Pharmacological Reports
2010, 62, 220–232
ISSN 1734-1140

Review

Guillain-Barré syndrome (GBS)

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Abstract:
Guillain-Barré syndrome (GBS) is an autoimmune and post-infectious immune disease. The syndrome includes several pathological subtypes, the most common of which is a multifocal demyelinating disorder of the peripheral nerves. In the present review, the main clinical aspects and the basic features of GBS are discussed along with approaches to diagnosis and treatment. Furthermore, the pathophysiology of GBS is reviewed, with an emphasis on the production of symptoms and the course of the disease.

Key words:
Guillain-Barré syndrome, *Campylobacter jejuni*, antiganglioside antibodies, immunoglobulin treatment, plasma exchange

Abbreviations: AIDP – acute inflammatory demyelinating polyneuropathy, AMAN – acute motor axonal neuropathy, AMSAN – acute motor and sensory axonal neuropathy, CMV – cytomegalovirus, GBS – Guillain-Barré syndrome, IVIg – intravenous immunoglobulin, LOS – lipooligosaccharide, MFS – Miller-Fisher syndrome, PE – plasma exchange SIADH – syndrome of inappropriate antidiuretic hormone

Introduction

Guillain-Barré syndrome (GBS) is an acute inflammatory demyelinating polyneuropathy (AIDP), an autoimmune disease affecting the peripheral nervous system that is usually triggered by an acute infectious process. GBS is an inflammatory disorder of the peripheral nerves. The peripheral nerves convey sensory information (e.g., pain, temperature) from the body to the brain and motor (i.e., movement) signals from the brain to the body [32]. GBS is characterized by weakness and numbness or a tingling sensation in the legs and arms and possible loss of movement and feeling in the legs, arms, upper body, and face. It is frequently severe and usually presents as an ascending paralysis marked by weakness in the legs that spreads to the upper limbs and the face along with complete loss of deep tendon reflexes. The exact cause of GBS is unknown, but it is sometimes triggered by a respiratory infection or the stomach flu. This potentially deadly disorder is relatively rare, occurring worldwide in only one or two people per 100,000, with slightly more males than females affected. All age groups can be affected; the incidence rises with age, and there is a minor peak among young adults [1].

There is no cure for the disorder, but several treatments can ease symptoms and reduce the duration of the illness. Most people recover completely from even the most severe cases of GBS [55]. Its relation to infection and its status as an autoimmune disease have stimulated much research over the years, which have resulted in the discovery of antiganglioside antibodies in at least one third of GBS patients. These antibodies appear to cross-react with antigens in the lipopolysac-

charides of some antecedent infective agents, providing a possible mechanism for the disease [39, 57].

Epidemiology

Based on well-controlled population-based studies, the incidence of GBS in Europe is 1.2–1.9 cases per 100,000, whereas worldwide, the incidence is 0.6–4 cases per 100,000. Atypical presentations, such as Fisher syndrome, are much less frequent, with an incidence of 0.1 per 100,000. Men are 1.5 times more likely to be affected than women, and the incidence increases with age from 1 per 100,000 in those aged below 30 years to about 4 cases per 100,000 in those older than 75 years [58]. In China, the incidence in adults is 0.66 cases per 100,000. About two thirds of GBS cases have an antecedent infection within six weeks prior to symptom onset, generally an upper respiratory tract infection or gastroenteritis. Although the pathological organism is not often identified, the usual infectious agents associated with subsequent GBS include Epstein-Barr virus, *Mycoplasma pneumoniae*, *Campylobacter jejuni* and cytomegalovirus. In China, summer epidemics of the AMAN form of GBS were found to be secondary to infection with *Campylobacter jejuni*. In addition to antecedent infections, GBS develops after vaccination. Concerns about vaccine-induced GBS were first raised following the 1976–77 influenza vaccinating season, when a statistically significant increased risk of GBS was reported within 6–8 weeks of receiving the ''swine flu'' vaccine. Subsequently, studies that investigated the relationship between GBS and influenza immunization reported low relative risks that were not statistically significant. A combined analysis of the 1992–93 and 1993–94 vaccine campaigns in the USA reported a marginally increased risk of GBS (1 extra case of GBS for every 1 million vaccines) following influenza vaccination during the 6 weeks following immunization, a result recently confirmed in a Canadian study. Further, GBS has been reported after immunization with the hepatitis vaccine and the meningococcal conjugate vaccine (MCV4) [10, 45, 50, 51, 59, 79, 81, 85]. However, the incidence of GBS after immunization was not different from the background incidence of GBS, thereby precluding any firm conclusions about the significance of these findings.

However, because of the close temporal association of GBS with selected vaccines, the risks and benefits of immunization merit individual review by the clinician and patient. GBS has also been reported following surgery and head trauma [19, 60, 78, 84]. The mechanisms that link GBS with surgery and trauma remain unclear. However, several hypotheses have been proposed. Surgery and trauma may alter both cellular and humoral immunities [9]. Specifically, head trauma imparted by injury or surgery may be associated with depressed cell-mediated immunity and production of antimyelin antibodies [18, 22, 35, 76]. Furthermore, the major stress of head trauma or surgery may result in activation of latent processes that in turn affect the immune system as has been documented following spinal cord injury [30, 31]. It is surprising in this regard that GBS has not been linked to peripheral nerve injury; one might postulate that exposure of the peripheral nerve to circulation would permit the creation of autoantibody against nerve tissue and thus stimulate GBS [91].

Pathophysiology

GBS is a post-infectious, immune-mediated disease. Cellular and humoral immune mechanisms probably play a role in its development. Most patients report experiencing an infectious illness in the weeks prior to the onset of GBS. Many of the identified infectious agents are thought to induce antibody production against specific gangliosides and glycolipids, such as GM1 and GD1b, distributed throughout the myelin in the peripheral nervous system [77]. Most of the pathogens that are known to cause GBS gain entry to the body through mucosal or gut epithelium. The innate immune response results in the uptake of the pathogens by immature antigen presenting cells (APCs). After migration to lymph nodes, a mature, differentiated APC can present peptides in MHC class II molecules and activate CD4 T cells that recognize antigens from the infectious pathogen. B cells can also be activated by newly activated Th2 cells. This produces a cell-mediated humoral response to the pathogen [49]. Two thirds of GBS cases are associated with prior acute infection by several bacterial species and viruses. *Campylobacter jejuni*, cytomegalovirus, Epstein-Barr virus, *Mycoplasma pneumoniae*, *Haemophilus influenza*, and Varicella-zoster virus have been found in

patient serum after the onset of GBS [33, 53]. In the case of *C. jejuni* infection, antibodies are produced, leading to activation of the complement system, and phagocytosis of the bacteria takes place. However, in rare cases the antibodies produced against certain *C. jejuni* antigens will also bind to gangliosides of the nervous tissue, causing complement activation and damage by phagocytes. This results in damage to peripheral nervous tissues, which leads to demyelination and axonal damage [82].

The most commonly proposed mechanism for the development of autoimmune disease is molecular mimicry [83, 94]. Molecular mimicry refers to the situation where the pathogen and host share nearly identical antigens, which induces an antibody and T cell immune response that is cross reactive. There is more than one way in which an immune response can become cross-reactive. The pathogen and host can have homologous or identical amino acid sequences, or the host B cell receptors and T cell receptors can recognize non-homologous peptides [2]. The strongest evidence for the molecular mimicry hypothesis has come from discoveries in research with *C. jejuni* strains, the most common pathogen associated with GBS (specifically AMAN) [70, 95].

Peripheral nervous system inflammatory response

The peripheral nervous system refers to the network of nervous tissue beyond the central nervous system (brain and spinal cord). The peripheral nerves are covered by a blood-nerve barrier that prevents the normal infiltration of macromolecules, but lymphocytes can move in and out of peripheral nervous tissue [36]. This allows for immune protection of the macrophages and endothelial cells that reside in the tissue. In the case of GBS, which is an inflammatory disorder, autoantibodies are able to cross the blood-nerve barrier while in its normal state. The blood-nerve barrier is made up of endothelial cells with tight junctions that can be modified under inflammatory conditions to allow passage of effecter cells and macromolecules [6]. However, when the autoantibody cross the barrier and bind to gangliosides of neural tissue, they can activate complement cascades and resident macrophages by their FcIII receptors, inducing cytokine production and inflammation within the nerve tissue. It has also been found that endoneural macrophages have the capacity to express CD1 (CD1a, b, and c), which allows them to present glycolipids such as gangliosides to some T cell subsets along with dendritic cells [41].

The inflammation due to cytokines causes recruitment of leukocytes and damage to the nerve tissue by one of four mechanisms: CD8 T cell lysis, complement-mediated attack, cytokine and free radical damage *via* phagocytes, and antibody-mediated interference in nerve conduction. There are several places in the peripheral nervous system where the inflammatory response of GBS can begin, depending on the subtype that develops and the infectious pathogen that is involved. The targets of such immune attacks are thought to be gangliosides, which are complex glycosphingolipids present in large quantities on human nerve tissues, especially in the nodes of Ranvier. An example is the GM1 ganglioside, which can be affected in as many as 20–50% of cases, especially in those preceded by *Campylobacter jejuni* infections. Another example is the GQ1b ganglioside, which is the target in the Miller Fisher syndrome variant [53]. The virulence of *C. jejuni* is thought to be based on the presence of specific antigens in its capsule that are shared with nerves. Immune responses directed against the capsular components produce antibodies that cross-react with myelin to cause demyelination. Ganglioside GM1 appears to cross-react with *C. jejuni* lipopolysaccharides antigens, resulting in immunological damage to the peripheral nervous system [48]. This process has been termed molecular mimicry. The end result of such autoimmune attacks on the peripheral nerves is inflammation of myelin and conduction block, leading to muscle paralysis that may be accompanied by sensory or autonomic disturbances. However, in mild cases, axonal function remains intact, and recovery can be rapid if remyelination occurs.

In severe cases, such as in the AMAN or AMSAN variants (see below), axonal degeneration occurs, and recovery depends on axonal regeneration. Recovery becomes much slower, and there is a greater degree of residual damage. Recent studies of the disease have demonstrated that approximately 80% of GBS patients experience myelin loss, whereas in the remaining 20%, the pathological hallmark of the disease is indeed axon loss. Pathological findings in GBS include lymphocytic infiltration of spinal roots and pe-

Tab. 1. Types/variants of GBS

Types	Symptoms
Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP)	Most common variant, 85% of cases. Primarily motor inflammatory demyelination ± secondary axonal damage ('bystander effect'). Maximum of 4 weeks of progression
Acute Motor-Sensory Axonal Neuropathy (AMSAN)	Motor and sensory involvement with severe course respiratory and bulbar involvement. Primary axonal degeneration with poorer prognosis
Acute Motor Axonal Neuropathy (AMAN)	Motor only with early and severe respiratory involvement. Primary axonal degeneration. Often affects children, young adults. Up to 75% positive *C. jejuni* serology, often also anti-GM1, anti-GD1a positive
Miller-Fisher Variant	Ophthalmoplegia, sensory ataxia, areflexia. 5% of all cases. 96% positive for anti-GQ1b antibodies
Pharyngeal-Cervical-Brachial Variant	Often associated with IgG anti-GT1a. Presents with proximal descending weakness. Must distinguish from botulism and diphtheria
Acute Pandysautonomia	Widespread sympathetic and parasympathetic failure

ripheral nerves, followed by macrophage-mediated, multifocal stripping of myelin [74]. This phenomenon results in defects in the propagation of electrical nerve impulses, with eventual conduction block and flaccid paralysis. In some patients with severe cases of the disease, a secondary consequence of the severe inflammation is axonal disruption and loss. A subgroup of patients may experience a primary immune attack directly against nerve axons, resulting in a similar clinical presentation.

GBS is a form of autoimmune disease with a delayed hypersensitivity reaction, a rare manifestation of serum sickness, or a transient syndrome resembling serum sickness with loss of appetite, nausea, vomiting, and stomach pain accompanied by weakness (tired feeling), chills, low-grade fever and possible evidence of brain involvement as indicated by lethargy and migraine headaches. One theory of the cause of migraine is a central nervous system (CNS) disorder or Bickerstaff's brain stem encephalitis, a regional variant of GBS. Typical migraine pain is occipital, or in the back of the head. Alterations of consciousness accompany this headache type through its affect on the brainstem, which is implicated in the maintenance of arousal; this is a worrisome feature of this type of headache, called a Bickerstaff migraine.

Pathogens and autoimmunity in GBS subtypes

Several variants of GBS are recognized. These disorders share similar patterns of evolution, recovery, symptom overlap, and probable immune-mediated pathogenesis. Types and variants of GBS are listed in Table 1 [38].

AIDP-associated infection

Cytomegalovirus (CMV), a cause of respiratory tract infections, is the second most common pathogen linked to cases of GBS in Europe and Japan. Autoantibodies against the human ganglioside GM2 have been isolated in patients with a CMV infection and GBS symptoms. Development of AIDP is seen predominantly in the cranial and sensory nerves as opposed to motor nerves. The immune response elicited in AIDP is focused on the Schwann cell or myelin sheath. Damage to the myelin or Schwann cells results in demyelination, which is characteristic of AIDP [90].

AMAN-associated infection

Infection by *C. jejuni*, a cause of bacterial gastroenteritis, is the leading cause of AMAN worldwide. Studies show that the production of autoantibodies by *C. jejuni* infection occurs in only 1 out of 3285 patients with *C. jejuni* enteritis. It has been found that only certain strains of *C. jejuni* are associated with GBS/AMAN cases [54]. The strains are divided by serotype based on their low molecular weight type lipopolysaccharide (LPS), called a lipooligosaccharide (LOS) [67]. Serotypes most commonly associated with AMAN are HS:19 and HS:41. A polymorphism in the gene *cstII* (Thr51) has been found to be closely associated with development of anti-GM1 and anti-GD1a autoantibodies [53]. The hypothesis of molecular mimicry is based on the fact that the bacterial LOS induces IgG, IgA, and IgM autoantibody against human gangliosides due to LOS ganglioside-mimicking epitopes [67]. Autoantibody have been isolated in GBS patients' serum and found to recognize *C. jejuni* LOS and human gangliosides GM1, GM1b, GD1a, and GalNAc-GD1a epitopes, providing evidence for molecular mimicry. Furthermore, Moran et al. concluded that the IgG LOS-induced anti-GM1 antibodies bound to sites at the nodes of Ranvier in humans. This is important because other studies have concluded that antibodies bound to nodes of Ranvier disrupt Na^+ and K^+ channels, interfering with nerve conduction.

MFS (Miller-Fisher syndrome)-associated infection

MFS is a common variant of GBS, and is observed in about 5% of all GBS cases. The syndrome consists of ataxia, ophthalmoplegia (problems controlling eye movements), and areflexia (loss of neurological reflexes). Ataxia is primarily noted during gait and in the trunk, with lesser involvement of the limbs. Motor strength is characteristically spared. The usual course is one of gradual and complete recovery over weeks or months. A close association exists between antiganglioside antibodies and the Fisher variant. Anti-GQ1b antibodies triggered by certain *C. jejuni* strains have a relatively high specificity and sensitivity for the disease. Dense concentrations of GQ1b gangliosides are found in the oculomotor, trochlear, and abducens nerves, which may explain the relationship between anti-GQ1b antibodies and the ophthalmoplegia presented by MFS patients in addition to symptoms similar to those seen in other forms of GBS. Autoantibodies have been isolated from these patients that bind to human ganglioside GQ1b as well as the GQ1b epitope present within the LOS of *C. jejuni* isolated from MFS patients. The dominant *C. jejuni* serotypes associated with MFS are HS:2 and HS:4. The gene polymorphism associated with the development of anti-GD1b autoantibodies was found to be *cstII* (Asn51). This provides a clear link to the clinical presentation of MFS because the GQ1b ganglioside is found predominantly in human oculomotor nerves. The axonal form of GBS, also referred to as acute motor-sensory axonal neuropathy (AMSAN), often presents with rapid and severe paralysis, with delayed and poorer recovery. Like AMAN, axonal GBS is associated with preceding *C. jejuni* diarrhea. Pathological findings show severe axonal degeneration of motor and sensory nerve fibers, with little demyelination [11, 17]. A pure sensory variant of GBS has been described in the medical literature, typified by a rapid onset of sensory loss and areflexia in a symmetric and widespread pattern [72]. Lumbar puncture studies show albuminocytologic dissociation in the cerebrospinal fluid (CSF), and electromyography (EMG) shows characteristic signs of a demyelinating process in the peripheral nerves [93].

Dysfunction of the sympathetic and parasympathetic systems results in severe postural hypotension, bowel and bladder retention, anhydrosis, decreased salivation and lacrimation, and pupillary abnormalities. The pharyngeal-cervical-brachial variant is distinguished by isolated facial, oropharyngeal, cervical and upper limb weakness without lower limb involvement. Other unusual clinical variants with restricted patterns of weakness are observed only in rare cases.

Role of anti-ganglioside antibodies

Anti-ganglioside antibodies that react to self-gangliosides are found in autoimmune neuropathies [56, 82]. These antibodies were first found to react with cerebellar cells. These antibodies show the

strongest association with certain forms of GBS [12, 47]. Autoantigenic gangliosides that are currently known are GD3, GM1, GQ3 and GT1 [24].

Anti-GD3

Anti-GD3 antibodies have been found in association with specific forms of GBS. *In vivo* studies of isolated anti-GM1 and GD3 antibodies indicate that these antibodies can interfere with motor neuron function. Anti-GD1a antibodies were highly associated acute motor axonal neuropathy, while high titers of anti-GM1 were more frequent, indicating that GD1a possibly targets the axolemma and nodes of Ranvier [34].

Anti-GM1

Levels of anti-GM1 are elevated in patients with various forms of dementia. Antibody levels correlate with increased severity of GBS [92]. In Japan, levels of GM1 were elevated in patients with prodromal diarrhea. Titers of GM1 are also elevated in other diseases (rheumatoid arthritis and systemic lupus erythematosus). Additionally, a highly significant association was found between rheumatoid arthritis and peripheral neuropathies [37]. The autoimmune role of anti-GM1 is still unclear [13].

Anti-GQ1b

Anti-GQ1b antibodies are found in Miller-Fisher syndrome. Studies of these antibodies reveal large disruptions of the Schwann cells. Anti-GQ1b IgG levels were elevated in GBS patients with ophthalmoplegia [15].

Diagnosis

GBS is called a syndrome rather than a disease because it is not clear that a specific disease-causing agent is involved. Several disorders have symptoms similar to those found in GBS, Collectively, the signs and symptoms form a certain pattern that helps to differentiate Miller-Fisher syndrome from other disorders [61]. The diagnosis of GBS may be challenging, and given an extensive differential diagnosis (Tab. 2), a thorough medical assessment may be needed to exclude "mimic disorders" [7, 8].

Nerve conduction studies (NCS) and CSF analysis are important to confirm the diagnosis of GBS. NCS and electromyography (EMG) are important to establish the diagnosis of GBS, and different neurophysiological diagnostic criteria have been proposed [63]. NCS may support a suspected clinical diagnosis of GBS, identify the GBS subtype and help to exclude mimic disorders. NCS rely on abnormalities in motor nerves to identify features of demyelination (Tab. 3), with sensory nerve conduction studies helping to differentiate different forms of axonal GBS, that is,

Tab. 2. Differential diagnosis of acute onset flaccid paralysis. Disorders of the central nervous system (CNS) may present with acute generalized flaccid paralysis [38]

Differential diagnosis of Guillain-Barré Syndrome
Peripheral neuropathy
• Vasculitic neuropathy
• Diphtheric neuropathy
• Acute intermittent porphyria
• Critical illness neuropathy
• Lymphomatous neuropathy
• Heavy metal intoxication
• Post-rabies vaccine neuropathy
• Diabetic–uremic neuropathy with acute peritoneal dialysis
Disorders of the neuromuscular junction
• Myasthenia gravis
• Eaton-Lambert syndrome
• Biological or industrial toxin poisoning
Disorders of muscle
• Inflammatory myopathy
• Toxic myopathy/acute rhabdomyolysis
• Periodic paralysis
• Hypokalemia
• Hypophosphatemia
• Infections
Disorders of the central nervous system
• Brainstem stroke
• Brainstem encephalitis
• Acute myelopathy (high cervical)
• Acute anterior poliomyelitis

Tab. 3. Neurophysiological criteria for Guillain-Barré syndrome (GBS) [90]

GBS subtype	Distal CMAP amplitude (mV)	Conduction block	Temporal dispersion	Motor conduction velocity (m/s)	Distal motor latency (ms)	F-wave latency (ms)[@]
AIDP	Normal or reduced	* Proximal: distal ratio of CMAP amplitudes	> 30% Increase in proximal negative peak CMAP duration	< 70% Lower limit of normal	> 150% Upper limit of normal	> 120% Upper limit of normal
AMSAN[+]	Absent or reduced					
AMAN[§]	Absent or reduced					

AIDP – acute inflammatory demyelinating polyneuropathy, CMAP – compound muscle action potential, AMSAN – acute sensory and motor axonal neuropathy, AMAN – acute motor axonal neuropathy. [@] Although prolonged F-wave latency is a diagnostic feature of AIDP, absence of F-wave responses in two or more nerves when the CMAP amplitude is > 20% of the lower limit of normal is suggestive of a proximal block. * For diagnosis of probable conduction block, a > 30% reduction in the proximal to distal CMAP amplitude ratio is required, while a definite conduction block is diagnosed when there is a > 50% reduction in proximal to distal CMAP amplitude. If the CMAP amplitude is markedly reduced (<1 mV), conduction block cannot be diagnosed. [+] For the AMSAN form of GBS, the sensory potentials are either absent or markedly reduced. Further, there should be no features of AIDP, except for the presence of one demyelinating feature in a single nerve, if the distal CMAP amplitude is < 10% of the lower limit of normal. [§] In AMAN, the sensory responses are within normal limits. In AIDP, the abnormalities must be present either in two or more nerves or, if only one nerve is excitable and the distal CMAP is > 10% of the lower limit of normal, at least two neurophysiological abnormalities must be present in one nerve

AMAN from AMSAN. The diagnostic yield of NCS is increased by studying at least three sensory and four motor nerves in addition to F-waves and H-reflexes [11, 46].

The classical findings on NCS include the presence of a partial motor conduction block, abnormal temporal dispersion of motor responses, prolonged distal motor and F-wave latencies, and reductions in maximum motor conduction velocity. Diagnostic criteria typically used for research purposes include a combination of these findings (Tab. 2). Although in over 85% of patients NCS reveal demyelination consistent with the AIDP form of GBS, in up to 13% of cases the initial NCS are normal; in these cases, retesting in 1 to 2 weeks might be required to confirm the diagnosis [33, 88].

Cerebrospinal fluid examination

In addition to NCS and EMG, CSF analysis may confirm a diagnosis of GBS. A raised CSF protein concentration is present in 80% of patients, with the mononuclear cell count being either normal (albuminocytologic dissociation) or < 50 cells/mm [3–7]. The CSF is normal in the first week of the illness [29]. Other investigations that may be helpful in diagnosing GBS are outlined in Table 4.

Clinical features

The disease is characterized by weakness that affects the lower limbs first and rapidly progresses in an ascending fashion. Patients generally notice weakness in their legs, manifesting as "rubbery legs" or legs that tend to buckle, with or without numbness or tingling. As the weakness progresses upward, usually over a period of hours to days, the arms and facial muscles also become affected. Frequently, the lower cranial nerves may be affected, leading to bulbar weakness (oropharyngeal dysphagia, which includes difficult swallowing, drooling, and/or trouble maintaining an open airway) and respiratory difficulties. Most patients require hospitalization, and about 30% require ventilatory assistance. Sensory loss usually takes the form of loss of proprioception (position sense) and areflexia (complete loss of deep tendon reflexes), an important feature of GBS. Any loss of pain and temperature sensation is usually mild. In fact, pain is a common symptom in GBS, usually presenting as deep aching pain in the weakened muscles, which patients compare to the pain resulting from

Tab. 4. Investigations of Guillain-Barré syndrome

Studies related to establishing diagnosis
• Nerve conduction studies and electromyography
• Cerebrospinal fluid analysis
• Stool culture and serology for *Campylobacter jejuni*
• Serology for human immunodeficiency virus, Hepatitis A and B, Mycoplasma, pneumoniae, Epstein-Barr virus, cytomegalovirus
• Anti-ganglioside antibodies: GQ1b, GM1, GD1a, GT1b
• Vasculitic screen
• Antinuclear antibodies, extractable nuclear antibodies, anti-neutrophil cytoplasmic antibodies, erythrocyte sedimentation rate, C-reactive protein
• Nerve and muscle biopsy
• Electrolyte, urea, creatinine levels
• Blood sugar levels
• Urine porphobilinogen and serum delta-aminolevulinic acid for porphyria
• Drugs and toxins
• Acetylcholine receptor and muscle-specific tyrosine kinase antibodies
• MRI of the brain and spinal cord
Studies related to patient management
• Measuring respiratory function
• Arterial blood gases
• Pulmonary function tests (vital capacity)
• Biochemical screening (monitoring for hyponatremia)
• Chest radiograph
• Electrocardiogram

overexercising. These pains are self-limited and should be treated with standard analgesics. Bladder dysfunction may occur in severe cases. Acute paralysis in GBS is usually related to the presence of Na^+ channel blocking factor in the cerebrospinal fluid. Morbid and iatrogenic events involving IV salt and water may occur unpredictably in this patient group, resulting in SIADH (syndrome of inappropriate antidiuretic hormone). This syndrome results from a deficit of sodium or a surplus of water due to iatrogenic fluid overload. It occurs in patients with GBS, meningitis, encephalitis, pneumonia, septicemia, severe malaria, bronchitis, or as a direct result of clinical insult. SIADH is often the first symptom of GBS. Na^+ overload is almost always iatrogenic. Rapid correction of hyponatremia can cause osmotic brain demyelination [14, 16, 18, 21]. When infection precedes the onset of GBS, signs of infection subside before neurological features appear. Other possible precipitating factors include surgery, rabies or swine influenza vaccination, viral illness, Hodgkin's disease or some other malignant disease, and systemic lupus erythematosus [51]. Muscle weakness, the major neurological sign, usually appears in the legs first (ascending type) and then extends to the arms and facial nerves within 24 to 72 h. Sometimes muscle weakness develops in the arms first (descending type) or in the arms and legs simultaneously. In milder forms of the disease, muscle weakness may affect only the cranial nerves or not occur [27].

The clinical course of GBS is divided into three phases:

I. The initial phase begins when the first definitive symptom develops; it ends one to three weeks later, when no further deterioration is noted.

II. The plateau phase lasts several days to two weeks.

III. The recovery phase is believed to coincide with remyelination and axonal process regrowth. This phase extends over four to six months; patients with severe disease may take up to two years to recover, and recovery may not be complete.

Significant complications of GBS include mechanical ventilatory failure, aspiration pneumonia, sepsis, joint contractures, and deep vein thrombosis. Unexplained autonomic nervous system involvement may cause sinus tachycardia or bradycardia, hypertension, orthostatic hypotension, and loss of bladder and bowel sphincter control. Up to two thirds of patients with GBS report an antecedent illness or event one to three weeks prior to the onset of weakness. Upper respiratory and gastrointestinal illnesses are the most commonly reported conditions. Symptoms of this initial illness have generally resolved by the time of medical presentation for the neurological condition [68, 69]. Autonomic changes can include tachycardia, bradycardia, facial flushing, paroxysmal hypertension, orthostatic hypotension, anhydrosis and/or diaphoresis. Urinary retention and paralytic ileus can also be observed. Bowel and bladder dysfunction is rarely present as an early symptom or persists for a significant period of time. Dysautonomia is more frequent in patients with severe weakness and respiratory failure. Upon presentation, 40% of patients have respiratory or oropharyngeal weakness. Typical complaints include dyspnea on exertion, shortness of breath, difficulty swallowing and slurred speech. Ventilatory failure with required respiratory support is observed in up to one third of patients at some time during the course of their disease. Facial weakness (cra-

nial nerve VII) is observed most frequently, followed by symptoms associated with cranial nerves III, V, VI, IX, X, and XII. Limitation of eye movement most commonly results from a symmetric palsy associated with cranial nerve VI. Ptosis from cranial nerve III (oculomotor) palsy is also often associated with a limitation of eye movements. Pupillary abnormalities, especially those accompanying ophthalmoparesis, are relatively common as well.

Effective treatments

Currently, there is no known cure for GBS. The goal of the treatment plan is to lessen the severity of the illness and to assist in the patient's recovery. Treatment of GBS can be subdivided into techniques for managing the severely paralyzed patient requiring intensive care and respiratory support and specific therapy aimed at ameliorating or reversing the nerve damage. Treatments may include:

1. High-dose immunoglobulin therapy – Miller-Fisher syndrome involves administration of proteins by intravenous injections to attack invading organisms;
2. Physical therapy – to increase muscle flexibility and strength; and
3. Plasmapheresis – a process in which whole blood is removed from the body and the red and white blood cells are separated from the plasma and returned to the body

Steroids

Six eligible trials have addressed the value of steroids in treating acute GBS. These involved 195 patients. Mean disability at 4 weeks, the proportion of patients who were improved by one grade at 4 weeks, and the improvement in grade at 12 months all remained unaltered by steroids, which appear to be safe but ineffective. This contrasts with the treatment of patients with more chronic demyelinating neuropathies, who respond well to steroids. This lack of response to steroids is not easily explained; it may be that any benefit that steroids have in reducing inflammation is outweighed by some other detrimental effect on repair processes [26]. A Cochrane analysis revealed that a single pilot study addressing combined treatment with methylprednisolone and intravenous immunoglobulin was not randomized. However, it suggested a possible advantage [86]. A randomized study that has recently been presented but not yet published just fails to find a significant advantage of the combination. *Post-hoc* manipulation of the data for known risk factors does suggest an advantage to combination therapy; however, such analyses are known to be rather unreliable and can be misleading [4, 40, 42].

Plasma exchange

The first effective treatment option for GBS was plasmapheresis, or plasma exchange (PE). This treatment involves removing plasma from the blood and using centrifugal blood separators to remove immune complexes and possible autoantibodies. The plasma is then reinjected into the patient along with a 5% albumin solution to compensate for lost protein concentration. Many studies have found that this treatment involves high risk and substantial adverse effects for hemodynamically unstable patients [82]. Studies have found that the most effective number of treatments for moderate and severe cases of GBS is four. A post-treatment worsening of symptoms was seen as well in 10% of patients in some studies. Risks and results like these began the search for more effective and safer treatments [3, 4, 5, 20, 23, 52, 62, 66].

The value of plasma exchange has been addressed in six randomized studies, again reviewed by the Cochrane group. Overall, 649 patients received plasma exchange, and their outcomes were compared with supportive treatment alone because PE was the first treatment shown to be effective in GBS [67, 71].

Intravenous immunoglobulin

Another treatment for GBS is *iv* administration of immunoglobulins (IVIg). The antibodies used have been shown to modulate the humoral response in their ability to inhibit autoantibodies and suppress autoantibody production. By inhibiting autoantibodies, the complement-mediated damage can be attenuated.

IVIgs also block binding of Fc (gamma) receptors, preventing phagocytic damage by macrophages. Studies have shown that an optimal amount of IVIg is 400 mg/kg administered over six days. In comparison studies, PE and IVIg were proven to be similar in overall effectiveness, and no increase in effectiveness was seen when combining therapies. However, it was noted that IVIg was considered safer due to its reduced risks and complications [25, 28, 43, 80]. IVIg was introduced for the treatment of auto-immune thrombocytopenia and tried for the treatment of chronic inflammatory demyelinating polyneuropathy. A favorable response in patients with GBS was reported in 1988 and led to the first randomized controlled trial [87, 89].

A meta-analysis of IVIg for GBS found three randomized trials that compared IVIg with PE, and the only trial comparing IVIg with supportive treatment was considered inadequate to establish its value. With prompt treatment by plasmapheresis or IVIg and supportive care, the majority of patients will regain full functional capacity. However, death may occur if severe pulmonary complications and dysautonomia are present [46, 52, 66, 73]. Supportive care with monitoring of all vital functions is the cornerstone of successful management in the acute patient. Of greatest concern is respiratory failure due to paralysis of the diaphragm. Early intubation should be considered in any patient with a vital capacity (VC) < 20 ml/kg, a Negative Inspiratory Force (NIF) < –25 cm H_2O, more than a 30% decrease in either VC or NIF within 24 h, rapid progression of disease, or autonomic instability [44]. Once the patient is stabilized, treatment of the underlying condition should be initiated as soon as possible. Either high-dose IVIg at 400 mg/kg for 5 days or plasmapheresis can be administered as they are equally effective, and a combination of the two is not significantly better than either alone. Therapy is no longer effective 2 weeks after the first motor symptoms appear, so treatment should be instituted as soon as possible. IVIg is usually used first because of its ease of administration and safety profile, with a total of 5 daily infusions for a total dose of 2 g/kg body weight (400 mg/kg each day). The use of intravenous immunoglobulins is not without risk and can occasionally cause hepatitis or, in rare cases, renal failure if used for longer than five days.

Following the acute phase, the patient may also require rehabilitation to regain lost functions. This treatment will focus on improving ADL (activities of daily living) functions, such as brushing teeth, washing and getting dressed. Depending on the local health care system, a team of therapists and nurses will be assembled according to the patient's needs. An occupational therapist can offer equipment to help the patient achieve ADL independence. A physiotherapist can plan a progressive training program and guide the patient to correct, functional movement, avoiding harmful compensations that might have a negative effect in the long run. A speech and language therapist is essential for the patient to regain speaking and swallowing ability if he or she was intubated and received a tracheotomy. The speech and language therapist can also offer advice to the medical team regarding the swallowing abilities of the patient and can help the patient to regain their communicative ability. After rehabilitation, the patient should be able to function in his or her own home and attend necessary rehabilitation appointments as needed [64, 65].

Role of complement inhibitors in GBS [75, 77]

Clinical data indicate that complement activation followed by membrane attack complex (MAC) formation is an important mechanism for neuronal and glial injury in GBS. SC5b-9 (a marker for complement activation) has been detected in GBS sera, and C9neo antigen (a component of MAC) has been found in segments of myelinated nerve fibers of a GBS patient. In GBS patients, deposits of complement components along myelinated fibers, C9neo antigen at sites of active myelin breakdown, and MAC on Schwann cell membranes have been reported. GBS is divided into two subtypes, acute inflammatory demyelinating polyneuropathy and acute motor axonal neuropathy (AMAN).

Modeling of AMAN was established in rabbits sensitized with GM1 ganglioside. Anti-GM1 IgG antibodies cause complement-mediated disruption of clusters of voltage-gated Na^+ channels at the nodes of Ranvier in peripheral motor nerve fibers of the disease model. Because nodal channels are responsible for nerve conduction, disruption of their clusters is likely to cause limb weakness at onset in AMAN rabbits. Several serine proteases activate classical and al-

ternative pathways of the complement system, and a synthetic serine protease inhibitor, nafamostat mesilate (NM: 6-amidino-2-naphthyl-*p*-guanidino-benzoate dimethanesulfonate), which has been used clinically in Japan for more than 20 years with no serious adverse effects, has anti-complement activity.

Because NM efficiently inhibits the early classical pathway components C1r and C1s, it was shown to inhibit C3 fragment deposition at the higher rate of 0.8 mg/kg/h for 7 days in an animal experiment. NM inhibits C3/C5 convertase in the classical and alternative pathways of the complement system. Preserved Na^+ channel clusters associated with restricted deposits of activated C3 fragments were present, suggesting that NM inhibits complement activation steps beyond the C3 convertase step leading to MAC formation. In other words, NM inhibited C3 fragment deposition followed by MAC formation, thereby preventing axonal injury.

Conclusion

High-quality intensive care remains the most important aspect of the management of severe cases of GBS. Clinical trials indicate that plasma exchange is more effective than supportive treatment alone in reducing the median time taken for patients to recover. Intravenous immunoglobulin appears to be as effective as plasma exchange for treating GBS and may have fewer side effects. Corticosteroids alone do not alter the outcome of GBS, and there is insufficient evidence that their use in combination with immunoglobulin is effective. Other treatments such as CSF filtration remain experimental and unproven. Ongoing research on GBS will identify appropriate molecular targets of intervention and novel diagnostics and, more importantly, will enable the development of new and more effective as well as cost-effective therapies.

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Received:
May 21, 2009; in revised form: October 20, 2009.