IVIG) is a sterile solution of concentrated highly purified antibodies taken from several thousand healthy people and put directly into a vein of the patient. IVIG is equally as effective as plasma exchange in the treatment of

CIDP patients. Gammunex, a form of IVIG, received an indication in October, 2008 from the Federal Drug Administration for treatment of CIDP in the United States

The treatment is given through a medium size vein in the forearm over two or five days in equal daily doses. Due to the safety of IVIG, it is usually given in an outpatient clinic or at home by an infusion service. The response of the patient may be seen as early as three to five days after starting the infusions. Improvement can continue over three to six weeks. Like plasma exchange, the improvement may be lost unless the patient is re-treated. A positive clinical response can be frequently maintained with IVIG given repeatedly each month. IVIG is well tolerated, and the IVIG preparations available today are safe without risk of viral infection. Side effects can occur in a limited number of patients some of which are more severe than others. Most common side effects reflect the IVIG infusion rate and occur at the time or immediately after the infusion. These include headache, muscle aches, fever, chills, rapid heart beat, and high blood pressure. This type of side effect can be avoided by slowing the infusion rate or by giving aspirin, Tylenol, methylprednisolone or Benadryl prior to the treatment. Very rarely, serious side effects can occur in patients with a prior history of kidney disease, stroke or heart attack. Studies are currently ongoing to determine if Immunoglobulin can be self-administered by injections under the skin or subcutaneously. Subcutaneous administration would eliminate the side effects associated with intravenous infusions and reduce the costs for nurses, clinics and patient related travel.

Other drugs that decrease immune function or inflammation are used in the treatment of CIDP. The use of these drugs is supported by the experience of individual physicians treating patients who have failed one or more of the primary treatments that we have just talked about, or patients that have side effects from primary treatments. In these cases immunosuppressive drugs such as cyclophosphamide, cyclosporin, tacrolimus, mycophenolate mofetil, azathioprine and type 1 interferon (INF-1?) and IFN-beta can be used to limit corticosteroid and immunoglobulin use and may be indicated because of disease progression or poor response despite aggressive treatment with established therapies. The

immunosuppressive drugs are not as frequently used in younger patients where exposure may increase their risk of cancer, sterility or birth defects in their offspring.

Are other forms of chronic inflammatory neuropathies treated the same way as CIDP?

Multifocal motor neuropathy (MMN) is clinically distinct from CIDP and responds differently to standard therapies discussed above. IVIG use in MMN is supported by randomized controlled trials and is considered to be the treatment of choice for this entity. In contrast to CIDP patients with MMN either do not respond to corticosteroids or plasma exchange or actually get worse. MMN is one of the most chronic acquired inflammatory neuropathies with disease potentially extending for decades. Despite treatment most patients show a gradual decline in nerve function, although this is slowed by IVIG. Other immunosuppressive drugs can be effective such as cyclophosphamide and a monoclonal antibody to a protein, CD20, on the surface of some antibody producing white blood cells. Future trials using IVIG in combination with other immunosuppressive drugs may be of greater benefit.

Other individual cases of chronic inflammatory neuropathies such as multifocal sensory neuropathy, distal acquired demyelinating sensory and motor neuropathy (DADS) and a multifocal motor and sensory neuropathy called Multifocal Acquired Demyelinating Sensory and Motor Neuropathy (MADSAM), or the Lewis Sumner syndrome have been reported to respond to corticosteroids or IVIG but because of the rarity of these disorder have not been tested in controlled trials.

CIDP is increasingly recognized as a cause of chronic progressive neuropathy and some propose a higher incidence of this disorder than is represented in this presentation. Most CIDP patients, if treated early and aggressively, respond well to therapy that limits peripheral nerve damage, thereby contributing to improved patient function and quality of life.

