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Guillain-Barré Syndrome and Variants

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Synopsis

Guillain-Barré syndrome (GBS) is characterized by rapidly evolving ascending weakness, mild sensory loss and hypo- or areflexia, progressing to a nadir over up to four weeks. Cerebrospinal fluid evaluation demonstrates albuminocytologic dissociation in 90% of cases. Acute inflammatory demyelinating polyneuropathy (AIDP) was the first to be recognized over a century ago and is the most common form of GBS. In AIDP, the immune attack is directed at peripheral nerve myelin with secondary by-stander axon loss. Axonal motor and sensorimotor variants have been described in the last 3 decades and are mediated by molecular mimicry targeting peripheral nerve motor axons. Besides the Miller-Fisher syndrome (MFS) and descending weakness, other rare phenotypic variants have been recently described with pure sensory variant, restricted autonomic manifestations and the pharyngeal-cervical-brachial pattern. It is important to recognize GBS and its variants due to the availability of equally effective therapies in the form of plasmapheresis and intravenous immunoglobulins.

Keywords

Guillain-Barré; syndrome; acute inflammatory demyelinating polyneuropathy; acute motor axonal neuropathy; acute motor and sensory axonal neuropathy; Miller-Fisher syndrome; Bickerstaff's brain stem encephalitis; diagnosis; nerve conduction testing; treatment

Historical Note

Jean-Baptiste Octave Landry in 1859 (3) first described a case of distal sensory "formications" and ascending weakness after a prodromal fever, malaise and pain who progressed to paralysis over 3 weeks and died from respiratory failure in addition to another 4 cases. Sixty years later, Georges Guillain, Jean-Alexandre Barré, and Andre Strohl (4) reported two cases with albuminocytologic dissociation on cerebrospinal fluid (CSF) testing and distinguished this syndrome from poliomyelitis-induced paralysis. Although occasinonally referred to as the Landry-Guillain-Barré-Strohl syndrome, it is commonly

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called the Guillain-Barré-Strohl syndrome or, more often, the Guillain-Barré syndrome (GBS), after the two French army neurologists.

Epidemiology

GBS is an acute monophasic immune-mediated polyradiculoneuropathy with a mean age of onset of 40 years that affects slightly more males than females of all ages, races and nationalities. The worldwide incidence of GBS ranges from 0.6 to 4.0/100,000 people (5, 6, 7, 8, 9). A systematic literature review of the epidemiology of GBS found the overall incidence of GBS to be 1.1 to 1.8/100,000 and it was however lower in children at 0.34 to 1.34/100,000 (10). In comparison to younger cases, the incidence of GBS increases after age 50 years from 1.7/100,000 to 3.3/100,000. Two-thirds of cases of GBS are associated with an antecedent infection. Most cases are sporadic although summer epidemics in Northern China of the axonal variant with *Campylobacter Jejuni* (*C. Jejuni*) infection were reported. While 5% of GBS in North America and Europe are due to axonal GBS (11), this variant is much more common in Northern China, Japan and the rest of America (12, 13, 14, 15).

Clinical Features

The most common initial symptom of GBS is acroparesthesia with little objective sensory loss (16). Severe radicular back pain or neuropathic pain affects most cases. Within a few days, weakness ensues commonly in a symmetric “ascending pattern”. Most patients present initially with leg weakness and arm weakness (32%) or selective proximal and distal leg weakness (56%) often spreading to the arm while some have onset of weakness in the arms (12%). A descending presentation mimicking botulism, with onset in the face or arms, is less common. Besides prominent weakness, patients are hypo- or areflexic within the first few days but this may be delayed by up to a week. Weakness can be somewhat asymmetric, and sensory loss can also be variable, rarely presenting with a pseudo-sensory level suggesting myelopathy. Facial nerve involvement occurs in up to 70% of cases, dysphagia in 40%, and rarely (5%) patients may develop ophthalmoplegia, ptosis, or both suggesting botulism or myasthenia gravis (2). Hearing loss, papilledema and vocal cord paralysis are less common. Axonal GBS occurs in up to one-third of cases and is more likely to be associated with antecedent *C. Jejuni* infection.

Nadir of weakness is reached within two weeks in half of cases and 90% by four weeks (2). Symptom progression beyond one month suggests an subacute inflammatory demyelinating polyradiculoneuropathy and if progression continues beyond 8 weeks chronic inflammatory demyelinating polyradiculoneuropathy is a consideration. Some patients progress rapidly to become ventilator dependent within hours or days , while others will have very mild progression for several weeks and never lose ambulation. Occasional patients will have a stuttering or step-wise progression. Weakness ranges from mild to severe flaccid quadriplegia and in up to 30% respiratory failure within a few days of onset. Dysautonomia affects most patients (2), and consists most commonly of sinus tachycardia, but patients may experience bradycardia, labile blood pressure with hyper- and hypotension, orthostatic hypotension, cardiac arrhythmias, neurogenic pulmonary edema, changes in sweat. Even more confusing and mimicking a spinal cord lesion are the 5% of cases that experience bladder (urinary retention) and gastrointestinal (constipation, ileus, gastric distension, diarrhea, fecal incontinence) dysfunction. The revised diagnostic criteria have been published (Table 1) several years ago and are well established. These include clinical, cerebrospinal fluid and electrophysiologic criteria (see **Electrophysiologic Features** section below).

Moderate to severe neuropathic or radicular pain is a common is seen in the whole spectrum of GBS including MFS, mildly affected, and pure motor patients (18). Persistent pain was reported in the 2 weeks preceding weakness in 36% of patients while 66% reported pain in the acute phase and 38% reported pain after 1 year. The mean pain was most intense in patients with non-MFS GBS), those with sensory disturbances, and in severely affected patients.

GBS Variants

Besides classic presentation of GBS, clinical variants are based on the types of nerve fibers involved (motor, sensory, sensory and motor, cranial or autonomic), predominant mode of fiber injury (demyelinating versus axonal), and the presence of alteration in consciousness. The first GBS variant was Miller Fisher Syndrome (MFS) and consists of ophthalmoplegia, ataxia, and areflexia without any weakness (19). Most of the patients with MFS present with at least two features and have in support an elevated CSF protein and characteristic autoantibody. Though MFS represents 5 to 10% of GBS cases In Western countries, it is more common in Eastern Asia, accounting for up to 25% of Japanese cases (20). Some MFS cases may progress to otherwise classic GBS. In addition, five percent of typical GBS cases may have ophthalmoplegia. Bickerstaff's brain stem encephalitis (BBE) is a variant of MFS characterized by alteration in consciousness, paradoxical hyperreflexia, ataxia, and ophthalmoparesis (21). BBE cases represent a variant of MFS with antecedent infection (92%), elevated CSF protein (59%) and anti-GQ1b antibody (66%) (22, 23). Brain magnetic resonance imaging (MRI) abnormalities are present in only 30% of BBE cases (23) and the frequency of BBE variant is 10% of that of MFS (24). The pharyngeal-cervical-brachial motor variant manifests in up to 3% with ptosis, facial, pharyngeal and neck flexor muscle weakness that spreads to the arms and spares leg strength, sensation and reflexes thereby mimicking botulism. A less common paraparetic motor variant affects the legs selectively with areflexia mimicking an acute spinal cord lesion and is associated with back pain (25). Other rare variants include ptosis without ophthalmoplegia, and facial diplegia or sixth nerve palsies with paresthesias (25, 26). Pure sensory ataxic and pandysautonomic variants are also less commonly reported without predominant weakness.

Following the first detailed description of an axonal variant of GBS (27), an axonal motor variant of GBS termed acute motor axonal neuropathy (AMAN) was report in 1993 from Northern China and hence the name Chinese paralytic illness (13). Soon after that, reports of an acute motor and sensory axonal neuropathy (AMSAN) were published (28). Since then, these axonal variants have also been described from other countries. AMAN and AMSAN are associated with *C. Jejuni* infection which is alone a poor prognostic factor (29). As a group, patients with AMAN have a more rapid progression of weakness to an earlier nadir than in AIDP resulting in prolonged paralysis and respiratory failure over a few days (30). AMAN can present with transient conduction block without axonal loss and this led to the term acute motor conduction block neuropathy. In this AMAN variant, patients present with symmetric proximal and distal weakness without sensory abnormalities following *C. Jejuni* enteritis and may have normal or brisk tendon reflexes. The first two described cases had elevated titers of IgG antibody titers to GD1a and GM1 and serial nerve conduction studies have shown transient partial conduction block in intermediate and distal nerve segments that dissipated within 2 to 5 weeks (31).

Pathogenesis

Although GBS is presumed to be autoimmune, the precise molecular pathogenesis of GBS and its variants is uncertain. Data has implicated essentially every component of both the cellular and humoral immune systems. GBS is a complex autoimmune disease of especially

the proximal peripheral nerves and the nerve roots mediated in AIDP by lymphocytic mononuclear cell infiltration and intense macrophage-associated segmental demyelination. Much of the evidence for disease pathogenesis is derived from experimental allergic neuritis which is the working animal model of GBS and is caused by a combination of T-cell-mediated autoimmunity to myelin proteins and antibodies to myelin glycolipids. Antibodies to peripheral nerve myelin were identified in the sera of GBS patients with a decline in titers corresponding to clinical improvement. Antibodies to myelin glycolipids are indicative of humoral autoimmunity in GBS variants. An autopsy study supporting humoral autoimmunity demonstrated an antibody-mediated complement deposition on the schwann cell abaxonal plasmalemma but not on the myelin sheath followed by vesicular paranodal myelin degeneration and retraction (32). Macrophages are then recruited to strip off the myelin lamellae. By-stander axon loss may occur with severe inflammation (2).

Unlike AIDP, AMAN is characterized by the paucity of lymphocytic infiltration and sparing of the dorsal nerve roots, dorsal root ganglia and peripheral sensory nerves. The two early changes are the lengthening of the node of Ranvier followed by the recruitment of macrophages to the nodal region (33). Nodal lengthening is reversible and results in impaired electrical impulse transmission due to the absence of sodium channels as in acute conduction clock neuropathy. Subsequently, complement activation results in macrophage recruitment. Macrophages distort paranodal axons and myelin sheaths, separate myelin from the axolemma and induce condensation of axoplasm in a reversible fashion. Alternatively, motor axons may undergo Wallerian-like degeneration in severe cases, explaining the delayed recovery in some AMAN cases which is still more readily accomplished given the distal motor nerve terminals involvement. However, AMAN can be fatal and in seven such cases immunoglobulin G and complement activation products were identified bound to the nodal axolemma of motor fibers. The suspected target autoantigen is likely GD1a since IgG antibodies to GD1a are detectable in 60% of AMAN cases and only 4% of AIDP (34). Molecular mimicry is suggested as the pathogenetic mechanism of AMAN based on the strong association with *C. jejuni* infection. The lipopolysaccharide capsule of the *C. jejuni* shares epitopes with GM1 and GD1a resulting in cross-reacting antibodies. GM1 is found in high concentration at the nodes of Ranvier, where antibody binding might be particularly disruptive to nerve function. AMSAN shares many similarities with AMAN although the attack in AMSAN is more severe or longer lasting resulting in more intense and ultimately diffuse Wallerian-like degeneration of both sensory and motor axons. In addition to AMAN and AMSAN, molecular mimicry is the most plausible mechanism in MFS where 90% of cases have antibodies to GQ1b. These autoantibodies have also been described in most BBE cases (23).

Antecedent Events

An antecedent infection is noted two to four weeks prior to the onset in most GBS cases (32). The commonest are upper respiratory infections without any specific organism identified. Known viral precipitants such as Epstein-Barr virus (mononucleosis or hepatitis), and cytomegalovirus (CMV) occur in only 6% of cases. CMV affects younger patients with cranial neuropathies, severe disease and a higher likelihood of respiratory failure. In HIV, GBS occurs at the time of seroconversion or early in the disease. When suspected, it would be important to obtain an HIV viral load measure through the polymerase chain reaction which is more sensitive than HIV antibodies. Bacterial infections such as those due to *Mycoplasma pneumonia* and Lyme disease are rarely associated with GBS.

C. jejuni enteritis is the most common identifiable antecedent infection and precedes axonal GBS in up to 33% of patients. Since GBS develops about nine days after the initial gastroenteritis, stool cultures for *C. jejuni* are often negative but serologic evidence of recent

infection remains. Although two million cases of *C jejuni* infection occur each year in the United States, only about one per 1,000 of these patients have the genetic susceptibility to develops GBS (35) in association with specific HLA haplotypes (36). Other anecdotal antecedent events that have been associated with GBS include surgery, epidural anesthesia, concurrent illnesses such as Hodgkin's disease and immunizations.

There was an increased incidence of GBS after the swine flu vaccine of 1976 in the USA with an excess risk of 10 cases per million vaccinations (37). In the 1992-3 and 1993-4 seasons, the increased incidence of GBS within six weeks of the administration of influenza vaccine led to an estimated excess of one GBS case per million immunizations based on an adjusted relative risk of 1.7 (38). Besides influenza, the hepatitis vaccine amongst others has been associated with GBS but less frequently than the flu vaccine (39). With the 2009–2010 H1N1 immunization campaign, CDC surveillance data identified an excess GBS risk of 0.8 cases per million vaccinations (40) which is similar to the risk conferred by seasonal influenza immunization. The 2009 H1N1 influenza virus has been associated with a hospitalization rate of 222 per million and a death rate of 9.7 per million inhabitants. Therefore, the risk of this illness outweighs the risk of the vaccines. A more complex question is whether patients who have experienced GBS within 6 weeks of influenza immunization should be allowed to be re-immunized with the flu vaccine a year later. In such cases, the established benefits of influenza vaccination might outweigh the risks for those who have a history of GBS and who also are at high risk for severe complications from influenza itself (41). The limited available data suggests that if a patient's GBS episode was associated with the influenza vaccine, most will do well when re-challenged. There may be a small risk (3.5%) of a repeat episode but the frequency of serious GBS recurrence requiring admission is about 1.2% (42).

Electrophysiologic Features

When GBS is suspected, electrophysiologic studies are essential to confirm the diagnosis and exclude its mimics. The differential of pure motor syndrome includes other diseases associated with quadriparesis/paralysis such as myasthenic crisis, acute presentation of the idiopathic inflammatory myopathies and the unusual motor neuron disease patient presenting with acute respiratory failure. Associated clinical features are often helpful in distinguishing these from GBS. The finding of multifocal demyelination on early electrodiagnostic testing (or repeated a week later) is extremely helpful in confirming the diagnosis of AIDP with a high sensitivity and specificity. Needle electrode examination is non-specific as it demonstrates reduced recruitment initially and fibrillations potentials three to four weeks after onset.

The earliest findings in AIDP are prolonged F-wave latencies or poor F-wave repeatability due to demyelination of the nerve roots. This is followed by prolonged distal latencies (due to distal demyelination) and temporal dispersion or conduction block. Slowing of nerve conduction velocities is less helpful as it tends to appear two to three weeks after the onset. However, the sensitivity of nerve conduction studies (NCS) based on reported criteria may be as low as 22% in early AIDP (17), rising to 87% at five weeks into the illness (43). There are several reasons for limited sensitivity of NCS in AIDP. First, the common sites of demyelination are at the level of the nerve roots, most distal nerve segments and at entrapment sites. The nerve root is outside the reach of routine NCS, and entrapment sites are usually excluded when assessing the diagnosis of AIDP. However, slowing of nerve conduction velocities at multiple common entrapment sites is unusual in an otherwise normal young adult and may therefore support the clinical impression of GBS. Second, the number of motor nerves studied or those with an elicited response may be inadequate and finding prolongation of blink reflex latencies may be helpful. Finally, changes in the sensory

NCS lag behind the motor abnormalities. However a potential clue is the preservation of a normal sural nerve response when the median and and/or ulnar sensory potentials are reduced in amplitude or absent (43). A variety of motor NCS criteria have been published in an attempt to optimize sensitivity while maintaining specificity (see Table 2). A comparison of 10 published sets of criteria in 53 patients with AIDP, with amyotrophic lateral sclerosis and diabetic polyneuropathy controls, yielded a new set with 72% sensitivity and 100% specificity (44). Clinicians should not expect each AIDP patient to meet strict research criteria for demyelination particularly early in the course. Since treatment is most effective when given earlier, GBS patients should be treated based on clinical suspicion after the exclusion of potential mimics (Table 3).

AMAN, CMAP amplitudes are significantly reduced in the first few days and then in severe cases become absent (45). It is difficult in AMAN to ascertain if the absence of CMAP is due to axon loss, conduction block due to sodium channel dysfunction distal to the most distal stimulation site or an immune attack on the nodes of Ranvier. For this reason, fibrillation potentials may occur early on in the course of AMAN and needle electrode examination is helpful. In AMAN, nerve conduction testing may alternatively shown transient partial conduction block in intermediate and distal nerve segments that disappears within 2 to 5 weeks (31). In AMSAN the sensory potentials are reduced in amplitude and often absent (28). H-reflexes absence may be the only abnormality in 75% of MFS and BBE cases (24).

Laboratory Features

Routine laboratory testing is unrevealing in GBS such as a mild and non-specific elevation of creatine kinase /or transaminases. Hyponatremia should in the proper setting raise suspicion for porphyria or SIADH. Marked vomiting, delayed hair loss or Mee's lines may support the need for heavy metal testing. CSF analysis is critically important in all GBS cases and reveals albuminocytologic dissociation; that is an elevated protein up to 1,800 mg/dl (47) with 10 or less white cells/in most cases. Half of GBS cases may have a normal CSF protein in the first week but that proportion declines to 10% if the test is repeated a week later (1,2). Pleocytosis of 10–20 cells/mm3 is seen in ~5% of cases and should not dissuade one from a diagnosis if the clinical and electrodiagnostic features are otherwise typical. If there are more than 50 cell/per mm^3 particularly two weeks of after the onset of symptoms, one should consider early HIV infection, leptomeningeal carcinomatosis, CMV polyradiculitis and sarcoidosis. Most MFS cases and half of BBE cases have albuminocytologic dissociation (24).

Most cases of *C jejuni* enteritis are self-limited, resolving after several days, and require no specific treatment. Although antimicrobial therapy can hasten the clearance of *C jejuni* frorn the stool, (48) there is no evidence to suggest that such treatment would have an effect on GBS after the onset of neuropathic symptoms. Therefore, stool cultures or antibody measurements of *C jejuni* do not change management of GBS cases but may indicate a less favorable prognosis for recovery.

Antibodies to GM1 gangliosides have been described more frequently in AMAN and some of the reports correlated coexistence of GM1 antibodies and AMAN with greater functional disability at six months (49). *C jejuni* has GM1-like oligasacahrides on its surface that may cross-react with GM1, explaining why an antibody directed against the bacteria may also produce a neuropathy (50). In another study, all three GBS patients with poor recovery and inability to walk at 1 year had serological evidence of recent *C jejuni infection* but no antibodies to GM1 or GD1b (51) indicating that GBS patients with antibodies to GM1 or GD1b may have excellent recovery. Antibodies to GM1 or GD1b do not necessarily mediate

the extensive axonal damage seen in severely affected patients. However, IgG antibodies to GD1a are highly associated with AMAN, being detectable in 60% of AMAN cases and only 4% of AIDP (34).

GT1a antibodies correlate with the presence of bulbar signs and symptoms and may be seen with Bickerstaff's brainstem encephalitis in addition to GQ1b antibodies. While we do not recommend antibody testing in GBS, MFS is a notable exception (52, 53) since polyclonal GQ1b antibodies are highly sensitive and specific to MFS but can also be seen in typical GBS cases with prominent ophthalmoparesis. These may also be seen in GBS cases with marked ophthalmoparesis and in 66% of BBE cases (20).

Gadolinium-enhanced MRI scan of the lumbosacral spine reveals cauda equina nerve root enhancement in most AIDP cases (54, 55), MRI can be especially useful in the paraparetic variant of GBS, since it establishes the site of the lesion in the setting of typically unrevealing nerve conduction studies.

Treatment

General Supportive Care

Observational studies and expert opinion consensus provide guidance to the general management of GBS (56). Given that up to 30% of GBS cases progress to respiratory failure, good supportive care is the most important element of management. GBS patients are mostly admitted to the neurological intensive care unit or an intermediary care telemetry unit to allow for close and frequent monitoring of respiratory, bulbar and autonomic function. A rapid decline of the expiratory forced vital capacities to less than 15cc/kg of ideal body weight (adjusted for age) or of the negative inspiratory force to below 60 cm H_2O each indicate the need for urgent intubation and mechanical ventilation before hypoxemia supervenes (2). This is associated with marked weakness of neck muscles and inability to count out loud till 20. Patients with severe dysphagia may require nasogastric or feeding tubes. Intubation should also be considered for patients who cannot handle their secretions or who have an ineffective cough. After two weeks of intubation, tracheostomy should be considered in those without improved pulmonary mechanics. In those intubated but with improved pulmonary parameters at two weeks, an additional week of intubation may be judicious to allow for successful weaning from the ventilator (56). It is important when managing autonomic instability to be conservative and avoid aggressively treating blood pressure fluctuations since patients are sensitive to medications and use of long-acting antihypertensives is contraindicated. For those with marked radicular back pain or neuropathic pain refractory to acetaminophen or NSAIDS, treatment with pain modulating drugs such as antidepressants, gabapentin, pregabalin, carbamazepine, tramadol and mexiletene is indicated (56). Bed-ridden patients should have deep venous thrombosis prophylaxis with compressive hose and/or anticoagulants in the form of subcutaneous heparin or enoxaprin. Bedside passive range of motion can help prevent muscle contractures in paralyzed patients bit it is also important to be mindful that these patients are most often alert and cognitively intact. A means for communication must be established for patients who are on mechanical ventilation. Vigilance towards urinary and pulmonary infections is important since most severe cases develop one or the other. Treatment with plasmapheresis or IVIG is indicated for patients with weakness impairing function or any respiratory involvement. Before initiating any of these therapies, patients and their families should be educated about the fact that it takes on average two to three months for patients to walk without aids no matter what therapy is used.

Plasma Exchange

Plasma exchange (PE) directly removes humoral factors such as autoantibodies, immune complexes, complement, cytokines and other nonspecific inflammatory mediators and was the first treatment shown in randomized controlled trials to be effective in GBS (see Table 4) (57, 58). In both studies, PE performed within two weeks from symptom onset consistently demonstrated a statistically significant reduction in the time to weaning from the ventilator by 13 to 14 days and time to walk unaided by 32 to 41 days. In addition the French Cooperative Group showed a reduction in the proportion of patients who required assisted ventilation, a decrease in the time to onset of motor recovery, and a reduction in time to walk with assistance (57). The Guillain-Barré syndrome Study Group identified similar benefits with more PE recipients improved at four weeks, and the 1 grade improvement occurring three weeks earlier (57, 58). The volume of PE is well-defined at 50cc/kg administered five times, daily or every other day over five to 10 days, totaling 250cc/kg. PE beyond the standard amount will not offer additional benefits (59).The French Cooperative Group on Plasma Exchange in Guillain-Barré syndrome showed that patients with mild GBS on admission (could walk with or without aid but not run, or those who could stand up unaided) would benefit from two PEs (59). For those who could not stand up unaided (moderate group), four PEs were more beneficial than two for time to walk with assistance (median, 20 vs 24 days) and for 1-year full muscle-strength recovery rate (64% vs 46%). Six exchanges were no more beneficial than 4 in the severe mechanically ventilated GBS cases.

PE is performed at specialized centers and involves removing 3–6 liters of plasma over several hours and replacing it with preferably albumin or in some cases fresh frozen plasma. Limitations include IV access as it requires large double-lumen catheter through subclavian, internal jugular or femoral venous access. Potential complications include pneumothorax, hypotension, sepsis, pulmonary embolism, hemorrhage from vein puncture, low platelets, prolonged clotting parameters, hypocalcemia, citrate toxicity and anemia. For a 70 kg adult, the total exchange volume is approximately 15,000 cc. During PE, it is important to monitor blood pressure, pulse, and amount of fluids intake and output. We obtain daily CBC, platelets, calcium, PT, PTT and INR and hold apheresis one to two days if coagulation parameters become abnormal.

While the PE-treated groups in the North American and French studies did better than controls, the time to walk and to discharge, and the time spent on a ventilator, were still fairly long, even in PE-treated patients. Therefore, physicians, patients, and family members need to have realistic expectations about the extent of the effect of both PE and intravenous gamma globulin (see the following section). Dramatic improvement within days of beginning treatment is not the rule and if this occurs, it may have happened regardless of treatment.

Intravenous Immunoglobulin (IVIg)

The postulated mechanisms of action of IVIg in neuromuscular disorders include interference with costimulatory molecules involved in antigen presentation and modulation of autoantibodies, cyotokines and adhesion molecules production as well as macrophage Fc receptor. It also disrupst complement activation and membrane attack complex formation (60). Sialylated IgG Fc fragments are important for the in vivo activity of intravenous immunoglobulin (61) since they initiate an anti-inflammatory cascade through the lectin receptor SIGN-R1 or DC-SIGN. This leads to upregulated surface expression of the inhibitory Fc receptor, Fc gamma receptor IIb, on inflammatory cells, thereby attenuating autoantibody-initiated inflammation.

The first large study to demonstrate a favorable response to IVIg in GBS was by the Dutch Guillain-Barré Study Group two decades ago (62). They compared the efficacy of IVIg to PE in 147 patients and there was no control group. Their results showed that not only IVIg was effective but it was possibly more effective than PE as seen in Table 5. However there may have been a group imbalance to account for the later since PE efficacy in the Dutch trial did not match up with that of the North American study such as in the rate of 1-grade improvement at four weeks. A subsequent larger study by the Plasma Exchange and Sandoglobulin Guillain-Barré Syndrome Trial Group (63) has conclusively shown that there is no difference between the outcomes with IVIg or PE.

The total dose of IVIg is 2gm/kg administered over two to five days. Since most GBS patients are in the hospital for longer than two days, there is probably no advantage to giving it in less than five days for this disorder. While the side effects are usually mild, the infusions are generally better tolerated if given over five days We closely monitor patients with the first infusion, starting at a very slow rate of 25 to 50 cc/hr for 30 minutes and increasing it progressively by 50 cc/hr every 15 to 20 minutes up to 150 to 200 cc/per hr. Mild reactions (headache, nausea, chills, myalgia, chest discomfort, back pain) occur in 10% and are improved with slowing the infusion rate and are preventable with pre-medication with acetaminophen, benadryl and if need be IV methylprednisolone. Moderate rare reactions include chemical meningitis neutropenia and delayed red, macular skin reaction of the palms, soles and trunk with desquamation. Acute renal failure is uncommon and related to patient dehydration and the prior use of sucrose or maltose diluents. Other severe and rare reactions are anaphylaxis, stroke, myocardial infarction or pulmonary emboli due to hyperviscocity syndrome. The latter is more likely to occur in old age, immobility, diabetes, thrombocytemia, hypercholesterolemia, hypergammaglobunemia, and cryoglobunemia. We avoid using IVIG in patients with several of these risk factors and place IVIG recipients on 81 mg daily aspirin prophylactically. Total IgA deficiency is extremely rare but such patients may experience anaphylaxis when given IVIg. However obtaining quantitative IgA levels is not practical in this urgent scenario. Manufacturers take steps to eliminate the possibility of hepatitis virus transmission (heat pasteurization and solvent/detergent inactivation), so this potential issue has been eliminated. There has never been a reported case of HIV infection transmitted by IVIg. Nanofiltration and caprylate treatment reduce the risk of prion disease transmission.

Two reports raised the issue of relapses after treatment with IVIg (64, 65) also referred to as treatment related fluctuations, causing confusion for doctors attempting to make a rational treatment decision for a GBS patient. However, relapses had also been reported with PE (58). In the French study, the PE group had a relapse rate of 5.5% compared to 1% for the control group (59). Physicians have to accept that rarely some GBS patients may have minor relapses. While the relapse rate may be slightly higher with either IVIg or PE compared to no treatment, the weight of all available clinical and research evidence indicates it is better to treat GBS patients than not to. Both PE and IVIg are equally effective, but in the hemodynamically unstable patient, PE is contraindicated and furthermore IVIg is more often readily available in most hospitals.

PE followed by IVIg?

The management of the severe GBS patient who did not improve 10–14 days after PE or IVIg is problematic. The Plasma Exchange Sandoglobulin Guillain-Barre' (PSGBS) study group conducted a multicenter trial comparing PE monotherapy, IVIg monotherapy, and PE followed by IVIg (66). Combined treatment produced no significant difference in patient outcomes compared with either therapy given alone (Table 6). This study also showed that PE and IVIg treatments were equally effective in GBS and found no significant difference in the incidence of side effects, thus further settling the lingering question from the Dutch IVIg

study. Based on that, there is no added benefit in treating PE recipients subsequently with IVIG (66).

Corticosteroids (CS)

CS are of no benefit in the treatment of GBS. In fact, in one of the early studies, the oral corticosteroid treated patients did worse than the controls (67). Intravenous methylprednisolone was evaluated in GBS in three studies. In the large randomized British study, 124 patients received methylprednisolone 500 mg daily for five days within 15 days of onset and 118 patients received placebo (68) and about half the patients in both groups received PE. There was no difference between the two groups in the degree of improvement at four weeks or in secondary outcome measures. The researchers concluded that “a short course of high-dose methylprednisolone given early in GBS is ineffective.” In the second study, a smaller Dutch open-label pilot study (69) suggested that 25 patients receiving intravenous methylprednisolone and IVIg did better than 74 patients from the earlier Dutch study who received IVIg alone. This led to a randomized controlled study by the Dutch group in patients unable to walk independently and who had been treated within 14 days after onset of weakness with IVIg to receive either intravenous methylprednisolone (500 mg per day; n=116) or placebo (n=117) for 5 days within 48 hours of administration of first dose of IVIg (70). There was no statistically significant difference between the groups in the pre-specified primary outcome measure of improvement from baseline in GBS disability score of one or more grades at 4 weeks after randomization (68% in the methylprednisolone group versus 56% in the controls, p=0.06). Thus, intravenous corticosteroid is not recommended therapy for GBS.

AAN practice parameters

They (71) recommend PE for nonambulant adult patients with GBS who seek treatment within four weeks of the onset of symptoms (level A). PE should also be considered for ambulant patients examined within two weeks of the onset of symptoms (level B). IVIg is recommended for nonambulant adult patients with GBS within two (level A) or possibly four weeks (level B) of the onset of neuropathic symptoms. It also indicates that sequential treatment with PE followed by IVIg, or immunoabsorption followed by IVIg is not recommended for patients with GBS. As stated earlier, corticosteroids are not recommended for the management of GBS. In children with severe GBS, PE and IVIg are treatment options.

Prognosis

Most patients with GBS begin to recover at 28 days with mean time to complete recovery being 200 days in 80% of cases. However, many (65%) have minor residual signs or symptoms often making recovery less than complete (1,2). Besides that, major residual neurologic deficits affect 10–15% of patients. In a study of 79 cases a year after the onset of GBS, 8% had died (all older than 60), 4% remained bedbound or ventilator dependent, 9% were unable to walk unaided, 17% were unable to run, and 62% had made a complete or almost complete recovery (72).

In the majority of GBS cases with complete to almost complete recovery, functionally significant residual deficits are commonly detectable on careful evaluation. Forty GBS patients were compared at a mean of seven years after the acute attack to 40 healthy control subjects showing residual neuropathy affecting large- and medium-sized myelinated motor and sensory fibers in approximately half of all patients (73). There was also a trend toward impaired self-reported physical health status and other long-term studies have demonstrated similar functionally relevant neurological deficits up to 7 years after the acute GBS attack.

These deficits were predominantly in the lower extremities and in some cases there was evidence of persistent dysautonomia (74, 75).

Five percent of GBS cases succumb to their illness due to complications of critical illness (infections, adult respiratory distress syndrome, pulmonary embolism), and rarely dysautonomia. The relapse rate is 5% and it usually occurs within the first eight weeks. The alternative diagnosis of relapsing-remitting chronic inflammatory demyelinating polyneuropathy (CIDP) should be considered in relapsing cases (76). When the first relapse is delayed by more than two months following an acute attack or the number of relapses exceeds two instances, either should raise suspicion for relapsing-remitting (CIDP) (77). Further clues favoring CIDP in relapsing cases include maintaining the ability to ambulate independently at nadir, absence of cranial nerve dysfunction and the presence of marked demyelinating slowing on nerve conduction studies.

Slowed recovery and a reduced likelihood of walking unaided at six months may be attributable to a suboptimal increase in IgG levels at two weeks after infusion (76). After a standard dose of IVIg treatment, GBS patients show a large variation in its pharmacokinetics, which is thought to be related to clinical outcome. In a retrospective analysis of 174 GBS patients enrolled previously in a randomized controlled clinical trial, patients with a minor increase of serum IgG level two weeks after standard single IVIg dose recovered significantly slower (76). Additionally, fewer of these patients reached the ability to walk unaided at six months after correction for known clinical prognostic factors. This may indicate that patients with a small increase in serum IgG level at two weeks could benefit from a higher dosage or second course of IVIg but this hypothesis is yet to be tested in a prospectively designed study.

McKhann et al. (78) identified four factors that indicated a poor prognosis in the North American GBS study (regardless of whether patients received plasmapheresis). These were older age (> 50–60), a rapid onset prior to presentation within seven days, the need for mechanical ventilation, and severely reduced distal motor amplitudes (to 20% or less of the lower limit of normal). A preceding diarrheal illness with *C jejuni* can be added to this list but not GM1 autoantibodies. A preceding infection with CMV may also result in a delayed recovery (Table 6) (79).

Recently, the Erasmus GBS outcome score was derived from data of 388 patients enrolled in two randomized controlled trials and one pilot study (80). This 1 to 7 score consists of three items: age (0=up to 40 years, 0.5=41–60 years or 1= for age > 60), preceding diarrhea (0 or 1), and modified GBS disability score at two weeks after entry (1 to 5). This score obtained at two weeks was validated in another GBS sample as a predictor of the probability of independent ambulation at six months. Predictions corresponding to these prognostic scores ranged from 1% to 83% for the inability to walk independently at six months with a very good discriminative ability (AUC 0·85) in both data sets (Table 7). Of patients with an Erasmus GBS outcome score of 5 at two weeks, 27% are unable to walk independently at six months whereas a score of 5.5–7 markedly raises that proportion to 52%. More recently, an earlier clinical model in the first week of disease accurately predicted the outcome of GBS in 397 patients at 6 months (81). High age (>60), preceding diarrhea, and low Medical Research Council sumscore (<31; range 0–60 scale) at hospital admission and at 1 week were independently associated with being unable to walk at 4 weeks, 3 months, and 6 months.

Most AMAN patients have more delayed recovery than AIDP (82) while some cases recover quicker (83) (Ho TW, Hsieh ST, Nachamkin I, et al. Motor nerve terminal degeneration provides a potential mechanism for rapid recovery in acute motor axonal neuropathy after

Campylobacter infection (83). In the later report, Ho et al demonstrated on motor-point biopsy denervation of the neuromuscular junction and reduction in the intramuscular nerve fiber count. Since GM1 antibodies can bind at nodes of Ranvier, they suggested that these might induce failure of electrical conduction. Quicker recovery may therefore be due to reversible changes of the sodium channels at nodes of Ranvier as acute motor conduction block variant of AMAN or by degeneration followed by regeneration of motor nerve terminals and intramuscular axons.

Most MFS patients recover by six months (84). In that study, all 28 untreated MFS cases returned to normal activities with a respective median period of 32 days between onset and disappearance of ataxia and 88 days for ophthalmoplegia. In a follow up study, Mori et al analyzed the clinical recovery of 92 patients with Miller Fisher syndrome who had been treated with IV immunoglobulin (IVIg; n = 28), plasmapheresis (n = 23), and no immune treatment (n = 41). Though IVIg slightly hastened the amelioration of ophthalmoplegia and ataxia , 96% of cases were free of all symptoms and signs one year after the onset of neurologic symptoms, whether or not they received immunotherapy (84). In a large case series, most of the 62 patients with BBE with and without limb weakness were given immunotherapy including steroids, plasmapheresis and IVIg (23). Six months after BBE onset, 37/56 (66%) for whom outcome data were available showed complete remission with no residual symptoms. A Cochrane review indicates that there are no randomized controlled trials of immunomodulatory therapy in Miller Fisher syndrome or related disorders on which to base practice (20).

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Key Points

Besides the classic presentation of ascending paralysis in demyelinating GBS, clinical variants are based on the types of nerve fibers involved (motor, sensory, sensory and motor, cranial or autonomic), predominant mode of fiber injury (demyelinating versus axonal), and the presence of alteration in consciousness.

Treatment should not be delayed when electrophysiology is not confirmatory of GBS.

All patients should be treated with either PE or IVIG, even if the disease is mild.

Although therapy should be initiated within 2 weeks of onset, it is still appropriate to treat patients after 2 weeks, particularly if they are still progressing.

Both PE and IVIg are equally effective in shortening the time to independent ambulation but the combination is no more effective.

While PE is available at specialized centers IVIg is more readily available in most hospitals.

In hemodynamically unstable patients, PE is contraindicated. Caution with administering IVIg is advised in patients with hypercoagulability or renal insufficiency.

There is no justification to use recurrent courses of IVIG or PE unless the patient has recurrent disease.

Prognosis is overall good as eighty percent of GBS cases have slow but “complete” recovery within 6 months.

However, sixty-five percent have mild to moderate residual symptoms or signs and persistent major residual neurologic deficits affect 10–15% of patients despite appropriate therapy.

Newer prognostic tools are helpful in identifying in the first 2 weeks those at higher risk of poor recovery at 6 months.

Table 1

Diagnostic Criteria of Guillain-Barré Syndrome

Required	Supportive	Exclusionary
Progressive symmetric weakness of > 1 limb	Sensory symptoms or signs	Other causes excluded (toxins, botulism, porphyria, diphteria)
Hyporeflexia or areflexia	Cranial nerve involvement especially bilateral VII	
Progression <4 weeks	Autonomic dysfunction	
Symmetric weakness	CSF protein elevation	
	CSF cell count < 10/mm3	
	Electrophysiologic features of demyelination	
	Recovery	

* suspect HIV, lyme, sarcoidosis, lymphoma

Adapted and modified from reference 17.

Table 2

GBS Electrophysiologic Criteria

	Percent conduction velocity slowing			Percent distal latency prolongation			Percent F-wave latency prolongation			Amplitude Conduction block		Abnormal temporal dispersion		
Amplitude	**≥ 80% of LLN**	**< 80% of LLN**	**No. of nerves**	**≥ 80% of LLN**	**> 80% of LLN**	**No. of nerves**	**≥ 80% of LLN**	**< 80% of LLN**	**No. of nerves**	**%**	**No. of nerves**	**%**	**No. of nerves**	**Abnormal parameters required**
Albers 1985 (45)	>5	> 15	2	>10	>20	2	>20	>20	2	>30	2	>30	1	1
Albers 1989 (47)	>10	>20	2	>15	>25	2	>25	>25	1	>30	1	>30	1	3
Asbury 1990 (17)	>20	>30	2	>25	>50	2	>20	>50	2	>20*	1	>15	1	3
Hadden 1998 (48)	>10¶	>15	2	>10	>20°	2	>20	>20	2	>50†	2	—	—	1
Van denBergh 2004 (46)	>30	>30	2	> 50	>50	2	>25	>50	2	>50†	2‡	>30	2	1

LLN, lower limit of normal

† distal amplitude > 20% of LLN

‡ alternatively 1 finding with another NCS abnormality

* by area or amplitude

¶ distal amplitude >50% LLN

° distal amplitude < LLN

Table 3

Mimics of GBS presenting as quadriparesis:*

1	Anterior Horn cell: poliomyelitis or West Nile virus infection (asymmetric weakness)
2	Peripheral Nerve:
	a. Critical illness neuropathy
	b. Lymphoma / leptomeningeal carcinomatous meningitis
	c. Toxic neuropathies: solvent or heavy metals
	d. Porphyria
	e. Lyme
	f. Diphtheria
	g. Vasculitic neuropathy
3	Neuromuscular Junction:
	a. Myasthenia Gravis
	b. Botulism
	c. Tick paralysis (children)
4	Muscle:
	a. Idiopathic inflammatory myopathies
	b. Periodic paralysis
	c. Critical illness myopathy
	d. Rhabdomyolysis
	e. Severe hypokalemia or hypophosphatemia
5	Acute spinal cord lesion

* Psychogenic is an exclusion diagnosis

Table 4

Guillain-Barre' Syndrome: North American and French Plasmapheresis Trials

	Plasma Exchange*	Control*
North American (1985)		
Number of patients	122	123
Time to improve 1 grade	19 Days	40 Days
Time to walk unaided – all patients	53 Days	85 Days
Time to walk unaided –respirator	97 Days	169 Days
Time on ventilator	9 Days	23 Days
% improved 1 grade at 1 month	59%	39%
% improved at 6 months	97%	87%
French (1987)		
Number of patients	109	111
Time to weaning	18 Days	31 Days
Time to walk unaided	70 Days	111 Days
Time in hospital	28 Days	45 Days
% patients to ventilator after entry	21%	42%

* All differences in both columns are statistically significant.

Source: Adapted from Guillain-Barre Syndrome Study Group. Plasmapheresis and acute Guillain-Barre syndrome. Neurology 1985;35:1096-1104.

and French Cooperative Group on Plasma Exchange in Guillain-Barre Syndrome: Role of replacement fluids. Annals of Neurology 1987;22:753-761.

Table 5

Guillain-Barre' Syndrome: Dutch IVIg vs. Plasmapheresis Study (66) Compared to the North American Plasmaphersis Study (59)

	Dutch		North American	
	IVIg	**PE**	**PE**	**Control**
Total patients	74	73	108	120
Improved 1 grade (4 weeks)	53%	34%	59%	39%
Days to improve 1 grade (median)	27	41	19	40
Days to grade 2	55	69	19	40
Number of multiple complications	5	6	--	--
Ventilator dependent by Week 2	27%	42%	--	--

Table 6

Guillain-Barre' Syndrome: PE monotherapy, IVIg monotherapy, versus PE followed by IVIg (69)

	PE	IVIg	PE followed by IVIg
Total patients	121	130	128
Days to walk unaided	49	51	40
Median days to hospital discharge	63	53	51
% Unable to walk unaided after 48 weeks	16.7	16.5	13.7
Median days to stop artificial ventilation	29	26	18
Deaths	4.1%	4.6%	6.3%

Table 7

Poor Prognostic Factors in GBS

1	Older age (>50–60)
2	Rapid onset prior to presentation (<7 days)
3	Ventilator dependency
4	Severely reduced distal CMAP amplitudes (<20% LLN)
5	Preceding infection with CMV
6	Preceding diarrheal illness / *C. Jejuni*
7	Erasmus GBS outcome score at 2 weeks ≥ 5 (reference 80):
	A. Ventilator dependence, or
	B. Bed/chairbound and elderly (>60), or
	C. Bed/chairbound and preceding diarrheal illness