



GBS | CIDP

Foundation International

Guillain-Barré Syndrome, CIDP and Variants

An Overview for the Layperson

Serving patients with GBS, CIDP and variants with
support, education, research and advocacy

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To
Susan, Adina & Jennifer



In Honor of
Robert & Estelle Benson

Guillain-Barré Syndrome

(Acute Inflammatory Polyneuropathy)

An Overview for the Layperson

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PREFACE TO THE TENTH EDITION

The origin of this overview dates back to 1982 when Estelle Benson, emotionally traumatized by her husband Robert's bout with paralyzing Guillain-Barré Syndrome (GBS), sought a means to help others deal with this disorder. She brought some recovered patients together around her dining room table in suburban Philadelphia to start a support organization. Attending this meeting were Joel Steinberg, a still-recovering physician, as well as experts on GBS, Arthur K. Asbury MD, Professor of Neurology at the local University of Pennsylvania, and two of his trainees, David Cornblath, MD, and Gareth Parry, MD. The group recognized the need of patients and loved ones for emotional support and accurate, understandable information to carry them through the often fearful ordeal of GBS. Out of that meeting the GBS Support Group was born, an organization that now serves patients with this and related disorders worldwide as the GBS/CIDP (chronic inflammatory demyelinating polyneuropathy) Foundation International. The GBS/CIDP Foundation has over 170 local chapters and sister organizations on 5 continents to serve patients and families. You the reader are invited to contact the Foundation to continue this growth. The Foundation's goals are to:

- Expand our network of global support groups and chapters to provide patients and caregivers with support and accurate information
- Provide educational programs to heighten awareness and improve the understanding and treatment of GBS, CIDP and variants
- Expand research support and patient advocacy

Foundation membership is over 28,000 and growing. We are supported by a medical advisory board of internationally recognized experts who have made major contributions to the understanding and treatment of GBS and variants.

As part of the Foundation's educational outreach, Dr. Steinberg wrote an overview in 1982 to provide a comprehensive, detailed source of information for the lay and medical communities. The last decade has seen significant advances in our understanding of GBS and related disorders. Some of these advancements were supported through research grants awarded by the Foundation. Carol Lee Koski, MD, a GBS expert, has played a key role in facilitating much of this research. This current 2010 edition of the overview has the added benefit of her input to explain many of these advances. We are grateful to the many investigators and clinicians who have contributed to the material in this booklet. Finally, we extend thanks to Mary Beth Brooks for professional editing of this publication.

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OVERVIEW: GUILLAIN-BARRÉ SYNDROME

Introduction

The disorder called Guillain-Barré (ghee'-yan bah-ray') syndrome, or GBS, is a rare illness typified by the rapid onset of weakness, often accompanied and sometimes even preceded by abnormal sensations, such as tingling or pain. These various changes reflect damage to peripheral nerves, that is, nerves located outside the brain and spinal cord. Peripheral nerves, discussed in more detail below, include motor nerves to muscles that enable movement, sensory nerves from the skin and joints that detect texture, limb position, etc., and autonomic nerves that automatically regulate functions such as heart beat, blood pressure, pupil size, and a sense of bladder fullness. GBS can occur at any time without warning. It affects both genders and all age and ethnic groups. It varies greatly in severity from mild cases of brief weakness that may not even come to a doctor's attention, to a devastating, life threatening illness with complete paralysis, respiratory failure and inability to swallow. GBS is rare. Most people have never heard of it, or if they have, know little about it. The goal of this overview is to acquaint the reader with the clinical features, causes, and treatments of GBS and variants, as well as the effect of these disorders on the life of patients and their families. The sections in brackets are intended for health professionals. References are provided in the back of the booklet.

What is GBS: Historical Background and Clinical Features

In 1859, a French neurologist, Jean-Baptiste Landry, described ten patients who, over days to two or so weeks, developed ascending weakness and paralysis of, in sequence, the legs, arms, neck and breathing muscles of the chest (*Landry, 1850*). The weakness was sometimes preceded by abnormal sensations in the toes and fingers. Deep tendon reflexes such as the knee jerk, found in most people, were absent and presumably lost. Most of the patients recovered spontaneously over time. Some patients had difficulty breathing and an abnormal heart beat. During recovery, the paralysis receded in reverse order of development, with the upper body improving first, followed by return of leg strength. Landry called the disorder "acute ascending paralysis." Several similar reports followed from other countries. The demonstration by Quinke in 1891 of spinal fluid removal by passing a needle into the low back paved the way for three Parisian physicians, Georges Guillain, Jean Alexander Barré and Andre Strohl to report in 1916 the characteristic abnormality found in GBS of increased spinal fluid protein with a normal cell count. Neurologists call this cytoalbuminologic dissociation, meaning that the fluid contains a

normal amount of cells, indicated by use of the prefix 'cyto' for cells, but the amount of protein or albumin in the fluid is abnormally elevated (*Guillain, 1916*). Studies have shown that this disorder can affect any of the peripheral nerves mentioned above: motor, sensory and autonomic nerves. GBS is usually self limited; that is, recovery starts spontaneously. Most patients will usually improve and often fully recover if, as they get weaker, their vital functions, such as breathing, are supported. GBS is usually monophasic; that is, it occurs only once. Additional episodes are rare. The underlying problem in most GBS patients is damage to the myelin covering the peripheral nerves (discussed below).

The Several Names for GBS

GBS has several other names, including acute inflammatory demyelinating polyneuropathy (AIDP) (acute, for sudden onset; inflammatory, to indicate inflammation in the nerves; demyelinating, to indicate damage to the outer coating of the nerve called myelin; polyneuropathy, a disorder involving many nerves); acute inflammatory polyneuropathy, acute idiopathic polyneuritis (inflammation, hence 'itis', of many nerves due to idiopathic or unknown causes), acute idiopathic polyradiculoneuritis, Landry's ascending paralysis, acute dysimmune polyneuropathy (dys- for bad, as explained below); French polio, reflective of the neurologists who recognized it; and post-infectious neuropathy (since many cases develop after [ergo, 'post'], an infection). Currently, however, this syndrome is most commonly referred to as the Guillain-Barré Syndrome or GBS.

What's a Syndrome?

Use of the term 'syndrome' indicates that GBS is diagnosed by identifying a specific combination of findings characteristic of the disorder. In GBS these include the symptoms (what the patient feels and describes, such as difficulty walking), signs (what is found on physical examination, for example, lack of knee jerk or other deep tendon reflexes), clinical course (rapidly progressive ascending weakness), along with confirmatory laboratory tests (for example, slow conduction of nerve signals, elevated spinal fluid protein).

Types of Peripheral Nerves

An explanation of the function of peripheral nerves helps to understand what happens to the patient in GBS. For a person to perform an activity, such as walking, the brain sends an electric signal down a nerve path to stimulate nerve cells or neurons in the spinal cord. The cells in turn conduct the

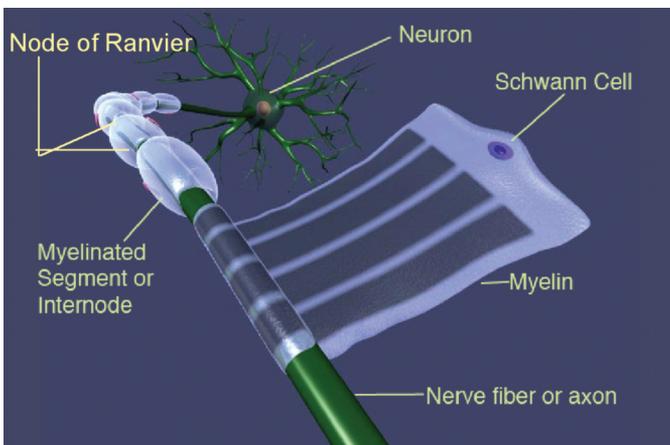
electric impulse out of the cord and along the nerve's axon, a long narrow extension of the neuron. The axon travels out of the cord as nerve roots, through openings between adjacent backbones or vertebrae, and to the muscle where the impulse stimulates muscle fibers. Nerves that carry signals to muscles are called motor nerves. If enough motor nerves excite enough muscle fibers, the muscle contracts or shortens producing limb movement, e.g. walking. Individual axons are too small for the naked eye to see; they are microscopic. Hundreds of nerve axons are bundled together and called a peripheral nerve. An example is the sciatic nerve. If motor nerve axons are damaged, muscles don't get a sufficiently strong signal to contract; weakness, even paralysis, ensues.

Sensory nerves carry information from various parts of the body, such as skin and joints, to the spinal cord and then up to the brain where the signal is registered as a sensation. Examples of sensations include temperature, pain, hard versus soft textures and joint position, such as a bent or straight elbow.

Autonomic nerves carry signals to and from the internal organs to automatically regulate their activities such as heart rate, blood pressure and the urge to void.

Myelin Aids Peripheral Nerve Signal Conduction

Peripheral nerves carry electrical signals from the spinal cord to muscle, and from skin and joints to the spinal cord and up to the brain. Many axons, the central signal-conducting core of peripheral nerves, are covered by an outer insulation called myelin (my'-eh-lin). In GBS, the most common part of the nerve initially damaged is the myelin. Myelin acts like the insulation on electrical household wires, and assists rapid and accurate signal conduction, preventing the axon signal from short circuiting or slowing



down. Myelin is produced by Schwann cells. Myelin is wrapped around segments of axons and aligned end to end. Small gaps between the segments are called nodes of Ranvier. In the gaps, a thin porous surface of the underlying axon, a membrane called the axolemma, is bare and exposed. Ions [eye'-onz], such as potassium and sodium, have an electric charge and can move rapidly through the channels in the axolemma, to create an electric nerve signal. The signal jumps from one node or gap to the next, a process called saltatory conduction. If myelin is damaged or lost, conduction of the nerve impulse is slowed, or lost all together and leads to muscle weakness or changes in sensations.

Nerve Damage in GBS

The main feature in most GBS patients at the microscopic tissue level is damage to the peripheral nerve myelin. The body's own immune system, which normally fights infection, causes this damage via special white blood cells called macrophages (mac'-ro-fages). Indeed, identification of cells of the immune system, lymphocytes (limf'-o-sites) and macrophages, at sites of myelin damage in GBS patients gave rise to the current understanding that GBS is caused by an abnormal or over reaction of the immune system. (*Asbury et al, 1969; Prineas, 1981*)

GBS is considered an autoimmune disorder since the immune system, normally protective of the patient's own tissue, attacks the patient's own tissue, or its 'self', hence use of the prefix, 'auto' (against 'self'). Just why the immune system acts out of control in some people but not others is not fully understood. Myelin damage on average occurs over about 3 weeks, although it can develop as rapidly as hours to days during which time the patient experiences progressive weakness and sensory loss. If conduction in the nerve is sufficiently slowed or completely blocked, the muscle it innervates becomes paralyzed. This can be life-threatening if the muscle is, for example, the diaphragm, a major muscle for breathing. After the peak of damage, the nerves usually undergo a slow healing process and are remyelinated or repaired; during this process the patient regains strength and sensation. In some cases, however, recovery may be slow or incomplete resulting in long term weakness, especially if the nerve axon is damaged. Such damage may be primary or secondary, and will be discussed later. As noted above, sensory nerves allow us to feel temperature, limb position, coarse and smooth fabric surfaces, etc. When the sensory nerves are damaged the patient may experience decreased or even abnormal sensations, poor balance and even pain. The brain and spinal cord clinically appear to be spared although autopsies have shown damage of small areas of myelin in the brain and spinal cord. Rarely, some patients may develop vision loss secondary to central myelin loss in the

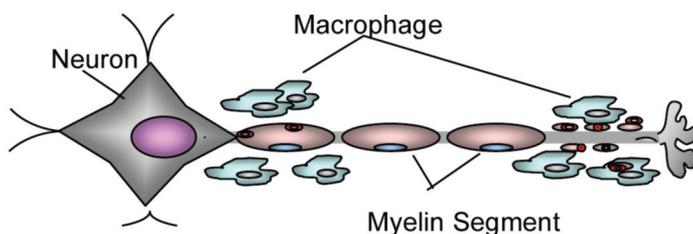
optic nerve (Lolekha and Phanthumchinda, 2008; Nadkarni and Lisak, 1993) or swelling of that nerve. GBS is not just a disorder of paralysis and abnormal sensations. Damage to myelin and axons of autonomic fibers can cause abnormal heart beat, high or fluctuating blood pressure, impotence, urine retention and bowel paralysis.

GBS and Other Inflammatory Neuropathies – a Family of Disorders

The disorders discussed in this booklet have in common the principal features of GBS: they are all 1) acquired rather than inherited, and 2) likely due to immune-mediated damage to the peripheral nerves. These various disorders differ by their onset, duration, symmetry of clinical findings, and whether the damage is primarily to the myelin, the axon or preferentially involves peripheral nerve fibers dedicated to motor, sensory or autonomic function. An accurate diagnosis of these various disorders is important since treatment and outcome among them varies (Koski, 2002).

The Rapid Onset (Acute) Disorders

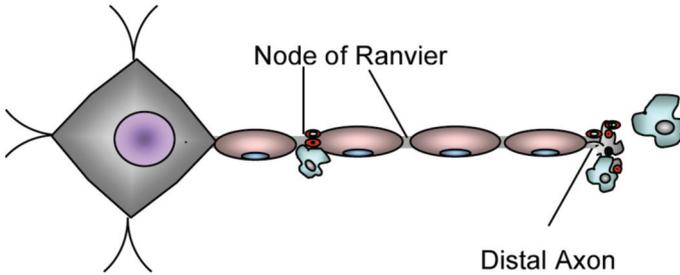
Acute inflammatory demyelinating polyneuropathy (AIDP). This disorder is most commonly called GBS. Its other names are described above. The incidence is rare and occurs in 1-2 people per 100,000 population each



year. In the western world, 75% to 80% of cases of acute acquired inflammatory neuropathies fall into this category of AIDP or 'classic' GBS with the immune attack directed at myelin (Vucic *et al*, 2009).

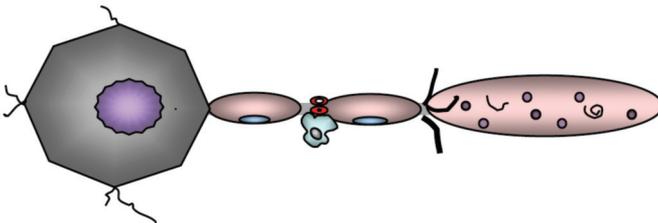
The pattern of myelin damage leads to symmetrical weakness and sensory loss or changes (tingling, etc.). Note that in medical terminology, symmetrical means 'equal on both sides of the body'. This contrasts with some disorders, such as many strokes, where only one side of the body is affected. Such disorders are thus asymmetric. Maximal deficit in AIDP develops over one to four weeks. Ten percent of patients, designated as subacute inflammatory demyelinating polyneuropathy, continue to worsen for up to six weeks but otherwise follow the same course as AIDP.

Acute motor axonal neuropathy (AMAN). This variant was initially recognized upon studying yearly summer epidemics of paralysis in children in rural areas of northern China (McKhann *et al*, 1993). It has also



been called the Chinese paralytic syndrome. Clinically it is similar to AIDP, with rapid onset of relatively symmetrical paralysis, but without any sensory changes. Outbreaks of AMAN have also occurred in Mexico and South America. Sporadic cases occur throughout the world, including the United States, Europe and Japan. In this variant, nerve damage occurs at areas of exposed axon, such as myelin gaps at the nodes of Ranvier, and at the end of the axon that is not covered with myelin just prior to its junction with the muscle fiber.

Acute motor sensory axonal neuropathy (AMSAN). This is a fulminant, severe form of GBS that usually develops over days, resulting in paralysis and



sensory loss due to severe axonal damage. Recovery is poor. Its recognition as a variant dates back to a report by Feasby in 1986 (Feasby and Brown, 1986). This variant is more prevalent in Asia and South and Central America and is often triggered by *Campylobacter jejuni* infection (Vucic *et al*, 2009).

Miller Fisher syndrome, or simply Fisher syndrome, is named after Dr. C. Miller Fisher. In its purest form, it is characterized by three features: 1) double vision from weak eye muscles, 2) a wobbly or ataxic walk or gait, appearing as loss of balance, and 3) loss of deep tendon reflexes.

Injury to the myelin of nerves controlling eye muscles causes their weakness so the eyes can't move together, creating double vision. Sensory

nerves in muscles detect muscle length and strength and allow us to walk normally, that is smoothly. Antibodies specific for molecules on these fibers damage these nerves, causing an ataxia (wobbly or unsteady gait) and double vision (S Kusunoki; *Rinsho Shinkeigaku*; 2008;48:1023). Blurred vision can also occur and is caused by paralysis of pupillary function. Some patients also develop weakness in the limbs as well as facial paralysis and difficulty swallowing, thus overlapping with features of GBS. The reverse is also true, in that patients with GBS can have ocular muscle weakness and double vision.

The Slow Onset (Chronic) Disorders

Chronic inflammatory demyelinating polyneuropathy (CIDP). This neurologic cousin of GBS, described by Austin in 1958 (Austin, 1958), develops slowly over two months or longer and is also characterized by symmetrical weakness and sensory changes. Deep tendon reflexes are lost in the involved extremities. It may occur as a single or monophasic illness that extends over one to three years. Although this variety is self limiting, if untreated, the nerve damage can be severe and the nerves may not recover completely. More often CIDP is recurrent, with relapses and remissions occurring several times over the course of years. Occasionally the disorder may run a slowly progressive deteriorating course over years without improvement. In contrast to GBS it is often responsive to treatment with corticosteroids and other immunosuppressive agents. The incidence of CIDP is rare compared to GBS but because CIDP can persist for years, it is probably the most common chronic inflammatory neuropathy. Its prevalence, the number of people who have the disorder at any one time, is estimated to be as high as 8 patients per 100,000 population.

Multifocal motor neuropathy (MMN). This rare, asymmetric inflammatory neuropathy affects multiple motor nerves. Major features are the slow or stepwise development of weakness of initially distal muscles in the upper limb, i.e., the hand, more so than the lower limb. Sensory nerve fibers are not affected.

Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM). Also called Lewis Sumner syndrome after two neurologists who described it, this neuropathy is another rare variant of CIDP. It shares many features with multifocal motor neuropathy, but in addition to asymmetric weakness, the patient experiences sensory changes, i.e., tingling or loss of sensation, in the distribution of the damaged nerves. (Gorson *et al*, 1999; Van den Berg-Vos *et al*, 2000).

Rarer variants of GBS and CIDP are beyond the scope of this overview. Examples include disorders with only autonomic nerve damage, acute

autoimmune axonal neuropathies and focal autoimmune disorders involving weakness of the arm or leg.

Causes of Guillain-Barré Syndrome

Factors involved in the development of Guillain-Barré Syndrome are not completely understood. Evidence indicates that a variety of events can trigger the disorder in otherwise healthy people. GBS is self limiting so that most patients eventually recover if provided supportive care. The recurrence of GBS is rare; less than 5% of patients incur a second episode. In the United States and Europe 60% to 80% of GBS cases occur within four weeks of a preceding infectious illness. Of these, about three quarters follow an upper respiratory infection or 'cold' and 25 percent seemed to be precipitated by a diarrheal illness. A list of several infectious agents implicated as likely 'triggering' events are listed in Table 1.

Table 1: Infectious Agents Associated with GBS

<p>DNA VIRUSES <i>Cytomegalovirus</i> <i>Epstein Barr virus</i> <i>Hepatitis B</i> <i>Herpes Zoster</i> <i>Herpes Simplex</i> <i>Papovavirus</i></p>	<p>BACTERIA <i>Campylobacter jejuni</i> <i>Legionella</i> <i>Salmonella typhi</i> <i>Shigella boydii</i> <i>Yersinia</i></p>
<p>RNA VIRUSES <i>HIV</i> <i>Echo virus</i> <i>Coxsackie virus</i> <i>Parainfluenza</i> <i>Influenza</i></p>	<p>PARASITES <i>Malaria</i></p> <p>OTHER ORGANISMS <i>Mycoplasma</i> <i>Jacob Creutzfeldt</i> <i>Psittacosis</i></p>

The mechanism(s) by which these micro-organisms lead to GBS are slowly being made clear. Other cases appear to occur during pregnancy or follow seemingly unrelated events such as surgery, insect bites and various injections including spinal anesthesia and vaccinations. One of the most striking clusters of GBS cases occurred in the fall of 1976 in people immunized with the swine flu vaccine. The incidence of GBS is normally 1-2 new patients per 100,000 population each year. Some estimates suggested the incidence of GBS increased 7-fold in the vaccinated population. Other outbreaks or clusters of GBS have been reported, including summer epidemics in rural northern Chinese children (see AMAN described above),

a Jordanian outbreak in 1978 upon exposure to polluted water, and an outbreak in Finland after a nationwide oral poliovirus vaccination campaign, among others. The bacterium, *Campylobacter jejuni*, the most common cause of diarrhea in the world, is implicated as a triggering factor in the Chinese paralytic syndrome (AMAN); in other clusters contamination of water supplies by *Shigella* or *Salmonella* have been implicated. On rare occasions, GBS develops in patients with other systemic illnesses, including some malignancies, such as Hodgkin's disease, other lymphomas, multiple myeloma, other monoclonal gammopathies, and solitary plasmacytomas, as well as such disorders as systemic lupus erythematosus and infection with the human immunodeficiency virus (HIV) prior to the development of acquired immune deficiency syndrome (AIDS).

Although GBS often follows a viral or diarrheal illness, there is no evidence that the disorder can be transmitted from one person to another. In fact, often the virus or bacteria is no longer present in the patient when the peripheral nerve damage is developing. It is of interest that literally millions of people are exposed to events such as infections, surgery, and vaccines that have been identified as triggering agents for GBS, yet only a very small number of the people develop GBS. Why only certain people develop GBS is unclear. Might they have some unique genetic predisposition? Since it is rare for more than one member of a family to develop GBS, genetic factors likely do not play a significant role. Yet some research indicates that genetic factors do correlate with severity of disease (*Geleijns et al, 2005; Geleijns et al, 2006; van Sorge et al, 2005*). Indeed, GBS and variants may reflect a unique interaction between certain strains of an infectious agent (e.g., *C. jejuni*, Penner strains 0:19 and 0:41) and the genetically determined immune system composition of the patient (*Hughes et al, 1999*). Future research will hopefully improve our understanding of how and why GBS occurs.

The Biology of GBS

The different GBS variants likely reflect immune reaction to molecules associated with specific groups of nerves. Unique clinical features distinguish the GBS variants. Examples include ascending paralysis with sensory changes in classic GBS, double vision in Fisher syndrome, and weakness in AMAN and MMN. The unique features of each variant appear to reflect immune system mediated damage to nerve fibers dedicated to a specific function (such as eye muscle movement). Specific nerves appear to be attacked because they have molecules on their surface that are similar to those on the patient's triggering infectious agent. This condition of similar molecules on the microbe and nerve is called "molecular mimicry." It is best demonstrated in AMAN which can be triggered by an infection with a

bacterium, *Campylobacter jejuni*, (*C. jejuni*) that causes diarrhea. *C. jejuni* is commonly found in chicken droppings and mud where children play in rural villages in China. The micro-organism's outer covering contains complex fat or lipid molecules. Complex lipids on *C. jejuni* contain a group of sugars also present on a sugar-containing lipid, GM1, found on motor nerve axon membranes. Thus, some nerve molecules are similar to, or mimic, the microbe molecules. When an infection occurs, the immune system attacks not only the microbe but also the similar-appearing molecules on the patient's nerve fiber. The patient's nerve becomes the innocent bystander, injured in error by the patient's own immune defense system.

The immune system, which fights infections, is complex. It has two major parts: a group of special cells, the cellular component, and groups of special molecules within the body's fluids, the humoral system. These two parts work together to help fight infection. Examples of immune system cells are special white blood cells, lymphocytes and macrophages. The humoral system consists of several groups of molecules within the body's liquid compartments, such as plasma. Being in the liquid part of the body they are called the 'humoral' system, as historically the ancients suspected that humors, some amorphous material in the body's liquids, was responsible for some body functions and diseases. They were right, even without being able to identify those humors that we now recognize as specific families of molecules. We now know that the humoral system consists of antibodies, chemical signaling agents such as chemokines, and a group of protein molecules that accelerate antibody activity, called complement. These humors, 'good humors' if you will, serve with cells to fight infection. Antibodies and complement likely play an initiating role in immune activity by recognizing an infectious agent or microbe as foreign. Their selective recognition of and binding to myelin and other nerve parts is likely a key early event in nerve damage in GBS disorders.

Another factor that likely determines the course of GBS is access of the immune system to nerves. A 'blood-nerve' barrier protects the peripheral nerve. The barrier is composed of endothelial cells that line the lumen of blood vessels (supplying nutrients to the nerve) and fibrous tissue (connective tissue) that surrounds each individual nerve fiber and nerve fiber bundle. To allow entry into the nerve of immune system components, activated cells such as lymphocytes and macrophages bind to the endothelial cell surface and release signaling chemicals, cytokines and chemokines, to disrupt the barrier. The disruption allows greater access to the nerve of not only cells but also proteins, including antibodies, complement and cytokines. The mechanisms of barrier disruption are being studied as potential opportunities to create treatments to block breakdown of the 'blood-nerve' barrier as a means to treat the GBS disorders.

The molecular mimicry concept outlined above does not explain some cases of GBS and variants, such as those triggered by surgery or that occur during pregnancy. Nevertheless, molecular mimicry and the innocent bystander remain helpful working models to explain most of the GBS family of neuropathies.

Early Findings with Guillain-Barré Syndrome

The presenting symptoms of GBS can be quite varied and reflect the particular nerves involved. Often, initial symptoms may be abnormal sensations, called paresthesias, which occur in several forms. Examples are numbness, tingling, an “asleep” feeling, a sense of ants or something crawling under the skin (formications), electricity, or vibrations. They may initially only occur in one limb but quickly become symmetric, and are often experienced at the ends of the limbs, the distal aspects, in the feet and toes or hands and fingers, prior to the onset of weakness in that limb. Weakness can affect any extremity, but initially may be so mild as to be ignored until it progresses enough to interfere with motor functions that enable us to walk, breathe, talk, etc.; sensation changes reflect damage of sensory nerves that detect our surroundings (hot, cold, smooth, rough, other textures, limb position, etc.).

A common scenario in developing GBS is first a sense of paresthesias, such as tingling, in the toes and/or fingers. This may be followed shortly, in hours or a day, by ascending weakness, progressing up the body from the legs to the hands and then the face or, less often, descending weakness. The weakness, initially mild, over days becomes sufficiently noticeable and drives the patient to seek medical attention. Weakness of thigh and hip muscles causes a problem climbing stairs or getting up from a chair. If the arms or shoulder muscles become weak the patient may not be able to shave, comb hair or lift a heavy object. If the fingers or hands become weak or numb, handling common objects, such as a comb, pencil, button etc., may become difficult. Aches or cramps often accompany muscle weakness. Severe muscle cramps, often described as a ‘charley horse,’ in the back, buttocks, or thighs may cause the physician to suspect a variety of disorders other than GBS, such as back strain, an arthritic problem, etc. However, the development of widespread weakness, loss of tendon reflexes, etc., helps to identify the patient’s disorder as more likely GBS. The symmetry of weakness and sensation changes in GBS and development of symptoms over days rather than minutes to hours are important features that differentiate it from a stroke. In the motor axonal form of GBS, AMAN, weakness develops without accompanying sensory symptoms. In 70% of patients, the muscles that control breathing can become weak and the patient feels short of breath. In 40% of patients, the respiratory muscles become so weak that the patient

will require temporary placement on a ventilator. If muscles in the throat become too weak or throat nerves that sense liquids lose that ability, the patient may experience difficulty talking or swallowing and may begin choking on their own secretions. Facial muscle weakness, if on one side (that is, unilateral) can cause a lopsided expression or, if affecting both sides (that is, bilateral) will create the inability to smile; food may collect in a weak cheek pouch. Rarely, difficulty in urinating or inability to hold one's urine may be a patient's initial problem. As noted earlier, the syndrome may also involve the automatic or autonomic nerves of the body and alter blood pressure, heart rate, temperature and vision. Even brain and hormonal control of kidney function can be affected through the inappropriate release of anti-diuretic hormone leading to low serum sodium.

An occasional patient presents with a picture quite different from the classical ascending paralysis of GBS. Rather, nerve damage may occur elsewhere and the presenting findings in turn reflect that damage. An example is damage of some cranial nerves resulting in facial weakness, difficulty swallowing and talking, and neck weakness. Very rarely only the phrenic nerves that supply the diaphragm, the major muscle for breathing may be involved. The Miller Fisher syndrome is another example of atypical or limited nerve involvement; the primary findings are a triad of double vision, ataxic gait and loss of reflexes. Some variants involve only sensory or autonomic fibers. All of these various clinical syndromes are diagnosed and treated in the same fashion and with some exceptions all have good outcomes.

Diagnosis

No single test can establish the diagnosis of GBS. Rather, the disorder is suspected when a patient presents with findings typical of GBS, subacute onset of weakness, first of the legs, then the arms, often with numbness and/or tingling of the affected limbs. The neurological examination showing the loss of deep tendon reflexes such as at the ankle or knee supports the diagnostic suspicion of GBS. These findings are often sufficient to admit the patient to a hospital with a presumptive diagnosis of GBS. In the hospital a further work-up will usually be undertaken with confirmatory tests. These usually include spinal fluid examination to include protein and cell analysis, and electrophysiological testing of the peripheral nerves. As noted above, the clinical presentation can be varied. But since vaccines have led to the near eradication of polio, GBS is the most common cause of symmetric weakness developing over days to up to 3 or 4 weeks. Because of the potential for progressive paralysis, failure of breathing and cardiovascular complications, GBS is treated as a medical emergency. Even the suspicion of GBS may suffice to warrant hospital admission for observation.

Deep tendon reflexes (DTR) can be elicited in most normal persons. Since peripheral nerves carry the impulse signal required to generate these reflexes, the absence of tendon reflexes suggests peripheral nerve damage. Loss of DTRs occur in weak or paralysed extremities in GBS. (In contrast to the knee jerk that reflects peripheral nerve damage, damage in the central nervous system characteristically causes brisk or exaggerated deep tendon reflexes and abnormal reflexes such as an up-going toe upon stimulation of the sole of the foot, the Babinski sign.)

Early in the clinical course of GBS, the neurologic exam may also find loss of sensations carried by large myelinated sensory nerves susceptible to demyelination. Thus position sense may be lost as well as vibration sense in the fingers and toes. The patient will likely still sense pain and temperature as these are mediated by thinly myelinated or unmyelinated fibers and thus usually remain intact early on. Unmyelinated fibers may become impaired later in the disorder's course if axonal damage occurs.

Once the history and exam findings direct the physician toward a diagnosis of GBS, the disorder can be confirmed by electrodiagnostic testing of the nerves, and spinal fluid analysis. Nerve conduction velocity (NCV) studies can determine whether nerve damage is demyelinating, axonal or a mixture of both. The speed with which a peripheral nerve carries an electrical impulse (the conduction velocity of the signal) and stimulates a muscle to contract slows down as myelin is progressively damaged; if damage is severe, impulse conduction is blocked altogether. (In contrast to slowing of impulse conduction in GBS and other demyelinating peripheral neuropathies, when the axon is the primary target of damage, electrodiagnostic testing shows reduction in the size of the action potential or the conducted impulse while the conduction velocity is largely unchanged.) Slowing of conduction velocities continues to develop over the clinical course but may not be significantly slowed until 1-4 weeks into the development of neurological symptoms. Another measure of nerve function is the distal latency. A nerve exiting the spinal cord conducts an electrical impulse to its end at the nerve muscle junction. At the junction the nerve releases a chemical called acetylcholine (ACH) into a small space or cleft between the nerve and muscle. The ACH travels across this space to the muscle, causing it to contract. The time it takes for the electrical impulse at the end of the nerve to stimulate the muscle to contract is called the distal (for end) latency (time). This latency is abnormally long in GBS and the change can be evident within 1-3 days. So the finding of either slowed conduction and/or prolonged distal latency on the NCV study confirms demyelination of the nerve and thus helps to rule out neuropathies that are caused by metabolic conditions, such as diabetes, or toxins, that cause damage first to the axon rather than the myelin.

By the second to fourth week of symptoms, and often within 10 days, fluid bathing the spinal cord usually contains abnormally elevated protein levels while the white blood cell count remains normal. This combination of findings is supportive of GBS and other inflammatory neuropathies. Therefore spinal fluid measurements provide an important confirmatory test for GBS.

To obtain the spinal fluid, a long thin needle is inserted through the skin in the middle of the low back between two lumbar vertebrae just below the waist. Fluid is obtained from the spinal canal that houses the cord and peripheral nerves branching off of it. Protein elevation in large part reflects the accumulation of albumin in the spinal fluid due to active inflammation of peripheral nerves in the canal. If the white blood cell count is elevated, diagnostic considerations other than GBS will be entertained, such as infections including Lyme disease or inflammatory disorders of blood vessels. In rare cases cancer cells may be detected, thus redirecting the physician's diagnostic considerations.

Table 2: Diagnostic Criteria for Guillain-Barré Syndrome

- *Rapid onset, over a few days to 1-4 weeks of symmetrical weakness, in the extremities*
- *Altered sensations, numbness, tingling or pain, in affected limbs*
- *Elevated spinal fluid protein, usually within 1-4 weeks of symptom onset, with normal cell count*
- *Nerve conduction velocity-electromyography (NCV-EMG) evidence of nerve conduction slowing or blockage*
- *Absence of other causes of a peripheral neuropathy*
 - 1) *history of organic solvent inhalation, lead intake or intake of certain drugs, such as nitrofurantoin or dapson*
 - 2) *evidence of infectious causes of neuropathies, such as Lyme disease, HIV, diphtheria, and, in unvaccinated populations, poliomyelitis*
 - 3) *findings of acute intermittent porphyria as evidenced by normal urine studies for porphyrin metabolites (see Appendix)*

Findings supportive of the diagnosis of Guillain-Barré Syndrome

- *Monophasic course with return of strength starting at about 2 to 8 weeks*
- *Associated changes in blood pressure such as mild hypertension and rapid heart beat*
- *A preceding infection, such as an upper respiratory infection, or diarrhea, at 1 to 6 weeks before neurological symptom onset*

Hospital Care

The diagnosis of Guillain-Barré Syndrome is made or suspected most often in a hospital emergency department where the patient presents for progressive difficulty walking. Sometimes the patient presents to their family doctor with these complaints and is referred to a neurologist for further evaluation, leading to the diagnosis. GBS is usually self-limiting, with the weakness stopping on its own, followed by a slower recovery. That pattern of illness might make a person not familiar with GBS suspect that the patient can be followed without admission to see how they do. This thinking and plan of care is usually not advised. At its onset, the early and subsequent course of this syndrome is not predictable. Progressive weakness with impaired breathing or swallowing can occur over hours up to three to four weeks. The onset of autonomic nerve dysfunction can cause dangerous changes in blood pressure, heart rate, airway clearance and bladder control. Since these events can be life threatening, GBS is considered a medical emergency.

Except in very mild cases careful observation in the hospital is indicated, often in the intensive care or step down unit where changes in heart rate, blood pressure and breathing can be monitored. Rapid treatment can then be given if problems arise. One can not underestimate the importance of supportive nursing care throughout the patient's hospital stay. Much of this is directed toward preventing the many potential complications of paralysis, including decubitus ulcers or bed sores, pneumonia, contractures of the joints, and thrombosis in the deep veins of the legs to name a few. In summary, the new GBS patient warrants attention for several issues discussed in detail below. The many potential challenges for patient care can be conveniently grouped into 1) internal organ problems, including breathing management, so called supportive care, 2) emotional issues, 3) treatments that modulate or modify the immune system to reverse autoimmune causes of GBS, and 4) rehabilitation.

Internal Organ Problems

Impaired Breathing. This is a particularly dangerous problem usually caused by weakness of the diaphragm, the major muscle of respiration and other muscles used for breathing. Respiratory function can be determined at the bedside serially every 1-2 hours by measuring the patient's ability to take a deep breath with a hand-held monitor or spirometer. If serial breathing tests and the physical exam indicate sufficient weakness of breathing muscles, mechanical ventilation may be needed. For example, if an adult patient's vital capacity (the amount of air taken in with a deep breath) falls below 2 liters or quarts, respiratory

failure may be imminent. A further drop of even 500 ml or half a quart may signal a need for intubation, that is, the insertion of a breathing tube through the nose or mouth into the windpipe or trachea, in order to support the patient's breathing with a ventilator. Decreasing levels of oxygen and increasing levels of carbon dioxide in blood are signs of poor breathing and can be measured to confirm inadequate breathing. For example: a pulse oximeter, a small plastic sensing device gently clipped to the patient's finger or ear lobe, provides an ongoing display of the patient's blood oxygen content and thus their breathing ability. Values above 92% oxygen saturation of the blood are normal. Lower values reflect decreased lung function and suggest a need for urgent placement of the patient on mechanical ventilation. About 40% of GBS patients develop sufficient weakness of breathing muscles to require mechanical ventilation. The patient should be intubated by a professional well trained in this technique, such as an anesthesiologist. Intubation is best done when such trained personnel are available. An emergency intubation under less than optimal conditions may be associated with complications and is thus best avoided if possible.

Intubation and mechanical ventilation, although often necessary, are not without risk. Mechanical ventilation does not fully duplicate the natural mechanisms used by healthy people to clear the airway and open the lungs (e.g., cough, sigh, yawn etc.) and makes patients more susceptible to pneumonia. Intubation through the nose limits drainage of the sinus on the side of the tube placement with the potential to cause sinusitis. Other complications include incomplete expansion of the lungs with collapse of lung segments, called atelectasis, making patients more susceptible to pneumonia, low blood oxygen and high levels of carbon dioxide. Measures taken to reduce these complications include frequent suctioning of the airway or trachea and percussion or thumping of the chest wall over the lung bases to mobilize and loosen accumulated mucous in order to facilitate its clearing. Percussion is done by positioning the patient on their side and thumping the side of the chest with a hand or with a machine.

In spite of the risks of mechanical ventilation it can be life saving. Thus it should be used without hesitation if the patient's breathing is failing. Mechanical support of breathing is continued until sufficient respiratory muscle strength returns. This can take days, occasionally weeks, and, rarely, even longer. Various methods are used to determine when strength is adequate to allow unassisted breathing and weaning from a respirator.

Airway Protection. Some patients may require intubation because of inability to swallow. This can lead to aspiration of mouth or stomach contents into the lungs and subsequent pneumonia. Indeed, choking,

dribbling or other evidence of poor secretion-handling can signal the need to intubate the patient in order to protect the airway from aspiration, even if the patient is able to breathe adequately. (Poor secretion-handling is likely mediated through damage of cranial nerves that control the tongue and palate, which mediate the gag and cough reflexes.)

Decubitus Ulcers. The paralyzed patient on prolonged bed rest is prone to breakdown of tissue over bony prominences. The skin breakdown or ulcers are called bed sores or decubiti. Decubiti can be difficult to heal, so preventing them is important. Common sites of decubitus formation include the heels, low back (sacrum) and hips. Several methods are available to help prevent and treat decubiti. These include frequent turning of the patient, every two hours, to reposition the patient off bony prominences and the use of a foam or gel mattress to spread the patient's weight more evenly. Special beds designed to reduce local pressure, called low air loss beds or mattresses, and an air fluidized bed (e.g., Clinitron®), may be helpful for patient with prolonged paralysis.

Contractures. GBS patients develop weakness of muscles controlling the ankles and wrists. If weakness is substantial, foot and/or wrist drop develop because the patient is too weak to overcome the effect of gravity and keep the feet and hands in a natural, upward or flexed position. Over time, this results in shortening of the Achilles tendon and calf muscles. Fixed shortening of the Achilles tendon interferes with upward movement of the foot and the ability of the patient to stand flat on their feet; instead they stand on their toes, interfering with rehabilitation. Similar problems can occur with the forearm muscles and hand movement as well as the shoulders. To prevent shortening of tendons and muscles, passive range of motion exercises are given by a therapist several times a day. In addition splints or braces are placed around joints at risk for contractures to maintain the ankle and wrist in a more functional or normal position. A brace is a thin stiff piece of plastic molded to conform to the shape of the extremity to hold the foot and hand in the desired position. For the foot, the usual preferred position is a 90° or right angle to the leg; for the hand, the usual position is slightly cocked up, at about 20–30° above the forearm. Prevention of contractures facilitates patient participation in rehabilitation and shortens recovery.

Deep Vein Thrombosis ('phlebitis'). Muscle paralysis and inactivity increase the risk of blood clot development. Decreased calf muscle activity from paralysis and bed rest can lead to vein inflammation, called phlebitis, and formation of blood clots (thrombi) in the deep veins of the legs and pelvis. A bedside clue to formation of blood clots in deep veins, that is, deep venous thrombosis (DVT), is swelling of the leg(s), or edema. If blood clots

break off from leg veins they can travel to the lungs where they are called pulmonary emboli. If sufficiently large, they interfere with blood flow through the lungs, diminish oxygenation of blood, and are life-threatening.

Measures used to reduce the development of DVTs include injections of blood thinners (heparin injections), elastic stockings such as thigh length anti-embolism stockings, (e.g. TED®), and use of an air-filled inflatable bladder wrapped around the calves that intermittently inflates and deflates (pneumatic limb compression therapy), to help move blood in leg veins, reducing stagnation of flow and the risk of clots.

Autonomic Dysfunction. Damage can occur to any of the many autonomic nerves, both sympathetic and parasympathetic, in the body that serve the heart, blood vessels, bowel etc. Damage to autonomic nerves that regulate internal organ function can make these organs over reactive to medications. This over reactivity is called denervation sensitivity. Because of the risk of denervation sensitivity, the smallest effective drug dose should always be used. For example, treatment of elevated blood pressure with mid-range dosing could run the risk of too low a pressure.

Blood Pressure, Heart Rate. Both high and low blood pressure as well as unusually slow or rapid heart rates can occur in Guillain-Barré Syndrome. Low blood pressure when the patient is placed in an upright position (called orthostatic hypotension) may result from expansion or dilation of veins in legs with flaccid muscles. As a result of dilation and muscular inactivity, blood may pool in the dilated veins and not return to the heart as rapidly as usual. Intravenous fluids to increase total blood volume, as well as elastic stockings, mild leg elevation and sometimes medications can be used to correct this condition. Other medications are available to treat low heart rates (e.g., atropine), as well as rapid heart rates (e.g., beta blockers, calcium channel blockers and digoxin), and blood pressure elevation.

Urine retention. Nerve damage to the bladder can contribute to delayed or inadequate emptying of urine. Urine retention may require short-term use of a tube called a Foley catheter which is inserted through the urethra into the bladder to keep it draining until the patient's normal bladder function returns. To keep the Foley in place a balloon at its inner end, in the bladder, is inflated after the Foley is inserted. If a Foley catheter is used, its loose outer end is best anchored to the thigh with tape to avoid pulling on the inner balloon end inside the bladder. Such pulling risks moving the inner balloon end downward, into the urethra, where it can traumatize the narrow channel of the urethra with its fragile soft tissues and block urine flow. Urine retention can cause a bulge, or fullness as well as discomfort in the lower abdomen, just above the pubis. If pelvic fullness

and poor urine flow develop, a first step in evaluation is to place a Foley and check for urinary retention. Alternatively a non-invasive ultrasound image study of the bladder can guide care. If a Foley is already in place it should be checked for good flow or patency.

Constipation. This may result from several factors including bed rest, lack of exercise, reduced dietary fiber, decreased gut motility from autonomic nerve damage, the strange hospital environment, and the change in diet. A variety of methods can be used to treat constipation. These include simple measures such as prunes, milk of magnesia, bowel softeners such as sodium sulfosuccinate (Colace®), or agents such as psyllium (Metamucil®) and lactulose (Chronulac®). A suggested starting dose of lactulose is 3 tablespoons or 45cc 4 times a day until the patient has a bowel movement, then 1 to 3 tablespoons daily. Bowel stimulants in the short term can be effective for the neurologically compromised patient. Examples include bisacodyl suppositories (Dulcolax®, Corectal®) and senna tablets (Ex-Lax®, Senekot®).

Blood Chemistries. Blood chemistries are usually normal unless the patient has other underlying diseases, with the following exception. In GBS, the blood sodium level may be decreased due to excess secretion of a hormone used to decrease urine output (antidiuretic hormone or ADH). Excessive ADH secretion leads to more retention of plasma by the kidneys with its recirculation into the body, resulting in increased total body fluid volume that dilutes the blood sodium level. Treatments for this disorder may include restriction of water intake, and on occasion, intravenous administration of salt or saline solutions, such as normal saline solution.

Emotional Problems

During the early stages of the illness, especially for the patient in an intensive care unit, events can be frightening. Most patients with GBS were formerly healthy. Finding themselves suddenly paralyzed, helpless, with intravenous lines, a bladder catheter, and a heart monitor that continuously and monotonously beeps, can be upsetting. If the arms are too weak, even brushing teeth, feeding oneself or scratching an itch becomes impossible. If a ventilator is required for breathing, the inability to talk and communicate leads to a sense of isolation. Helplessness and thoughts of possible death, the threat of permanent disability, dependence, and income loss can be overwhelming. It is helpful for both patient and family to keep in mind that most Guillain-Barré patients get better, eventually walk, and many ultimately resume a normal life. During the hospital course the patient may benefit from the following suggestions for the hospital staff and family as shown in Table 3.

Table 3: Measures Healthcare Providers Can Take To Reduce Anxiety in the Paralyzed Patient

- *Express optimism and emphasize to the patient and family the relatively good chance for recovery*
- *Provide the paralyzed patient on a respirator with a method for communication to reduce frustration. Communication Cards are available from the GBS Foundation. These list in large print common problems that a patient may develop. A nurse or family member can flip through these cards with the patient, pointing to various items and getting the patient's "yes" or "no" response indicated by a head nod, eye movement to the right or left or eye blink*
- *Explain all procedures to the patient to alleviate anxiety*
- *Identify a key family member to serve as contact with a hospital representative with good rapport (a physician or nurse), to provide accurate information on the patient's status and care plans. Multiple members of the family calling causes confusion and physician fatigue*
- *Encourage frequent visits by family and friends to provide needed emotional support*
- *Provide a clock, electric calendar, radio and night light helps the patient keep track of day and night hours, maintain awareness of the outside world and minimize confusion while in the ICU*
- *Give the patient opportunities to express emotions (anger, frustration, and fear) and help them deal with issues*
- *Encourage family and friends to reduce patient isolation during a prolonged hospital stay by participating in bedside activities (e.g., grooming, reading get well cards,...)*

Specific Treatment: Immune System Modulating (Modifying) Therapy

Several studies support the effectiveness of aggressive treatment with some therapies that modify the immune system. Two types of therapy that have been shown to shorten the course of GBS are plasma exchange and high dose intravenous immunoglobulin.

Plasma exchange (PE)

Introduction. Plasma exchange, also called plasmapheresis, was the first immune therapy found effective for GBS. The term plasmapheresis is taken from the Greek language. Plasma means something molded, and as plasma is the liquid part of blood, it does, like all liquids, automatically mold to fit the

shape of its container. Plasmapheresis removes plasma that contains agents involved in the nerve damage of GBS. PE can also be used to collect plasma from normal healthy donors to be further processed into other treatment materials called biologicals. Indeed, this method is used to produce immune globulin which is used to treat GBS, as described in a later section.

The Procedure. As it applies to GBS, plasmapheresis (or plasma exchange) is used to collect some of the patient's blood so the liquid or plasma portion can be discarded. The plasma contains antibodies which most evidence suggests are instrumental in targeting nerve fibers for damage. To perform PE, first one or two tubes or catheters are inserted into a large vein in the neck or groin through which blood can be removed. The blood is spun (centrifuged) to separate and remove the plasma, and the red and white blood cells are then returned to the body.

Studies performed since the 1980's showed that plasmapheresis significantly shortens a GBS patient's illness (*McKhann and Griffin, 1987*). Benefits of PE include shortening of the length of time on a ventilator and time until patients can walk independently. Such benefits from PE support that the humoral immune system, (antibodies), plays an important role in the demyelination seen in GBS. Five studies have evaluated the effects of PE on GBS patients. In a large U.S. multicenter trial, PE when started within the first two weeks of onset of neurologic symptoms significantly reduced the number of days on a respirator and improved the six-month outcome. About 60 percent of PE-treated patients showed measurable improvement in four weeks, compared with about 40 percent in the group given only supportive or 'conventional' care. For older patients, around 60 years of age, who were respirator-dependent and had rapid onset of paralysis (ventilator dependent within 7 days), PE improved outcome and shortened duration of chronic deficits. Patients treated with plasma exchange were twice as likely to walk independently at three and six months than those treated with conventional supportive means alone.

PE is usually given in courses of five to 6 treatments over 10 days to 3 weeks. In the North American trial, patients were started on treatment an average of 11 days after developing neurologic symptoms. In each exchange, the plasma equivalent to 55ml (~2 ounces)/Kg (2.2 pounds) body weight was removed and replaced by solution of five percent protein in a salt solution (albumin in physiologic saline). A typical exchange rate is a total of 200-250 ml/kg body weight over 7-14 days. Plasmapheresis removes plasma and thus all molecules within it, including immunoglobulin or antibodies as well as complement proteins, clotting factors, and cytokines, signaling chemicals produced by white blood cells. In theory, if factors that cause demyelination are antibodies and complement, it should be possible to tailor therapy to remove only these

agents. However, such procedures are still not commonly available. Furthermore, it is possible that PE is also beneficial because it is also removing cytokines that may be participating in nerve damage and dysfunction. If so, current PE procedures may be optimal to treat GBS.

Plasma exchange is best performed by an experienced medical team to minimize complications. In experienced hands, risks are uncommon. Side effects and risks include an irregular heart beat from salt imbalance, citrate-induced low serum calcium, infection and blood clots at the site of venous catheter, and allergic reactions that can be severe with airway obstruction and collapse of circulation (that is, anaphylaxis and activation of coagulation, complement, fibrinolytic cascades, and aggregation of platelets). Patients are anticoagulated during treatments. PE does decrease platelets, used by the body for clotting, and clotting factors are removed but return to normal within 24 hours, except in the occasional patient with liver disease. Because of upper extremity weakness, it is frequently necessary to use a large bore rigid intravenous catheter to perform the procedures. Attempt at catheter placement in the central (subclavian) vein under the collar bone may cause lung puncture and collapse (pneumothorax) and, rarely, arterial bleeding or an abnormal connection between the artery and vein, an arteriovenous fistulae. In the U.S. multicenter trial, there was no increase in complications between the plasma exchange and conventional therapy groups. Thus, in spite of potential complications, the actual risks from PE are low.

High Dose Immunoglobulin (IVIG)

Another treatment for GBS is high-dose immunoglobulin, that is, the intravenous administration of high concentrations of normal antibodies purified from the plasma of normal, healthy donors. This treatment is abbreviated IVIg or IVIG.

Two large trials of almost 600 patients compared PE with IVIG in GBS patients. In the Dutch trial IVIG was given at a dose of 0.4 grams of immunoglobulin/Kg body weight daily for 5 days in newly diagnosed GBS patients (*van der Meche and Schmitz, 1992*). At four weeks, 54 percent of patients treated with IVIG had improved one grade of function (e.g., walking ability) compared with 33 percent in the plasma exchange-treated group. A second multicenter, 383-patient trial organized in the UK was designed to determine the efficacy of IVIG versus plasma exchange (*Plasma Exchange/Sando. GBS Study Group, 1997*). Patients were treated either with plasma exchange (200-250 ml/kg body weight over 5 treatments) or IVIG (at a dose of 0.4g immunoglobulin/Kg body weight for 5 days). Both studies showed that IVIG was the preferred therapy since immune globulin infusion were usually well tolerated and could be readily given through a small, safe

peripheral intravenous line. The second trial also looked at a combination of IVIG followed by PE. Patient outcomes suggested that this sequential regimen tended to be somewhat more effective than IVIG alone (improvement at four weeks was 1.1 grade and 0.8 grade respectively), but the difference was not statistically significant.

Complications and side effects from IVIG are usually mild. Temporary headache, chills, muscle aches and nausea are common and can be managed with non-steroidal anti-inflammatory medication (e.g., ibuprofen [Motrin®], etc.) and/or slowing the infusion rate (Koski, 2005). Other potential side effects include fever, hypertension, light-headedness and flushing. Severe headaches and other intolerable side effects may be prevented or their intensity reduced by the administration, 30 minutes prior to IVIG treatment, of steroids (e.g., methylprednisolone [60-100 mg IV] and diphenhydramine [Benadryl® 25-50 mg IV]. Immunoglobulin administration can occasionally lead to aseptic meningitis characterized by severe headache, stiff neck, vomiting, fever and increased eosinophil type white cells in the spinal fluid. Contraindications to receiving immunoglobulin are uncommon but include immune globulin A (IgA) deficiency, a prior history of systemic reactions to immune globulin infusion, and poor kidney function. In older patients with accompanying atherosclerotic cardiovascular disease, IVIG use can potentially contribute to excessive thickening (hyperviscosity) of the blood with, in turn, slower flow or sludging of the blood in vessels and can potentially place the patient at greater risk for heart attack (acute myocardial infarction), chest pain due to inadequate blood flow to the heart (angina) and stroke.

IVIG's mechanism of action is less clear than that for plasmapheresis. Several mechanisms have been proposed, such as suppression of harmful white blood cells, supplying a large pool of naturally occurring and safe antibodies to neutralize harmful antibodies, blocking production of harmful antibodies, interference with the immune system's complement protein cascade that in GBS may cause nerve damage and inhibition of cytokines that attract myelin-damaging macrophages. Physicians call these anti-idiotypic antibodies. IVIG may work by inhibiting macrophage function via upregulation of the Fc IIb receptors, by containing pools of naturally occurring anti-idiotypic antibodies, by blocking B cell Ab generation through both B and T cell mechanisms or limiting IL-1 production. It may work by inhibiting natural killer cell activity or by modulating activation of neurological symptoms of the complement cascade preventing formation of C5b-9. (Kuwabara, 2004)

Relapses of GBS can occur after the use of either IVIG or PE in about 5% to 10% of patients. Patients usually improve with another course of

treatment (*Farcas et al, 1997; Rudnicki et al, 1992*). Thus, close monitoring of the patient's breathing, strength and overall clinical condition is still warranted after they receive IVIG or PE, to watch for deterioration. General weakness, difficulty breathing, softer voice, poor secretion or mucous handling, and drop in oxygenation via pulse oximetry readings are some markers to prompt careful re-evaluation of the patient for relapse and potential retreatment in an acute care setting. Close monitoring of the patient is particularly important during the weeks after IVIG or PE to watch for evidence of relapse following initial improvement, especially if they are promptly transferred to a rehabilitation or other facility.

Corticosteroids. Corticosteroids (a.k.a., steroids) are anti-inflammatory medications that were previously used to treat GBS patients. This class of drugs is known by several other names, including cortisol, prednisone, prednisolone and methyl prednisolone. Since GBS is understood to be a disorder of inflamed nerves, it might seem reasonable to expect that steroids could be a helpful treatment. To address this possibility, more than six randomized controlled trials were performed and the findings were summarized in a review by the Cochrane Colloquium. (*Hughes et al, 2006*). The review found that steroids are not helpful to speed recovery, and in fact at least one study suggested that steroids actually may delay improvement (*Hughes et al, 2001*). Accordingly, corticosteroids are not usually recommended for the treatment of GBS.

Recommended immune therapies for new GBS patients

Recommendations by the American Academy of Neurology based on literature review concluded that IVIG and PE are equally effective treatments for GBS. Either should be started within 4 and preferably within 2 weeks of the onset of symptoms. Either can be considered for use in children. Using both treatments, PE then IVIG, does not provide any greater benefit than using either alone. Corticosteroids are not recommended.

Investigational Treatments

Both PE and IVIG are to some extent shotgun methods of treatment. They are designed to inhibit the immune system's ongoing nerve damage by blocking its activity, such as antibody mediated nerve demyelination. Not all patients respond to these treatments. Drugs focused on blocking specific steps in immune system activity might facilitate improvement in more patients. Such potential therapies are in the investigational stage. One currently being discussed for human studies is Eculizumab ('ELM') (marketed as Soliris®) (G Parry; Newsletter of the GBS Support Group New Zealand Trust, Sept. 2009). It is a unique antibody that blocks the complement system, the series of protein molecules that help bad antibodies

damage nerves. In laboratory mouse models, ELM blocks nerve damage by complement (Halstead *et al*, 2008). ELM has already been shown to effectively treat another rare autoimmune but non-neurological disorder, paroxysmal nocturnal hemoglobinuria (PNH). In this disorder complement damages red blood cells leading to nighttime episodes of bloody urine and reduced numbers of red blood cells. Studies are planned to determine if ELM will limit ongoing nerve damage in GBS and hasten recovery by blocking antibody mediated complement activation.

Pain and Other Abnormal Sensations

During the earliest stages of GBS, as well as throughout its entire course, the patient may experience significant pain. The pain can be severe, difficult to control and underappreciated by hospital personnel. The GBS patient also may experience other unique sensations. One example is the sense of vibration in the limbs while lying perfectly still in bed.

Pain in GBS, occur in over half of newly diagnosed patients (Halstead *et al*, 2008; Moulin *et al*, 1997). Several mechanisms are implicated to explain the pain, including inflammation and swelling within the nerve, mechanical contact of enlarged nerves with bony ridges and damage to the nerve's conducting core, the axon. Pain, by definition, is a noxious or unpleasant sensation. It can be a challenging problem in GBS for several reasons. These include lack of physician awareness that pain can occur in GBS, inability of the patient to communicate their pain because of intubation and a lack of response of the pain to standard therapies. Pain in GBS may develop early in the illness, even before the diagnosis is made, as well as during both disease progression and recovery.

Pain during the onset of GBS is often felt in the lower back, buttocks, and/or thighs and sometimes between the shoulders and the arms. It may be achy, crampy or stab-like, or sometimes described as feeling like a Charlie horse (Ropper and Shahani, 1984), with a deep muscular pain quality. It may be mild to severe in degree, and last for several weeks. Interestingly, the very first symptom in GBS may occasionally be low back pain that radiates into the buttocks and/or thighs, thus mimicking a sciatica type syndrome usually associated with pinched nerves in the back or a referred pain from a kidney stone. Such a scenario may lead the physician to think of these or other disorders rather than GBS, and delay the correct diagnosis until other findings more typical of GBS develop, such as weakness and loss of reflexes.

Several options can be used to treat pain in the early or acute phase of GBS. It may improve with PE or IVIG. Turning, positioning and passive movement of the limbs may be helpful to relieve back and shoulder pain. Severe pain can contribute to increasing or even decreasing blood pressure

and an increased or rapid heartbeat. In such situations, aggressive use of pain medications, even narcotics, may help relieve vital sign instability [Parry, *GBS Fndn. Newsletter, Summer 1998*]. Pain may improve with administration of medications commonly used to treat neuropathic pain such as gabapentin, carbamazepine and amitriptyline (see below for more information). Rarely, a patient may develop a sciatica syndrome with low back and/or thigh pain and may benefit from local injections of narcotics or anesthetics at the site of pain or around the outer covering of the spinal cord (epidural injections) to provide relief. The latter is performed by insertion of a needle into the low back to deliver the medicine. This method avoids the side effects from narcotic medicines given orally or as intramuscular (IM) or intravenous (IV) injections (constipation, grogginess, decreased breathing and altered blood pressure). Non-steroidal anti-inflammatory drugs, also called NSAID's (pronounced en'-seds), such as ibuprofen, marketed as Motrin® and Advil®, are very popular to treat arthritic, muscle and other types of pain. Although sometimes beneficial, published experience with this drug class for GBS is limited. Clinical judgment may help guide its use.

Pain during recovery from GBS may change in character from that during the acute phase since it reflects axonal damage from the acute inflammatory process. It is often a burning pain but can have a stabbing quality or may be felt as heightened sensitivity, with even the touch of bed sheets causing pain. This type of pain may persist for weeks or occasionally years. As damaged sensory nerves undergo healing, the sensitive regenerating tip of the nerve spontaneously generates abnormal signals that can be exacerbated by exercise and weight bearing, and thus can interfere with rehabilitation. This type of pain typically occurs distally in the feet and sometimes hands. Interestingly, some sensations may be rather subtle and difficult for the patient to describe. The author (JSS), for example would cough, choke and aspirate ice cold water but could easily tolerate room temperature water. Such problems, although seemingly trivial can lead to aspiration and pneumonia. So changing from ice to room temperature water was a simple but important intervention.

Most sensation problems resolve with time. Persistent pain, if sufficiently bothersome, may respond to various treatment modalities. Over-the-counter enteric-coated aspirin, acetaminophen (Tylenol®) or ibuprofen, local heat application (especially moist heat), cold or creams such as capsaicin may be helpful. Capsaicin is a cream made from cayenne peppers and marketed as Zostrix® as well as other product names (Capzasin-P). Application of capsaicin cream to painful areas of skin can reduce local pain in arthritis and painful neuropathies. It comes in various strengths, 0.025%–0.075%. Local pain can sometimes be relieved by a transcutaneous

electrical nerve stimulator (TENS). TENS is a portable battery-powered device that supplies electric current to the skin and underlying nerves. Immersion in a therapeutic pool and exercise may also relieve pain. Should these relatively safe initial measures prove inadequate, alternative approaches such as prescription medications are used.

Prescription strength arthritis medications, the non-steroidal anti-inflammatory drugs, have not been widely used to treat neuropathic pain and may only be of modest benefit. Side effects, such as internal bleeding, heart and kidney damage, can limit their safe use (*Pandey et al, 2005*). Prescription medications in common use for neuropathic pain include antiepileptic, antidepressant and narcotic drugs. Antiepileptic drugs act to stabilize nerve membranes and are often helpful to relieve pain. These include two rather old drugs, phenytoin (Dilantin®) and carbamazepine (Tegretol®). Gabapentin, more recently developed to treat epilepsy, is safer and thus more commonly used to treat neuropathic pain. Its side effects can include dizziness, a cloudy mind, lower extremity edema and weight gain. A starting dose is 100–300 mg, taken at bedtime. The dose may be increased in a few days to twice a day, and thereafter increased to 3 to 4 doses a day, or the twice a day dose doubled every 3–5 days, until the patient's symptoms are relieved or side effects interfere with further dose increases. A slower increase in dose may reduce side effects and allow tolerance of a higher dose. Doses as high as 2,700 to 3,600 mg a day have been tolerated and effective. The more recently introduced prebaganin (Lyrica®) is part of the same family of drugs but requires lower doses twice a day. Other products such as levetiracetam (Keppra®) and lacosamide (Vimpat®) can be of benefit to treat neuropathic pain [*D.S. Saperstein, Communicator by GBS/CIDP Fdn., Summer 2009 edition, p. 6*].

Other effective drugs for management of pain are antidepressants. Examples are the tricyclics such as nortriptyline (Pamelor®) in doses up to 75 mg at bedtime and amitriptyline (Elavil®) at doses up to 150 mg at bedtime. Another class are the serotonin and norepinephrine reuptake inhibitors (SNRIs). The main drug in this group is duloxetine (Cymbalta®). Its potential side effects include nausea, sweating, insomnia and sedation. Not infrequently, a combination of drugs such as a tricyclic plus an anti-seizure drug such as gabapentin, may more effectively control pain at a lower dose than either drug used alone. If narcotics are used, long acting products are often safer, such as a slow release fentanyl patch (Duragesic Patch®), slow release morphine (MS Contin®), etc. It is however important to remember that side effects such as confusion and constipation are common as well as a need to gradually increase the amount of drug to maintain the same benefit.

When treating complications of GBS, it is important to realize that the

effects of therapeutic interventions may not be predictable. Therapies should be tailored to each individual patient and monitored carefully.

Intermediate Course and Rehabilitation

The progression of disability during the acute phase in Guillain-Barré Syndrome can vary from a few days to four weeks, and, infrequently, six weeks. Then a low stable level of impairment (paralysis, weakness, etc.) continues for a variable length of time, days to weeks, and, less often, months or longer.

When the patient has recovered from acute life threatening complications such as breathing difficulty and infections, and muscle strength has stabilized and perhaps even begun to return, treatment in an acute care hospital is usually no longer required. However, many patients will still require rehabilitative care including intensive physical and occupational therapy. Where this care is provided will depend in part on several factors. Choices available for further rehabilitation include:

- 1) In-patient care in a rehabilitation hospital. A common requirement to justify this intensive rehabilitation is the patient's ability to participate in at least 3 hours of therapy a day.
- 2) Sub-acute rehabilitation, in a nursing/rehab facility.
- 3) So-called day hospital care. The patient sleeps at home, and is transported, by a wheelchair-accommodating van, to the rehabilitation hospital or center for daytime therapy.
- 4) Out-patient rehabilitation.
- 5) Home-based therapy, via visiting therapists or by following instructions set up by a therapist for a home therapy program.

The decision as to the type and location for rehabilitation should be individualized to each patient's particular needs, taking into consideration such factors as overall physical condition, strength, endurance, amount of return of use of arms and legs, and insurance. For example, patients with mild impairment, who can walk with assistance of a quad (four footed) or straight cane may not need an in-patient rehabilitation facility, and may obtain sufficient care in an out-patient setting. In contrast, patients who can't walk, or require substantial assistance to do so, but are showing some improvement, may be transferred to an in-patient rehabilitation hospital setting for optimal care.

Physicians may occasionally be reluctant to place Guillain-Barré Syndrome patients in rehabilitation hospitals because of concern about depression or relapse of symptoms that could require readmission to an acute care facility for further treatment. Regardless, transfer of a patient to a rehabilitation center should be considered as a positive next step in the

patient's recovery.

The rehabilitation process itself does not improve nerve regeneration. Rather, the major goal of rehabilitation is to assist the patient in optimal use of muscles as their nerve supply returns, and to adapt to a lifestyle within their functional limitations. In addition to helping the patient regain use of muscles, the rehabilitation center treats any remaining medical complications. These can include control of high blood pressure, antibiotics for infections, treatment of blood clots, etc.

Strength usually returns in a descending pattern, so that arm and hand strength usually returns before leg strength. Often, right-handed persons note more rapid return of strength to the left side and vice versa. As arm strength returns, the patient is again able to do things that used to be taken for granted, such as brush their teeth, feed, groom and dress themselves, cut meat and so forth. As ability to perform activities of daily living improves, the success can be emotionally fulfilling.

Rehabilitation in many centers is accomplished by the coordinated efforts of several groups of professionals in a team approach. The team members may include, depending upon the particular patient's needs, a physiatrist (rehabilitation doctor), physical therapist, occupational therapist, registered nurse, neurologist, internist, psychologist, social worker, etc. Each team member contributes their particular expertise to the patient's care. Team conferences may be held at intervals, for example, weekly, to assess the patient's status, determine progress and plan further care. The team's overall goal is to assist the patient to maximize use of returned function and ultimately return to society. Most patients will eventually lead a normal or near normal life. For those patients with incomplete recovery, the goal is to adapt their lifestyle to persisting functional limitations.

The physiatrist (pronounced: fiz-eye'-a-trist) (not to be confused with a psychiatrist) is a physician who specializes in physical medicine and rehabilitation. A physiatrist usually coordinates and oversees the total rehabilitation program.

Principles of Rehabilitation for the GBS Patient. During the rehabilitation process, certain issues are unique to GBS patients. Most rehabilitation patients are exercised to maximum ability, to fatigue. This should be avoided in GBS patients as exhaustion requires some time to resolve and will delay the rehabilitation process without benefitting the patient. Substitution of stronger muscles for weaker ones will delay uniform return of strength and optimal function. So the therapist should be cognizant of the potential for substitution and customize exercises to strengthen weak muscles. Neuropathic pain can limit the patient's ability to undergo rehabilitation and should be recognized and adequately treated.

Occupational Therapy: An occupational therapist instructs the patient

in exercises to strengthen the upper limbs (shoulders, arms, hands and fingers) and help prepare them for return to their occupation. Usually arm strength and use returns before hand and finger dexterity. Help is given to re-learn activities previously taken for granted such as holding a pencil, using an eating utensil, etc. Muscle testing may be performed, and exercises designed to strengthen the weaker muscles. Repetitive squeezing of a rubber ball or silly putty can strengthen the hand grip while spreading two fingers apart against a rubber band placed across the fingers can be used to increase finger strength.

Tests may be utilized to determine the status of hand sensation. For example, the patient may be instructed to look away or close their eyes while articles of varied consistency and shape such as a marble, key, eraser, pen, closed safety pin, and the like are placed into their hand. The ability of the patient, without looking, to discern the presence of these objects and identify them indicates that their sensory nerves can perform fine touch discrimination. In another test, the patient inserts their hand, with eyes closed, into a bowl of sand or rice containing such items as chalk, keys, eraser, etc. The ability of the patient to locate these, and, upon removing them, identify their particular shape and consistency provides an index of return of finger sensation. Some patients may experience persistent difficulties in using their hands and fingers to perform such activities as using a zipper, buttoning a shirt, writing, using utensils and handling coins. Methods are available to compensate for these problems. For example, to circumvent difficulty in buttoning clothes, a button-hook device may be utilized. Velcro® straps or zippers with large pull handles may sometimes be practical alternatives to buttons. Because of the potential for fatigue, severely affected patients are taught energy conservation techniques that include using shortcuts to maximize hand and arm use. Splints may be used to position the wrist slightly cocked, and to support the thumb, to optimize hand use.

Physical Therapy: The physical therapist emphasizes strength and function of the lower limbs, and ultimately teaches the patient to walk as independently as possible. A variety of methods are used to accomplish these goals. Initially, the patient, fitted with a life jacket (personal flotation device), may be lowered into a pool, and assisted into a suitable depth of water so they can walk with partial weight bearing, the life jacket and water providing buoyancy to enable this. Immersion in a therapeutic pool may also relieve muscle pain. As strength returns, exercises are preformed on mats to help strengthen various muscle groups against gravity and resistance. For example, the patient may be placed on a mat on his back, with the knees raised on a triangular foam support; progressively increasing weights are placed on the ankle and the patient is directed to slowly and repeatedly

straighten and lower the leg. This exercise can help the patient increase thigh muscle endurance. Slowly raising and lowering the leg affords greater use of muscles and facilitates better development of strength rather than allowing the lower leg to fall with gravity. Other exercises are used to strengthen the hip musculature, such as lifting the upper leg with the patient on their side and maintaining it in an upward position against gravity. As nerve innervation returns, other exercises can be used to maintain muscle strength. A stationary rehabilitation exercise bicycle may be used to apply an adjustable force to the leg as it pedals the bike, thus providing progressive resistive exercise to improve strength and endurance.

As leg strength improves sufficiently for the patient to bear weight and begin walking, assistive devices provide added support and balance. The patient may be placed between two railings, called parallel bars, positioned at about waist level. These provide the patient with maximal support while walking by holding the bars with both hands. As balance improves a wheeled walker may be used. The patient rolls or slides the walker forward to provide support as they walk. As balance improves further a standard, non-wheeled walker can be used with the patient lifting it forward repeatedly as they walk. The next progression may then be to forearm crutches or directly to underarm crutches and then canes. A quad cane, with four small feet, provides a fair amount of stability. If the patient has enough balance and strength, a straight cane may be sufficient. Eventually, if possible, independent walking without an assistive device is accomplished. During the rehabilitation process emphasis is placed on proper body mechanics, avoidance of substitution of stronger muscles for weaker ones, and prevention of muscle strain and fatigue, and safety.

For patients with persisting muscle group weakness, various methods (orthotic devices) can be used to increase function and independence. For example, a dropped foot can be treated with a molded ankle foot orthosis (MAFO), a thin lightweight plastic device that fits behind the leg and under the foot. For the patient with a weak grip, utensil handles can be wrapped with a thick cylinder of foam rubber to enable better gripping of the utensil; the edge of a plate can be fitted with a metal wall so the patient can push food against it with a fork or spoon to help get the food onto the utensil. A Velcro® strap around a cane handle can hold the hand of a patient with a poor grip onto the handle and enable him to use the cane. Progressive resistive exercises may be designed to strengthen specific muscle groups and functions.

In addition to occupational and physical therapists, other persons may participate in rehabilitation, including speech therapists, nurses, social workers, and psychologists. The latter can play an important role in assisting the patient and family in dealing with the new and sometimes

overwhelming problems of paralysis, dependency, lost income, and a multitude of associated emotional problems including frustration, depression, self-pity, denial, and anger. Since the prognosis for the Guillain-Barré patient is optimistic, in spite of the potential gravity of the illness, a practical approach is to take one day at a time. Recovery, although greatest during the first year, can continue over two to five or more years. Participation in active physical therapy can be a positive factor in a patient's recovery both mentally and physically.

Speech Therapy: Speech is impaired in about 40% of GBS patients. Patients on a respirator will be unable to speak because the tube placed into the airway does not allow the vocal cord movement required to produce speech. These patients can usually communicate via Communication Cards. Typically, after an endotracheal tube is removed, the patient's speech returns within a few days. Even off a respirator, a patient may still have difficulty talking if the muscles used for speech are weak. These muscles control the vocal cords, tongue, lips, and mouth. Slurred speech or difficulty swallowing may occur. A speech therapist can help the patient learn exercises for the affected muscles, to improve speech patterns and clarity of voice, as well as recommend dietary changes to facilitate safe swallowing with adequate nutrition.

Long-range plans

As the patient progresses through the rehabilitation program, it may be appropriate to plan for multiple long-range problems. These problems include learning to drive and using convenient parking, re-employment, learning to pace activities, sexual activity, limitations of the wheelchair-bound patient and so forth. A social worker may assist in handling many of these problems. The majority of patients who were in a rehabilitation center may be placed on an out-patient therapy program when sufficient strength has returned. At home, living on a floor with a bathroom and bed may be temporarily helpful until the patient is able to climb stairs. As sufficient strength returns, driver retraining may be appropriate, especially if the patient had been hospitalized and not driving for a long time. Driver retraining, and adaptation of an automobile for hand controls, is available through some rehabilitation and hospital centers.

The frustration of physical exhaustion or shortness of breath associated with prolonged walking may be reduced in the recovering patient by parking near a building entrance in a handicapped parking space. A special parking placard or license plate is available in some states.

As the patient approaches the end of in-hospital rehabilitation, it is usually appropriate to plan for return to their employment or re-employment. This is hopefully a cooperative effort between patient, social

worker, former employer and, if available, a state bureau of vocational rehabilitation. A potential barrier to returning to work, as well as resumption of a normal overall lifestyle, is the onset, following a certain amount of activity, of muscle aches, physical exhaustion, and abnormal sensations, such as tingling and pain. These problems may be circumvented by returning to work part-time initially, and if possible, timing activity with intermittent periods of rest. Many patients learn by trial and error how much activity they can tolerate.

After discharge from a formal hospital-based in or out-patient rehabilitation program, there is often a role for continued exercise. Usually, some of the physical and occupational therapy exercises done as an in-patient can be performed at home. Also, activities of daily living, such as bathing, dressing, walking, and stair climbing may suffice as a practical out-patient exercise program. Should muscle or joint cramps or aches develop with activity, over-the-counter mild pain medications such as aspirin or acetaminophen (Tylenol®) may provide relief. Since pain relief does not relieve the muscle, tendon, or joint strains, rest periods or a temporary reduction of activity may be helpful.

Some caution is warranted with respect to the gradual institution of non-hospital-based exercise programs, jogging, and sports. Each recovering patient should be evaluated for their individual needs. Care should be taken to gradually expand activities in order to avoid tendon, joint, and muscle injury. Upon discharge, the patient can usually resume sexual activity. Positions that minimize muscle exertion, such as lying on the back, may prevent exhaustion until pelvic and other muscle strength has improved. A male patient that experiences erectile dysfunction not present prior to GBS should have his physician review his medications to screen for those that might inhibit normal erections or see a urologist experienced in these problems. In some cases medications such as sildenafil (Viagra®) may be helpful.

For the wheelchair-bound patient, architectural barriers (e.g., stairs) may be overcome by ramps to enter the home and other buildings. One-floor living, a stair lift, or an elevator may be required. A visiting nurse and physical therapist can treat the patient at home. Significantly handicapped patients are referred to their local rehabilitation center or other resources

Fatigue

Fatigue is a common problem during the early part of recovery and can even persist in some patients who appear to have recovered (*Merkies et al, 1999*). Such patients may have normal strength with standard testing of muscle function, and can perform normal activities, such as walking. Yet, with sustained activity, they may develop weakness or fatigue, and even

frank exhaustion and collapse. Fatigue may be preceded or accompanied by flares of muscle pain, or other abnormal sensations such as tingling. This problem of persisting poor endurance and fatigability in prior GBS patients was documented in a study of members of the United States Army who had apparently recovered (*Burrows and Cuetter, 1990*). In spite of some being able to return to their usual activities, formal physical fitness testing (a 2-mile run, sit-ups and push-ups) showed that some still had decreased endurance compared to their pre-GBS status. Two of the studied patients had normal electrodiagnostic tests (nerve conduction velocity-electromyography), in spite of diminished endurance capacity. In summary, both patient and physician should realize that limited endurance is a valid problem in GBS patients that is difficult to objectively measure with standardized office tests of muscle strength. At least one study suggests that formal endurance exercise training may help improve a patient's work capacity (*Pitetti et al, 1993*). Another study showed that three 20 minute aerobic courses of exercise per day also improved the symptoms of fatigue (*Garssen et al, 2004*).

As noted in the "Long-Range Plans" section, if a GBS patient senses impending weakness or, by experience, learns to recognize a flare of abnormal sensations that signal impending fatigue, the practical treatment is to pace activities by resting as needed to avoid exhaustion. Decreased endurance may necessitate a shortened workday or, alternatively, a less physically demanding job.

Natural history and prognosis

The overall outlook for most GBS patients is good. But the course of the illness can be quite variable. An occasional patient may experience a mild illness, with a brief period, days or weeks, of a waddling or duck-like gait, and perhaps some tingling and upper limb weakness. At the other extreme, more likely in the elderly, the patient may rapidly develop almost total paralysis, respirator dependency, and life threatening complications, such as abnormal heart beat and blood pressure, lung congestion, and infections. Rarely, paralysis may be so complete that the patient may not even be able to shrug a shoulder or blink an eye to communicate. The patient is said to be 'locked in.' Fortunately hearing is usually preserved, enabling the patient to hear and understand those around them. Thus, conversations about problems may best be spoken away from the patient.

Estimates of outcomes can be roughly approximated based on several studies. Up to 80 percent of patients will be able to walk without aid at three months and by the end of a year will experience only minor residual symptoms such as numbness of the bottom or ball of the foot. An eventual full recovery can be expected. A patient may experience persisting but mild abnormalities that will not interfere with long-term function. Examples

include abnormal sensations, such as tingling, achy muscles, or weakness of some muscles that make walking or other activities awkward or difficult.

At least 20% of patients have significant residuals and it is these patients who benefit the most from treatment intervention that modifies the immune system. Perhaps 5 to 15 percent of GBS patients will have severe, long-term disability that will prevent return to their prior lifestyle or occupation. Factors that often lead towards greater severity of the disorder, with a longer course and incomplete recovery include older age, more rapid onset of symptoms, becoming respirator dependent within 7 days and preceding diarrhea. Such patients are more likely to have a prolonged hospital course followed by rehabilitation for 3 to 12 months and may never be able to walk independently.

Strength returns at various rates. Some generalizations about speed of recovery can be made based upon the data published in 1988 by the Hopkins-based GBS Study Group and by the 2007 Erasmus study in the Netherlands. In the latter study patients were scored based upon their age, preceding diarrhea, and degree of weakness. The patients who could readily walk without assistance were assigned a disability score of 1. Non-walking patients were given a score of 5. The total score can range from the least impaired, 1, to the most impaired, 7. Patients with a low score of 1-3 have an excellent (95%) chance of recovery, being able to walk unassisted within 3 months from onset of their illness. Those with a score of 7 are less likely to have a good recovery (*van Koningsveld, 2007*). The scoring system is summarized in Table 4:

Table 4: Erasmus Prognostic Score

<i>Prognostic factors</i>	<i>Category</i>	<i>Score</i>
<i>Age (year)</i>	≤ 40	0
	> 40	1
<i>Diarrhea (within 4 wks. before GBS symptoms)</i>	<i>absent</i>	0
	<i>present</i>	1
<i>GBS disability score</i>	0-1	1
	2	2
	3	3
	4	4
	5	5
<i>EGOS*</i>		1-7

**Erasmus GBS Outcome Score*

Children with GBS seem to fare at least as well as do young adults, and some studies suggest that pediatric patients actually recover faster and more completely than young adults, who, in turn, appear to recover faster than older patients.

If, after recovery, a patient again develops abnormal sensations, it is usually appropriate to look for causes other than Guillain-Barré Syndrome. Evaluation by a neurologist may be warranted. Sometimes, for example, there may be a need for a repeat nerve conduction velocity test, a glucose tolerance test, and other studies to confirm the presence of nerve damage and to look for its cause. Recurrence or persistence of abnormal sensations or weakness may also conceivably signal the development of chronic idiopathic relapsing or progressive polyneuritis. These disorders are rare and the persistence or redevelopment of abnormal sensations should not be taken as an indicator of the presence of this disorder unless a neurologist experienced with chronic relapsing polyneuritis confirms the diagnosis. This disorder is described later in the section on CIDP.

Immunization Safety; Foreign Travel

Since the illnesses prevented by immunizations often lead to substantial medical complications, the benefits of most immunizations outweigh their risks. Most immunizations and medications used for foreign travel (from the USA) are safe and mentioned at the end of this section.

Influenza vaccine. The influenza vaccine developed in 1976 for a swine-derived influenza virus (swine flu) immunization program was implicated as the trigger of many GBS cases. Some studies reported a seven-fold increase in the number of GBS cases following immunization. Because of the large number of GBS cases the program was halted. Another study reported a smaller increase in GBS cases (about 1 extra person per 1,000,000 persons vaccinated each year) following administration of influenza vaccine for more common human strains of influenza during the 1992-93 and 1993-94 seasons. (*Lasky et al, 1998*)

The greater-than-expected number of GBS cases associated with the 1976 swine flu vaccine led to a concern by some patients that flu shots and other vaccines might trigger a recurrence of their illness. Compared to the risk of developing significant complications from the flu, the risk of new onset or recurrent episodes of GBS with the flu vaccine is very low. In patients 65 and over, typical candidates for a flu shot, 10,000 persons per million, or 1,000 people per 100,000 population, require hospitalization because of the flu, with a death rate as high as 1,500 per million. In contrast, the average number of GBS cases is only 0.5-2 per 100,000 each year (a very small percent of which is related to influenza vaccine), with a mortality rate of only 3% to 5% in that group. This translates to 1,000 people getting very

sick from the flu if not given a flu shot, compared to one or fewer people developing GBS in the general population given a flu shot. Accordingly, the risk of developing a significant complication from the flu is much greater than the risk of developing GBS. For these reasons, most experts recommend that former GBS patients who fulfill standard criteria to receive the flu shot should do so.

There is an exception to this guideline. If a patient developed GBS within 6 weeks of receiving a flu shot or other vaccine, such a time relationship increases the possibility that the injection might have triggered the original episode of GBS and thus may, if repeated, cause a recurrence. In such situations, the vaccine should likely be avoided indefinitely and if exposed to the virus, the patient should be preemptively treated with anti-influenza agents such as Tamiflu®.

The GBS patient who is still recovering presents a different situation from recovered patients. During recovery, the immune system may be more vulnerable to exposure to foreign proteins. Immunization in these patients is likely best deferred until they are stable, at least six months out from onset of their illness.

Sanofi-Pasteur received FDA approval to market a H1N1 swine flu vaccine. The product's literature does not include an absolute contraindication for former GBS patients to receive it and in the subsequent vaccination campaign was not associated with any unusual increase in GBS cases. It is recommended to discuss its use with a patient's treating physician.

Other vaccines. The following list of vaccines are likely safe for recovered GBS patient especially if they have underlying chronic illness (diabetes, heart failure, chronic lung disease, etc.) that make them more susceptible to infection or if the person travels to any area where the disease is common.

- Vaccines for cervical cancer/human papillomavirus vaccine (Gardasil®) [*Immunization Safety Office of Centers for Disease Control, 8/15, 17/07*]
- Pneumococcal vaccine for pneumococcal pneumonia (Pneumovax®23)
- Zoster vaccine (Zastavax®) to reduce the risk of developing shingles (herpes zoster)
- Hepatitis A and B vaccines (*Blumenthal et al, 2004*)(*McMahon et al, 1992*) (*Sindern et al, 2001*)(*Khamaisi et al, 2004*)
- Yellow fever vaccine (YF-Vax® by Sanofi-Pasteur)

Sporadic cases of GBS are reported following administration of these vaccines. The pros and cons of using these is usually best discussed with the patient's family physician who can take the entire medical history into consideration.

Meningitis vaccine (Menactra®). Bacterial meningitis is a rare but potentially fatal infection, affecting primarily children and young adults. It

can be caused by some strains of *Neisseria meningitidis*. The vaccine, meningococcal polysaccharide diphtheria toxoid conjugate vaccine (marketed by Sanofi-Pasteur as Menactra®) reduces the risk of developing meningitis. However, because of reports of cases of GBS following its use, a prior history of GBS is a contraindication to using Menactra®.

Guidelines for immunizations for foreign travel. Travel to some parts of the globe, such as much of Asia and Africa, carries risk of contracting infectious and other disorders. That risk often warrants the use of immunizations and/or medication. Most of these treatments are safe for most former GBS patients. Travelers can obtain recommendations for medical care and health precautions from the web site of the Centers for Disease Control, at <http://wwwn.cdc.gov/travel>. Recommendations are provided for immunizations as well as medications and health precautions during the trip ('Staying Healthy during Your Trip'). Plan in advance so immunizations have sufficient time to become effective. If more than one vaccine is recommended, for example, for hepatitis B and yellow fever, it is best to receive each one at a separate visit, spacing them apart by at least several days to identify the trigger if a reaction occurs. This latter point is an empiric suggestion by the author (JSS), rather than formal literature based advice on this matter.

Sources of medication and immunization for foreign travel. Family doctors do not usually stock travel medications and may not be aware of recommended regimens. As an alternative, the CDC, local yellow pages, and other resources can direct the traveler to medical centers/doctors who specialize in travel medicine with ready access to regimens of medical care and an office to provide immunization injections.

Summary

Guillain-Barré Syndrome, also called acute inflammatory demyelinating polyneuropathy (AIDP), is characterized by the rapid onset of weakness and even paralysis of the legs, arms, and other parts of the body, as well as abnormal sensations. Within four weeks in 90% of patients the disease plateaus and recovery proceeds over several weeks to months. About eighty percent of patients will have a complete or near complete recovery. Long term severe disability is uncommon. GBS frequently follows a viral or bacterial infection. The illness can present in several ways, at times making the diagnosis difficult to establish in its early stages. Early care is often given in an intensive care unit so potential complications can be recognized and treated quickly.

Treatments to limit the illness' progression and speed recovery include plasma exchange (plasmapheresis) and high-dose intravenous immune globulins. Easier administration of immunoglobulin makes this an attractive

option over plasma exchange. In the early stages of the illness, treatments are also directed at preventing complications of paralysis. If breathing muscles become too weak, a ventilator to support respirations is used. After acute hospital care is completed and if sufficient weakness is present, a comprehensive rehabilitation program in an appropriate center is often utilized. As muscle strength returns, efforts are directed towards returning the patient to their former lifestyle. Patient care involves the coordinated efforts of a neurologist, physiatrist (rehabilitation physician), internist, family physician, physical therapist, occupational therapist, social worker, nurse, and psychologist or psychiatrist. Emotional support from family and friends, and information about this rare disorder, may help the patient learn to deal with this frustrating, disabling, and potentially catastrophic illness.

A particularly frustrating consequence of this disorder is long-term recurrences of fatigue and/or exhaustion as well as abnormal sensations including pain and muscle aches. These problems can be aggravated by normal walking or working and can be alleviated or prevented by pacing activity and rest.

Pertinent facts about Guillain-Barré Syndrome include the following:

- Incidence: 1 to 2 cases in 100,000 population each year (0.001-0.002%).
- Greater than 50% of cases follow a viral or bacterial illness.
- Diagnosis can be difficult in the syndrome's early stages.
- The disorder is not contagious.
- About 50% of patients initially develop abnormal sensations; 25% present initially with muscle weakness (often difficulty walking); 25% present initially with both abnormal sensations and weakness.
- High-dose immunoglobulin infusion or plasma exchange may hasten recovery. Rehabilitation helps during the recovery phase. Corticosteroids are not helpful.
- Recovery may occur over 6 months to 2 years or longer.
- From 10% to 20% of patients have long-lasting disability.
- Death rate is low (3%) particularly in experienced centers.

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP)

CIDP and other Chronic Inflammatory Neuropathies

Immune or inflammatory mechanisms are implicated in a number of chronic disorders affecting the peripheral nerve. One of the more commonly recognized is idiopathic chronic inflammatory demyelinating polyneuropathy, or CIDP. The incidence of new cases of CIDP each year is estimated to be between 1.5 and 3.6 per million population and, because of the chronicity of the disease, to affect as many as 40,000 patients in the United States at any one time. Although this disorder can affect children and adults of any age, the peak period of life during which patients develop CIDP is in the 6th and seventh decade and the disorder is twice as common in men as women. (*Simmons et al, 1997; van Schaik, 2008*).

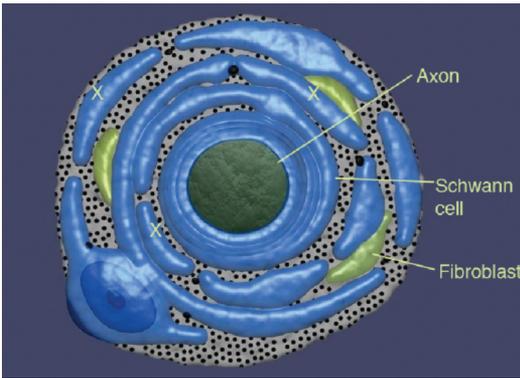
Clinical Course

CIDP is characterized by progressive symmetrical weakness and sensory loss in a patient's legs and arms that develops in a steady or stepwise fashion over more than eight weeks. Weakness is symmetric, occurring on both sides of the body about equally. The longer progression distinguishes it from acute neuropathies such as Guillain-Barré Syndrome, in which patients develop their peak weakness within 1 to 4 weeks. In GBS, 85% of patients will recover their strength and are able to walk independently after 3 months. Unlike Guillain-Barré Syndrome, CIDP is frequently not self-limiting and, if untreated, about 30% of patients will progress to wheelchair dependence. Sixty percent of patients are able to continue to work but with progressing disability. Early recognition and treatment can avoid a significant amount of this disability. Patients with CIDP may have different types of clinical courses.

A progressive form can extend over several years. In the recurrent form patients have multiple episodes of disease that may be separated by months or even years. In the third type, a single episode or monophasic disease process extends over one to three years without recurrence. Factors contributing to the development of chronic inflammatory polyneuropathy are not known. Some investigators suspect that certain patients may be genetically more prone to CIDP than others. At this time there is some evidence of a genetic basis for susceptibility to the more chronically progressive form of CIDP but there is no evidence of transmission between parent and child since only very rarely do cases of CIDP affect more than one family member.

Mechanism of Nerve Damage

The process underlying the development of CIDP is not well understood, but the theory that it is an immune mechanism is supported by the ability of a wide array of immune mediating treatments to improve its clinical course. In this disorder, the myelin sheath surrounding the motor and sensory nerves is destroyed. Myelin is a fat-rich covering that surrounds the nerve fiber or axon. The Schwann cell produces the myelin that wraps around a segment of the nerve fiber; and helps electrical current flow along the axon or fiber myelin is similar to insulating material around an electrical wire. Destruction of the myelin segments results in the loss of ability of the nerve to conduct an electrical impulse and leads to muscle weakness and altered ability to feel



Cross section of a peripheral nerve around which has formed an onion-bulb.

Blue=Schwann cells and myelin, green=fibroblasts

different sensations. In the nerves of CIDP patients, inflammatory cells destroy myelin tissue around nerves, leading to muscle weakness and sensory changes. With time and severity of disease the nerve fiber or axon itself can be damaged, leading to poor recovery even with adequate treatment, particularly in older patients. During this process the peripheral nerve continually tries to repair itself by regrowing the damaged nerve fibers and repairing the myelin sheath. Over time, with repeated episodes of myelin damage and attempted repair, layers of the myelin-producing Schwann cells and fibroblasts that form fibrous connective tissue produce a swelling called an onion bulb, shown in the figure above. Onion bulb formation limits the ability of the nerve to rapidly carry an electrical impulse.

Diagnosis of CIDP

One of the important issues facing the patient and neurologist is early recognition and treatment of CIDP, when the patient is more likely to respond to therapy and in some cases go into remission. Unfortunately there is no reliable diagnostic test for this disorder. Instead the diagnosis 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 spinal 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. Rarely, a nerve biopsy will be done to either confirm the diagnosis of CIDP or rule out other disease entities (Dyck *et al*, 1982; Koski *et al*, 2009).

Symptoms that the patient experiences and that the neurologist confirms by examination include muscle weakness, loss of deep tendon reflexes, poor balance, and loss of sensation that is maximal in the hands and feet. Lost sensation includes pain, light touch, vibration, and proprioception, the ability of a person to know the position of a body part relative to the rest of their body. Although most patients experience weakness early in their disease, a predominantly sensory form can occur that results in poor balance and falls. Most of these primarily sensory patients will develop muscle weakness within two to three years.

CIDP is clinically distinct from other inflammatory neuropathies including multifocal motor neuropathy (MMN), 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. 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 weakness with little or no sensory involvement. It is important to distinguish these disorders from CIDP since some are treated differently.

Diagnostic Tests: In addition to the history and physical examination one of the most important tests that helps support the diagnosis of CIDP is a study that measures the ability of nerves to carry an electrical signal. This test, a nerve conduction velocity (NCV) test, is performed by a trained physician or technician under the supervision of a physician. To diagnose CIDP, at least three different nerves in the arms and legs are directly stimulated by a brief electrical impulse in two or more places along the path of each nerve. Stimulation of the nerve is detected by contraction of a muscle that is innervated by that nerve and the contraction of the muscle is measured with flat electrodes applied to the skin overlying 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. This is called an electromyography (EMG) study.

A spinal fluid examination can also be helpful to support the diagnosis

of CIDP. During a lumbar puncture, the patient either lies on their side or sits upright. The back is cleansed with an antiseptic solution. A local anesthetic medicine like that used in a dentist's office, is injected into the skin. When the skin is numb from the local anesthetic, a thin needle is inserted into the middle of the back at the level of the hip bones below the bottom of the spinal cord. The needle is pushed forward gently until spinal fluid appears at the needle hub. For testing, 2 to 3 teaspoonfuls of fluid are collected into sterile tubes and studied in the laboratory. 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. Examples include the patient without weakness but only impaired sensations and the patient where other causes such as inflammation of blood vessels are suspected. Like NCV-EMG studies and lumbar puncture, a nerve biopsy may be annoying but is usually well tolerated.

Treatment

Up to eighty percent of CIDP patients respond to one or more therapies that modify the immune system. Several of these have been tested in randomized, controlled trials. As an initial measure, patients can be treated with corticosteroids, plasma exchange, or intravenous immunoglobulin (IVIG) (Dyck *et al*, 1982; Hughes R.A., 2002). For descriptions of plasma exchange and IVIG please see earlier discussions in the GBS section of this overview.

Corticosteroids are chemical substances normally made by our adrenal glands, small glands that sit above the kidneys. In high doses they suppress the immune system and improve autoimmune disorders such as rheumatoid and other forms of arthritis. Corticosteroids, nicknamed steroids, are very different from the androgenic type of steroids sometimes dangerously used to build up muscle mass in athletes and animals. One type of corticosteroid is called cortisol, and commercial preparations include prednisone, prednisolone, and methylprednisolone. Since all of these names can get confusing, just using the term 'steroid' is easier. Some preparations can be taken by mouth (p.o.) and others given intravenously (IV).

Results from a single randomized, controlled trial of 28 patients provided limited evidence that oral prednisone (60-100 mg per day or 1 mg/Kg/day), given in decreasing doses over nine months, induced a small but significant improvement in patients with CIDP as determined by improved muscle strength, and nerve conduction studies. Usually the full benefit of a fixed dose of corticosteroids is not seen for 5-8 weeks. Although treatment with corticosteroids is relatively inexpensive, a wide range of side

effects are associated with its chronic use. These include irritability, depression, psychosis, elevated blood sugar, calcium loss from the bones (or osteoporosis), high blood pressure, stomach ulcers, and weight gain. These side effects can lead to persistent disability as well as economic burdens that increase with treatment duration and higher doses of drug. Other approaches to corticosteroid therapy are used to limit these problems, such as giving the steroid every other day, or giving a series of doses of methylprednisolone through a peripheral vein each month. But, over time, side effects still develop in some patients.

Randomized, controlled trials have also demonstrated that both plasma exchange and IVIG induce a rapid although temporary improvement in neurologic function, nerve conduction studies, and strength within two to six weeks in most patients. In plasma exchange, the plasma that is removed contains antibodies and other agents that are thought to injure the myelin sheath and peripheral nerves in CIDP. An initial course of plasma exchange consists of five exchanges performed on alternate days. Clinical improvement is lost if treatments are not repeated each 4-6 weeks. Under the supervision of an experienced plasmapheresis team the procedure is usually well tolerated. Complications can include abnormal heart rhythms from salt imbalances in the blood, low blood calcium, red blood cell damage, infection and clotting at the site of the catheter, and bleeding. Because of all these issues, plasma exchange may be used to initially manage patients to establish their responsiveness to treatment, or in the short term while starting another form of treatment such as corticosteroids. Because of the need for repeated placement of large rigid catheters into large veins, most patients ultimately require alternative treatments for long term maintenance that may be required over years.

Intravenous immunoglobulin or IVIG is a product containing highly purified antibodies from the plasma of several thousand normal donors. It is as effective as plasma exchange in the treatment of CIDP patients. The usual initial course of treatment, a total of 2 grams of immunoglobulin per kilogram of patient body weight, is given through a peripheral vein in the arm, in divided doses over 2 to 5 days. Because of the ease of IVIG administration, the ability to give the drug in the outpatient setting, and the rapid response in a large number of patients, it is frequently used as an initial treatment. In many patients a beginning response can be documented with improved strength within 3-5 days of starting the infusions. Continued improvement can occur over 3 to 6 weeks before symptoms, i.e., weakness, recur. But improved strength can be frequently maintained with smaller doses of IVIG given monthly. If the patient was diagnosed 2-3 years after the onset of symptoms and already has significant nerve axon damage they may require three courses of treatment

over 2 months before benefit is seen. IVIG is usually well tolerated, particularly in initial courses, and preparations available today are usually safe without significant risk of viral transmission.

Complications with IVIG treatment are rare. Development of blood clots reflects many factors including a prior history of stroke or heart attack, dehydration, and a high concentration of the IVIG. If IVIG is repeatedly given to patients with a past history of blood clots, the IVIG concentrations should be reduced, the patient should be well-hydrated prior to infusion and can be on platelet inhibitors such as daily aspirin. Under some circumstances, (for example, the patient with a history of deep vein thrombosis), a blood thinner, heparin, will be injected under the skin prior to, during, and for a week following infusion. A history of kidney disease (chronic renal insufficiency) may at the very least prevent the use of IVIG products with a high sugar content or may prevent IVIG use altogether.

In some older patients with underlying disease of the kidney or blood vessels, IVIG or corticosteroids may be contraindicated. In these cases immunosuppressive drugs such as cyclophosphamide, cyclosporin, tacrolimus, mycophenolate mofetil, azathioprine and type 1 interferon (INF-1 α) and IFN-beta can be used to reduce the dose of corticosteroid and immunoglobulin. These drugs may also be tried because of disease progression or poor response to established therapies. 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.

CIDP is increasingly recognized as a cause of chronic progressive neuropathy and some experts propose a higher incidence of this disorder than most medical literature suggests. Most CIDP patients, if treated early and aggressively, respond well to therapy that can limit the damage to peripheral nerves and contribute to improved function and quality of life.

MULTIFOCAL MOTOR NEUROPATHY

Introduction

Multifocal motor neuropathy (MMN) is a rare, chronic, progressive neuropathy characterized by predominantly distal, asymmetric limb weakness, most often of the upper limbs, with minimal if any sensory changes (*Nobile-Orazio, 2008*). In medical parlance distal means that portion of the body farthest away from the center. Thus in MMN, the hands and forearms, and feet and legs are more often affected than, the shoulders and hips. Asymmetric means that one side of the body, right or left, is affected more than the other side.

Diagnosis

The diagnosis of MMN is based on a combination of the patient's clinical findings, electrical testing of nerve function and spinal fluid findings.

Presentation: MMN, a disorder of peripheral nerves, is characterized by the slow or step wise development of asymmetric weakness that may occur over decades (*Biessels et al, 1997*).

Sensory nerves are not primarily involved. Symptoms vary with respect to the speed of weakness onset and location from one patient to another. Typically weakness starts distally in the upper extremities. The peak incidence occurs in male patients between 50 and 60 years of age although cases have been reported in 20-to 75-year-old individuals. Women are affected a third as often. Initial weakness in the hand may present as difficulty turning a key in an ignition or a lock or handling small objects. Eventually weakness may occur perhaps at the ankle, so foot drop develops, and the patient has to lift the leg higher to walk or trip over his own foot.

Weakness is due to localized inflammation of specific nerves at sites other than those commonly subject to compression injury such as at the wrist (carpel tunnel syndrome) or elbow (tardy ulnar palsy). Inflammation of the median nerve in the forearm of a MMN patient can cause weakness of the thumb and grip. The result is diminished fine finger movement or dexterity. In the legs, foot drop may develop from peroneal nerve damage. The patient cannot lift or bend the foot up at the ankle against gravity. Over time, ongoing weakness may lead to muscle wasting or atrophy, fasciculations or small muscle twitches. Deep tendon reflexes are decreased in the distribution of the damaged nerves.

Sensory nerve fiber function is normal in the involved limbs of MMN patients. However, recent reports suggest that after 7 or more years of disease the patient may develop tingling or paresthesias in the distribution of the involved nerves. Indeed a loss or drop-out of sensory fibers may be demonstrated on nerve conduction testing. In contrast to GBS and some CIDP patients, weakness in swallowing and slurred speech does not occur in MMN. If such involvement occurs the patient does not have a disease of peripheral

nerves but instead likely has a form of motor nerve cell (neuron) disease called amyotrophic lateral sclerosis (ALS), often called Lou Gehrig's disease.

In summary, MMN presents as a chronic (slowly and or step-wise developing) multifocal (the problem develops in several different places of the body) motor (the chief symptom is weakness, with abnormal sensations being rare) neuropathy (the disorder consists of diseased nerves). The weakness is asymmetric, that is, the two sides of the body are affected unequally.

Nerve Conduction Testing

Electrical testing of nerve function is usually extremely helpful to clarify that a patient has MMN and not some other, similar appearing disorder. Testing is done to show blockage of electrical impulse conduction in nerves that supply the patient's weak muscles. Tests may show some evidence of myelin damage (as in GBS and CIDP) or even local axonal damage (*Katz et al, 1997*)

To diagnose MMN, selective electrical testing is required, with careful mapping of motor nerve conduction along the course of the nerve, or several nerves. This technique identifies motor nerve conduction block with preserved sensory nerve conduction. The conduction blocks in two or more motor nerves used to diagnose MMN may not include sites of common compression injury such as carpal tunnel syndrome at the wrist.

Spinal Fluid Analysis: In GBS and CIDP, elevated spinal fluid protein is the norm, without elevation of fluid cell count. However, in MMN, elevation of spinal fluid protein is infrequent, seen only in about 10% of cases.

Cause

The cause of MMN is not known. Several lines of evidence support damage by the immune system as the underlying disease process. These include the following: 1) demyelination and axonal damage are found in areas of conduction block, 2) antibodies in MMN patients are found at nodes of Ranvier and adjacent myelin of motor nerves and 3) patients improve with treatment to suppress immune system activity. However, in contrast to other chronic demyelinating neuropathies like CIDP (see above section) immune system cells (macrophages, lymphocytes) are not typically found in MMN lesions. GM1 molecules, composed of fat and complex sugars, are found on some nerves. Antibodies to GM1 are a potentially useful marker of MMN as they are found in 30% to 80% of patients. Demyelination may be only one part of the explanation for MMN symptoms. GM1 antibodies are found at sodium channels that are clustered at the axon's outer membrane, the axolemma, found at nodes of Ranvier in between myelin segments as well as at the end of motor nerves to muscles, called the terminal axons. Thus damage of these parts of nerves may also contribute to symptoms in MMN. To lend confusion about the significance of GM1, this antibody is also found in smaller amounts on sensory nerves even though MMN only affects motor nerves. Furthermore GM1

antibody levels don't fall with patient improvement from IVIG treatment but do fall with improved strength from cyclophosphamide and rituzimab. Thus GM1 is thought to be a marker for disease and not a cause of nerve damage. Other antibodies to other nerve components may yet be found to explain this disorder.

Treatment

IVIG: MMN often shows short and long-term improvement with intravenous immunoglobulin (IVIG) (*Umapathi et al, 2009*). Indeed the likelihood of benefit with IVIG makes it the first line treatment for MMN. Patients typically respond to a course of IVIG within hours to days, with improved strength that may last 3-6 weeks to months. Repeated doses of IVIG may be required if a patient initially gets stronger with this treatment and then relapses with weakness. (A typical dose regimen of IVIG is 0.4 g/kg body weight daily for 5 consecutive days to provide, overall, a total of 2 g of immunoglobulin/kg body weight, or, as preferred, divided over 2 to 5 days.) The pattern of response and relapse after a regimen of IVIG allows a doctor to plan a regular schedule of maintenance treatments so the patient can avoid a major deterioration and further nerve damage. Maintenance dosing is often 1- 2g/kg regimen, every 2-6 weeks. IVIG is expensive but usually quite safe. It is so often helpful that if a patient shows lack of benefit then the accuracy of the diagnosis may warrant reconsideration.

Other Treatments: No treatments other than IVIG have demonstrated efficacy in randomized controlled trials for MMN. Some treatments found helpful for CIDP, such as plasma exchange and corticosteroids, are not effective in treating MMN and may actually lead to deterioration. Nevertheless, results from several uncontrolled trials or case series suggest that benefits may be derived from adjunctive therapy with a number of immunosuppressive drugs including azathioprine, cyclosporine, cyclophosphamide, interferon, mycophenolate mofetil, and rituximab.

Most experience with immunosuppressants has been reported with cyclophosphamide (CTX) with perhaps a 50% rate of improvement. However because of the risk of harmful side effects it is typically used as a second line therapy, in MMN patients who don't respond to IVIG. (A recommended dose regimen is 3 g of CTX per meter squared of body surface area over 8 days, followed in a month by a dose of 2 mg/kg/day by mouth. Daily oral doses, 100-150 mg/day, or periodic intravenous [1 -3 gm/M²] regimens have been used for periods of up 6 months.)

Potential side effects of CTX include bone marrow suppression leading to decreased platelet and white blood cells with increased risk of bleeding and infections, hemorrhagic cystitis, infertility, teratogenicity, alopecia or hair loss, nausea, vomiting and an increased risk of hematological cancers.

A combination of cyclophosphamide with PE has been effective, but not PE alone. Individual patient reports indicate that other immunosuppressive drugs may be helpful, such as rituximab, interferon-beta, azathioprine and

cyclosporin. Thus to plan optimal treatment it is important to accurately determine the diagnosis of MMN. Diagnostic possibilities to consider, that may respond to steroids and plasma exchange, are multifocal demyelinating sensory and motor neuropathy, otherwise known as MADSAM or the Lewis Sumner syndrome, a variant of CIDP.

Recommendations: A working group of the European Federation of Neurological Societies and the Peripheral Nerve Society (EFNS-PNS) published the following recommendations: IVIG is the therapy of first choice in patients presenting with severe handicaps secondary to MMN. Patients should receive 2 g/kg of body weight over two to five days. If the initial IVIG therapy is effective, a repeated dose should be considered. The frequency of IVIG should be adapted to the individual needs of the patient, typically 1 g/kg body weight every two to four weeks, or 2 g/kg every two to eight weeks. If IVIG efficacy is insufficient, immune suppressants such as cyclophosphamide, cyclosporine, azathioprine, interferonbeta-1, and rituximab should be considered. Cyclosporin and cyclophosphamide are less desirable due to toxicity to the kidney and bone marrow. (*Joint Task Force of the EFNS-PNS, 2006*).

Natural History/Prognosis

How long MMN will last if untreated is very difficult to predict. There is a wide range of duration, reported to extend from as short a time as 2 years to as long as 20 years and longer. For those patients in whom disease extends over decades, IVIG, although effective, does not completely eliminate progression of axonal damage. Further investigation of regimens and combinations of therapy are needed.

Comparison with Other Disorders

MMN has many features of the chronic cousin of GBS, CIDP (chronic inflammatory demyelinating polyneuropathy), in that its onset is slow and it may persist for years. However, in contrast to typical CIDP, MMN is asymmetric, affecting the right and left sides of the body differently. MMN most closely resembles the rare CIDP variant, multifocal (upper limb predominant) CIDP or multifocal demyelinating sensory and motor neuropathy (MADSAM), described in the medical literature in 1999 by Lewis and Sumner (see more information on this under the heading of CIDP variants). MMN has features of other neurologic disorders. It can be confused with other lower motor neuron disorders (LMND) with damage to motor nerve cells in the spinal cord such as amyotrophic lateral sclerosis or (ALS), also known as Lou Gehrig's disease. A careful nerve conduction velocity-electromyography (NCV-EMG) study will show the block of nerve conduction proving the condition to be a disease of peripheral nerve and helps to distinguish MMN from other nerve disorders. MMN is a treatable condition whereas ALS is not. Therefore it is vital to make the correct diagnosis, to provide proper therapy and patient education.

APPENDIX

Disorders Potentially Similar to Guillain-Barré Syndrome

This section may be of interest only to patients in whom a diagnosis of Guillain-Barré Syndrome has been raised but other disorders are being considered. Several disorders can affect the nervous system or muscles and cause symptoms similar to Guillain-Barré Syndrome. Some of these disorders are even rarer than Guillain-Barré Syndrome, so their existence need not be of concern to most patients. However, if a patient's presented findings raise concern about them, the physician may wish to do studies to exclude their presence. In many of these disorders certain findings that are typical of Guillain-Barré Syndrome are not found. These include spinal fluid protein elevation, weakness of breathing, facial and eye muscles, and loss of deep tendon reflexes. The presence of such abnormalities is supportive of a diagnosis of Guillain-Barré Syndrome. Their absence helps differentiate Guillain-Barré Syndrome from other possible disorders. The following paragraphs supply brief descriptions of some disorders with clinical presentations similar to GBS.

Lyme disease is more prevalent in some parts of the United States. It is caused by the tick-borne spirochete bacterium *Borrelia burgdorferi* and was named after the Connecticut town where early cases were identified. Manifestations of this disease can include a GBS-like picture of acute peripheral neuropathy with pain. Appropriate blood tests and spinal fluid examination can establish the diagnosis so that proper antibiotic therapy can be instituted.

Poisoning with **heavy metals** such as arsenic (found in some insecticides), lead, and mercury can cause abnormal sensations and/or weakness. These symptoms can also be caused by other **industrial and environmental substances** including thallium, present in some pesticides, and rodent poisons; organic solvents including n-hexane, inhaled with glue sniffing; methyl n-butylketone, a solvent for some glues; acrylamide; and organophosphorous compounds. An appropriate history and urine and/or blood tests can help identify these substances as the source of the symptoms.

Attacks of acute intermittent **porphyria**, a genetic metabolic disorder, sometimes include muscle weakness and loss of sensations and tendon reflexes. Thus, attacks of porphyria can produce symptoms similar to those seen in Guillain-Barré Syndrome. However, with porphyria, abdominal pain, rapid heart beat, seizures, and behavior changes are common. Appropriate

screening blood and/or urine studies can help determine the presence of this rare disorder.

Post-Polio Syndrome is the term used to describe a recurrence of weakness in some patients who had previously developed paralytic poliomyelitis in the 1940s and 1950s. The syndrome is thought to represent a delayed death of spinal cord motor neurons previously injured during the acute polio infection. Thus, these patients' history of prior polio years before helps to distinguish the cause of their weakness from Guillain-Barré Syndrome. Also, with polio, as well as Post-Polio Syndrome, the weakness may affect the legs or arms unequally, there are few if any sensory problems, and the spinal fluid protein is not elevated.

A disorder similar or identical to Guillain-Barré Syndrome in symptomology, with both the features of abnormal sensations and weakness, can occur with some **malignancies**. These malignancies include those of lymph glands (including Hodgkin's disease and lymphoma) and of certain white blood cells (including chronic lymphocytic leukemia). Other malignancies in which similar neurological changes can occur include those of the lung, stomach, and special white blood cells (plasma cells) which make abnormal protein substances (multiple myeloma).

As with Guillain-Barré Syndrome, the disorder **transverse myelitis**, an inflammatory condition of the spinal cord, may occur after a viral illness and vaccinations. It is characterized by the development, over hours to several days, of weakness and abnormal sensations of the legs. Other common findings may include difficulty in controlling urination as well as bowel disorders and back pain. Typically, there is a lack of sensation below a certain level of the body indicating disease in the spinal cord. In contrast to Guillain-Barré Syndrome, transverse myelitis does not affect the upper limbs or face. Also unlike Guillain-Barré Syndrome, in which loss of deep tendon reflexes is common, in transverse myelitis, the knee and ankle reflexes are brisk or exaggerated. Spinal fluid protein can be elevated in transverse myelitis.

Diabetics can develop abnormal sensations of the feet, and also the fingers. Diabetics can also develop muscle weakness (diabetic amyotrophy) but often the weakness is asymmetric affecting one lower limb more than the other, and does not involve the breathing muscles, as may occur in Guillain-Barré Syndrome.

Some drugs can cause nerve damage as side effects. For example, nitrofurantoin (Macrodantin®), which is used for urinary tract infections, has been associated with severe and even irreversible peripheral nerve damage. Dapsone, used to treat leprosy and some skin disorders, has been associated with muscle weakness related to nerve damage. Muscle strength

usually returns if the medication is stopped.

Some abnormal **blood chemistries** can cause weakness. An example is **low potassium**, caused by several diuretics or water pills and occasionally by a genetic disorder, hypokalemic periodic paralysis. A simple history and blood test for electrolytes can make the diagnosis. Supplemental potassium medication or adjustment of diuretic medication can usually correct the weakness.

Some autoimmune **connective tissue or collagen vascular disorders**, including polyarteritis nodosa, systemic lupus erythematosus, Sjogren's syndrome, and progressive systemic sclerosis (scleroderma) may be complicated by abnormal sensations related to nerve changes.

Acute polymyositis and **dermatomyositis** are inflammatory conditions of muscle, causing muscle weakness and pain. However, nerve conduction is not affected, reflexes are preserved, and spinal fluid protein is not elevated. Abnormal blood studies (elevated CPK-MM fraction and aldolase) support the diagnosis of muscle necrosis which can be confirmed by a muscle biopsy. Other conditions that lead to muscle necrosis and weakness include acute thyrotoxicosis, and malignant hyperthermia with sensitivity to anesthetics.

In **tick paralysis**, weakness of the legs is followed, usually within a few days, by paralysis of the rest of the body, including muscles for breathing and swallowing. Deep tendon reflexes are decreased, as with Guillain-Barré Syndrome, but spinal fluid protein does not rise and NCV tests show disease of the nerve muscle junction. Several ticks including female wood ticks, the Rocky Mountain wood tick of western North America, the common dog tick of eastern North America and the Australian tick, *Ixodes*, have been associated with paralysis. If the patient recovers following removal of a tick, they probably didn't have Guillain-Barré Syndrome.

Botulism can resemble a descending form of Guillain-Barré Syndrome. It is a paralyzing disorder caused by food poisoning with the bacterium *Clostridium botulinum*, which is rarely found in canned foods and meats. Typically, within a half to one-and-a-half days of eating contaminated food, patients develop weakness of the eye muscles, with double vision and difficulty swallowing, as well as gastro-intestinal upset. The weakness pattern then descends and can involve breathing muscles.

Polio, a disease caused by the poliomyelitis viruses, is largely eradicated in the USA by the successful vaccine program. The occasional unvaccinated patient may experience weakness which, in this disorder, predominates over sensation abnormalities. The weakness may affect one side of the body more

than the other and the breathing muscles may also become weak. **West Nile virus** can also cause severe and sometimes irreversible damage to neurons in the spinal cord leading to rapid onset of paralysis which may be asymmetric. Fortunately, as is the case with diphtheria (*see below*), in countries with widespread immunization programs, polio is a very rare disorder.

A few weeks after the onset of **diphtheria**, a descending pattern of muscle weakness) may develop and affect the throat and eyes (with blurring of vision) and then other muscles of the face. Thus, it eventually produces a descending Guillain-Barré Syndrome-like phenomenon. Fortunately, this disease is quite rare in the United States and other countries with widespread immunization programs.

There are enumerable causes of weakness, including anemia; low blood potassium levels (hypokalemia) caused by some water pills or diuretics (e.g., hydrochlorothiazide [*HCTZ*], used to treat high blood pressure [*hypertension*], or furosemide [*Lasix®*], used to treat a weak heart [*congestive heart failure*]); and underactive thyroid gland hormone production (hypothyroidism). Presence of the latter disorder can be confirmed by finding an elevated thyroid stimulating hormone (TSH) level and a low normal or decreased thyroid hormone (T4) level in the blood. Diagnoses of the enumerable causes of weakness can usually be accomplished via an appropriate history, physical examination, and laboratory studies.

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A BRIEF DESCRIPTION OF THE FOUNDATION

The GBS/CIDP Foundation International was founded in 1980 by Robert and Estelle Benson to assist victims of this rare, paralyzing, potentially catastrophic disease of the peripheral nerves. The Foundation:

- Provides emotional support to patients and their loved ones
- Provides, when possible, personal visits by former patients to those currently in hospitals and rehabilitation centers
- Develops worldwide support groups
- Supplies literature about the syndrome, a comprehensive Overview for the Layperson, so patients and their families can learn what to expect during the illness
- Educates the public and medical community about the Foundation and maintains their awareness of the disorder
- Supports and fosters research into the cause, treatment and other aspects of inflammatory/immune mediated peripheral neuropathies
- Directs patients with long-term disability to resources for vocational and other assistance
- Holds International Symposia
- Encourages financial support for the Foundation's activities
- Advocates for early diagnosis, effective and affordable treatment for patients

The Foundation's Medical Advisory Board includes neurologists active in GBS and CIDP research, leading physicians in rehabilitation medicine and physicians who, themselves, have had the syndrome. Meetings are held by the Foundation's support group chapters to introduce new patients and present speakers who are knowledgeable about the disorder. All contributions to help us help others are appreciated. The GBS/CIDP Foundation International is a nonprofit 501(c)(3) volunteer organization, incorporated in the Commonwealth of Pennsylvania.

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Joel Steinberg, M.D., Ph.D. (physiology and biophysics), a specialist in peripheral vascular disease (circulation disorders) and internal medicine, joined the GBS-CIDP Foundation International after developing Guillain-Barré Syndrome. His neurologist suggested that he write about his experiences. Further impetus to write this Overview came from the Foundation's founders, Robert and Estelle Benson, who appreciated a need to supply patients with information.

Carol Lee Koski, M.D. is the Medical Director and a member of the Medical Advisory Board for the Guillain-Barré Syndrome/Chronic Inflammatory Demyelinating Polyneuropathy Foundation International (GBS/CIDP Foundation International).

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Dr. Koski received her medical degree from the University of Maryland School of Medicine. She completed residencies at the University of Maryland Medical System and Jackson Memorial Hospital in Miami, Florida, and fellowships in neuromuscular disease, neurochemistry, and neuroimmunology at University Hospital in Baltimore; the Eunice Kennedy Shriver Center in Waltham, Massachusetts; and the Neuroimmunology Branch of the National Institutes of Health in Bethesda, Maryland, respectively.

Copies of the Overview, Communication Cards and other literature are available through the:

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