Guillain-Barré Syndrome and Other Acute Polyneuropathies

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KEYWORDS

• Guillain-Barré syndrome • Diagnosis • Therapy • Disease management
• Dysautonomia • Aged

KEY POINTS

- Guillain-Barré syndrome (GBS) is an acute monophasic autoimmune neuropathy frequently preceded by respiratory or gastrointestinal infections, and the most common subtypes are acute inflammatory demyelinating polyradiculoneuropathy, acute motor axonal neuropathy, and Miller Fisher syndrome.
- GBS is a clinical diagnosis and diagnostic studies are useful to exclude GBS mimics and to characterize the neuropathy.
- Older patients are at increased risk for respiratory and cardiovascular complications associated with GBS and require close clinical monitoring.
- A multidisciplinary approach to treatment of motor impairment, pain, and fatigue is recommended in GBS patients.

INTRODUCTION

Guillain-Barré syndrome (GBS) is the most common cause of acute neuropathy, characterized by rapidly progressive weakness affecting the extremity and cranial muscles.[1] It is a heterogeneous disorder, with patients having varying degrees and severity of motor, sensory, and autonomic dysfunction, and recognized clinical variants, including acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN), and Miller Fisher syndrome.[1,2] Current evidence suggests that GBS is caused by an aberrant autoimmune response to a stimulation of the immune system, such as an infection.[3] Despite the many advances in the understanding of the pathophysiology of GBS, a diagnosis relies mainly on clinical

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findings of progressive weakness and areflexia.[4] These core clinical features are remarkably similar to the historic reports of GBS, including that by Landry, who in 1859, described 10 patients with acute ascending or generalized paralysis.[5] The 1916 descriptions by Guillain, Barré, and Strohl of a syndrome of progressive weakness, sensory abnormalities, diminished deep tendon reflexes, and albumin-cytological dissociation (elevated protein and normal cell count) in the cerebrospinal fluid (CSF) in 2 French soldiers included all major features of GBS.[6,7] This review discusses the clinical features, diagnosis, treatment, and pathophysiology of GBS.

EPIDEMIOLOGY AND RISK FACTORS

GBS is a rare disorder and the incidence is approximately 0.81 to 1.89 cases per 100,000 person-years in Europe and North America, although there are some geographic variations worldwide.[8,9] Men have a higher risk than women, and there appears to be an age-related increase in risk up to the ninth decade of life, with a 20% increase in incidence for every 10 years increase in age.[8,10] In approximately two-thirds of patients, the symptoms of GBS are preceded by an infection within the prior 4 weeks. The most common is a diarrheal illness caused by *Campylobacter jejuni*.[11] In the elderly, the preceding illness may be shorter in duration and may be more likely to be a flulike syndrome rather than a gastrointestinal disorder.[12] There are other infectious organisms associated with GBS, including human immunodeficiency virus (HIV), cytomegalovirus, Epstein-Barr virus, influenza A virus and influenza B virus, and, more recently the Zika virus.[11,13,14] The severe acute respiratory syndrome (SARS)–coronavirus 2 (SARS–CoV-2), which had infected more than 23 million people worldwide as of August 2020, raised concerns that there may be an increase in the number of GBS worldwide.[15] A recent review of the neurologic complications of SARS–CoV-2 showed that GBS infrequently occurs in COVID-19 patients, although long-term close surveillance for GBS cases remains necessary.[16]

Vaccination, surgery, anesthesia, trauma, and use of recreational drugs also are reported to be associated with GBS.[1,17] A frequent patient concern is the risk for GBS after influenza vaccination because of the association between GBS and the H1N1 influenza A vaccination in 1976 and 2009.[18,19] Epidemiologic studies of the relationship between influenza vaccination and GBS suggest that vaccine related GBS is rare.[20,21] Recurrent GBS also is not observed in patients who previously were diagnosed with GBS and subsequently received influenza vaccinations.[22,23] Furthermore, the potential risk for developing GBS after influenza infections may be greater than the risk for developing GBS after influenza vaccination.[21,24] For these reasons, clinicians should follow the Centers for Disease Control and Prevention guidelines when counseling patients about the risks and benefits of seasonal influenza vaccination.[25] The basis for the association between GBS and surgery is uncertain. A recent study suggests that autoimmune disorders and malignancies may be more common in patients who develop GBS after surgical procedures.[26] Any proposed mechanism based on these findings is speculative; however, the study does bring to attention the importance of considering GBS as a diagnosis in individuals who have acute postoperative weakness and a known history of autoimmune disease or malignancy.

CLINICAL FEATURES

In AIDP, the most common subtype of GBS, the earliest symptoms consist of abnormal sensation, such as tingling or numbness in the toes or fingers, followed by limb weakness.[1,2] Pain symptoms, such as sciatica; muscle pain involving the trunk, low back, or leg muscles; neck stiffness; and uncomfortable paresthesia, can

be prominent and severe, and may persist for several months after the acute phase of the disorder.[27–30] In a substantial number of patients, pain symptoms even may precede the onset of muscle weakness by up to 2 weeks.[30] Although the sensory symptoms tend to precede the motor symptoms in AIDP, weakness is the predominant finding on examination. The most common pattern of weakness is that of ascending paralysis, starting in the distal legs up to the thighs, followed by upper limb and cranial muscles.[1,7] Bulbar and respiratory muscles frequently are affected. In some patients, muscle weakness may be more prominent in the proximal muscles (ie, shoulder and hip girdle muscles), and rarely is the weakness confined only to the lower extremities.[31,32] Nearly all patients have diminished or absent deep tendon reflexes on neurologic examination.[33]

Autonomic dysfunction is a common and important clinical feature of GBS requiring vigilant monitoring because of the associated increase in morbidity and mortality.[34] Although sinus tachycardia is the most common abnormality, labile blood pressure and cardiac tachyarrhythmia can occur, requiring cardiac monitoring in the intensive care unit.[34] Pupillary, gastrointestinal, or urinary dysfunction or pandysautonomia also can occur.[35] Autonomic dysfunction may be more common in GBS patients who develop respiratory failure and is independently associated with the need for mechanical ventilation.[36] It is important to systemically assess symptoms of autonomic dysfunction so that medical interventions can be initiated early.

Acute Clinical Course

In most GBS patients, progressive motor weakness occurs over the course of 1 week to 3 weeks, and nearly all patients have maximum weakness by 4 weeks.[33,37] Rarely does weakness continue to worsen beyond 4 weeks or 5 weeks, and when it does, an alternate diagnosis should be considered.[33] Although the severity of symptoms in GBS can vary widely between patients, most GBS patients require close observation in the hospital because of the potential risk for life-threatening complications, such as respiratory failure. Older patients, in particular, tend to progress to maximum weakness over a shorter duration and more often have severe disease symptoms resulting in complete loss of independent ambulation, respiratory failure, or death.[10,12] Preexisting comorbidities and increased frequency of severe disease in older GBS patients necessitate more intensive clinical monitoring and symptomatic management to decrease risk for infections, thromboembolism, and decubitus ulcers.

In the course of GBS, approximately half of the patients have facial weakness and swallowing difficulty, which can cause malnutrition or dehydration and increase the possibility for aspiration.[1] Bulbar muscle weakness may be more common in older patients whereas facial weakness occurs less often.[10,12] One-third of patients have respiratory failure and require ventilatory support in the intensive care unit.[1,33] Because cranial and respiratory muscles function frequently are impaired, and may occur within the first week of symptom onset or during treatment, it is prudent to evaluate the respiratory status and swallowing function in GBS patients closely until the nadir of the weakness is reached.[31,38] The most consistent clinical features predictive of impending respiratory failure and need for mechanical ventilation are short duration from symptom onset to hospital admission (less than 7 days), severe limb muscle weakness, and facial and bulbar muscle weakness.[36,38,39]

Guillain-Barré Syndrome Variants

GBS is a heterogeneous disorder consisting of a few different subtypes unified by the shared feature that the cause is an autoimmune injury of the peripheral nerves (**Box 1**).[40] Although the terms GBS and AIDP frequently are used interchangeably,

Box 1
Guillain-Barré syndrome subtypes

- AIDP
- AMAN
- Acute motor and sensory axonal neuropathy
- Miller Fisher syndrome
- Acute autonomic neuropathy
- Bickerstaff brainstem encephalitis

GBS represents a spectrum of autoimmune neuropathies in which AIDP is the most common subtype. In AIDP, patients have symptoms of motor and sensory nerve dysfunction and dysautonomia.[1] The presence of a demyelinating neuropathy is determined by findings on nerve conduction studies.[1,41] In AMAN, unlike in AIDP, patients have motor symptoms and do not have sensory abnormalities.[40] Miller Fisher syndrome is a rare subtype of GBS in which the patients have the classic triad of ophthalmoplegia, ataxia, and areflexia.[42,43]

GUILLAIN-BARRÉ SYNDROME DIAGNOSIS

A diagnosis of GBS should be suspected in any patient who presents with an acute onset of progressive weakness. GBS is a clinical diagnosis. In the diagnostic criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke (now the National Institute of Neurological Disorders and Stroke [NINDS]), the only features required for diagnosis are cranial, truncal, and/or limb muscle weakness and diminished or loss of deep tendon reflexes.[4,37] There are clinical features that do not support a diagnosis of GBS (**Box 2**), and, when present, should prompt the clinician to consider an alternate diagnosis. There is no 1 single diagnostic test that is specific for GBS; however, diagnostic studies are useful to exclude GBS mimics and characterize the neuropathy. Although a diagnosis of GBS may be relatively straightforward in patients who have the characteristic history and findings on examination, the correct diagnosis may be missed in patients early in the disease course when the main symptoms are sensory abnormalities or pain. An important differential

Box 2
Neurologic features inconsistent with diagnosis of Guillain-Barré syndrome

- Progressive or relapsing weakness beyond 8 weeks
- Truncal sensory level
- Hyperreflexia[a] and pathologic reflexes (clonus or extensor plantar response)
- Persistent asymmetric weakness
- Prominent sensory symptoms without weakness
- Bowel and bladder sphincter dysfunction at symptom onset
- Severe respiratory dysfunction with preserved limb strength

[a] Rarely, the deep tendon reflexes can be hyperactive in the presence of anti-GD1a antibodies.

diagnosis to consider in patients who have progressing ascending paralysis is a spinal cord disorder. In contrast to patients with spinal cord disorders who tend to have a sensory level, hyperactive deep tendon reflexes below the cord lesion, and pathologic reflexes, such as Babinski sign, GBS patients have distal (ie, in the hands and feet) sensory abnormalities and hypoactive or absent deep tendon reflexes on examination. Spine imaging with magnetic resonance imaging should be performed in patients with possible spinal cord disorders.

The most helpful diagnostic studies to obtain when evaluating patients suspected of having GBS are CSF studies and electrophysiologic testing consisting of nerve conduction studies and electromyography.[2] Although these diagnostic tests are not required to diagnose GBS, they can be supportive of a diagnosis if the results show the typical abnormalities. The original CSF findings of increased protein and normal cell count, also known as albumin-cytological dissociation, described by Guillain, Barré, and Strohl in 1916, continue to be recognized as the characteristic CSF profile.[6,44] In most GBS patients, the CSF white blood cell count is less than 5 cells/μL, and cell count greater than 50 cells/μL should raise suspicion for an alternate diagnosis, such as infection or malignancy.[33,45] GBS can be the initial presentation of HIV infection, and HIV testing should be considered in patients who have CSF pleocytosis.[46] Importantly, the absence of elevated CSF protein should not dissuade a clinician from diagnosing GBS, especially when the test is obtained very early after symptom onset.[1] The CSF protein can be normal in up to half of GBS patients within the first week.[33,47] Elevated CSF protein in isolation is not diagnostic of GBS nor is it predictive of disease severity. A modest increase in CSF protein is nonspecific and can be seen in other neurologic and non-neurological disorders.[48–50] The finding of albumin-cytological dissociation to support a GBS diagnosis requires appropriate clinical context.

Nerve conduction studies and electromyography are electrophysiologic studies that are used to evaluate the integrity of the peripheral nervous system. These studies can support GBS diagnosis, determine GBS subtypes, prognosticate outcome, and exclude GBS mimics.[33,45] Although electrophysiologic studies can assist in diagnosing GBS and its variants, these tests may not be readily available in all hospitals due to the requirement for highly trained personnel and specialized equipment. Therefore, initiating treatment of GBS should not be delayed because of an inability to obtain these studies. Electrophysiologic studies can distinguish AIDP from AMAN. In AIDP, the nerve conduction studies show findings of a demyelinating neuropathy affecting motor and sensory nerves, whereas in AMAN, the nerve conduction studies show findings of an axonal neuropathy only affecting the motor nerves.[41,51] It may be helpful to distinguish AIDP from AMAN because some studies suggest a more favorable prognosis in AIDP compared with AMAN, although this is not a consistent finding.[52–55] There are some limitations to electrophysiologic testing. Nerve conduction studies can be normal or show minor nonspecific abnormalities in GBS patients during the first week after symptom onset.[41,54] Additionally, the study may not be able to determine the GBS subtype early in the disease course.[33] If an electrophysiologic study is performed within the first week of symptom onset and is nondiagnostic, repeat testing in 1 week to 2 weeks can be considered.

Routine laboratory studies do not contribute to diagnosing GBS, but they are helpful to exclude other causes of peripheral neuropathy that mimic GBS, such as infection, malignancy, or other autoimmune disorders.[56] Because neoplastic disorders are much more common in the elderly, it is important to consider and evaluate for a neoplastic or paraneoplastic cause of neuropathic symptoms in older patients.[57] Serum ganglioside antibody testing is not helpful in most GBS patients; however,

testing for anti-GQ1b IgG antibody should be considered in Miller Fisher syndrome, especially if there is diagnostic uncertainty.[43,58] Fecal testing and serology to detect *C jejuni* infection or serology to evaluate for infection by Epstein-Barr virus or cytomegalovirus can be obtained, but these studies do not contribute to GBS diagnosis and are not helpful in determining the clinical subtype or prognosis.[3] A complete blood cell count; electrolytes panel; glucose, renal, and liver function studies; and coagulation profile often are obtained to evaluate for other medical disorders and to monitor for side effects due to GBS treatments. Serial serum electrolyte panels are recommended in all GBS patients because hyponatremia secondary to syndrome of inappropriate secretion of antidiuretic hormone (SIADH) can be seen in up to half of all patients.[59,60] Older patients may be more vulnerable to this complication because of age-related loss of water regulation mechanisms and a predisposition to developing SIADH. Furthermore, older patients frequently have disorders requiring use of medications in which hyponatremia is a known side effect.[61]

PATHOPHYSIOLOGY

Pathologic studies of peripheral nerves from GBS patients provided the earliest evidence that GBS may be an inflammatory disorder.[62] The pathology was present in the nerve roots, nerve trunks, and distal nerve branches. The abnormalities on nerve biopsy included myelin and axonal destruction and infiltration by mononuclear cells and macrophages.[1,63] Subsequent studies showed that T cells and B cells, macrophages, and complement activation contributed to peripheral nerve injury in GBS.[1,3,31] The potential immune mechanism was clarified further by studies demonstrating an association between a preceding infection and GBS. The finding that respiratory and gastrointestinal infections by *C jejuni*, cytomegalovirus, and Epstein-Barr virus were associated with GBS led to the hypothesis that GBS may be a postinfectious immune-mediated disorder.[11,64] It is postulated that the epitopes on the surface of pathogens mimic components of the peripheral nerve ganglioside, triggering an aberrant activation of the immune system. In susceptible individuals, these events cause an autoimmune injury of the peripheral nerve myelin sheath and axons.[1,3,9]

GUILLAIN-BARRÉ SYNDROME MANAGEMENT

Acute Treatment

Treatment of GBS requires a multidisciplinary approach. On admission to the hospital, all GBS patients should be observed in an intermediate monitoring unit or in the intensive care unit. Serial pulmonary function tests, including forced vital capacity, maximum inspiratory pressure, and/or maximum expiratory pressure, are essential to evaluate for impending respiratory failure. These measures should be performed every 1 hours to 4 hours, depending on a patient's clinical status. Frequent blood pressure and heart rate measurements are necessary to evaluate for autonomic dysfunction, especially cardiovascular dysregulation, which can be present in approximately two-thirds of patients.[65] When stable, patients can be transferred to a medical unit with telemetry monitoring.

Intravenous immunoglobulin (IVIG) and plasma exchange are both effective in GBS, especially if IVIG is given within the first 2 weeks and plasma exchange is given within the first 4 weeks of disease onset.[66–68] There are no data suggesting that 1 treatment is superior to the other.[69] The choice of therapy should be based on the availability of IVIG or plasma exchange as well as the clinical characteristics of each patient.

IVIG can be administered 0.4 g/kg daily for 5 days or 1 g/kg daily for 2 days. The most common side effects include are headaches, aseptic meningitis, nausea, and

electrolyte abnormalities, such as hypocalcemia. Hemolytic anemia, renal dysfunction, and thrombotic events, such as deep vein thrombosis, pulmonary embolus, acute coronary syndrome, and cerebral ischemia, are among the possible complications. There may be an increased risk for serious complications in older patients receiving IVIG. Special attention should be given to the IVIG concentration and other solution additives and adequate hydration prior to IVIG infusions. Older patients require close clinical and laboratory monitoring for side effects during treatment and posttreatment.[70] Corticosteroid as a monotherapy is not effective in GBS.[71] Corticosteroids may be useful if aseptic meningitis develops as a side effect of IVIG.

In GBS, plasma exchange frequently is administered in 5 to 7 sessions over a course of 1 week to 2 weeks.[67] Plasma exchange combined with IVIG or corticosteroids does not provide better outcomes.[66,72] Administering plasma exchange immediately after IVIG may worsen the outcome because it risks removal of IVIG. Moreover, it is not considered cost effective.[73] Side effects of plasma exchange consist of, but are not limited to, allergic reaction, hypotension, hypocalcemia, and filter clotting. In addition, plasma exchange carries risks related to central catheter placement including infection, bleeding, and pneumothorax.[74] There are few data on the safety of plasma exchange in older patients. Because other medical comorbidities are more common in older GBS patients, the risk for complication related to plasma exchange likely is increased.[10,75,76]

During the acute hospitalization, all GBS patients should be engaged in physical and occupational therapy as early as possible to minimize complications related to prolonged immobility, such as deconditioning. Inpatient rehabilitation may be considered in the appropriate patient. Physical exercise is associated with long-term improved health outcomes in GBS patients. Cycling appears to be the most effective form of exercise.[77] A cautious approach to physical activity should be taken to avoid over exercise that can lead to extreme fatigue.[78] The long-term prevalence of health-related quality of life determinants, such as fatigue, pain, and depression, in GBS patients is not completely known.[79] Clinicians should be alert to these symptoms in the acute setting because of the impact on patient participation during rehabilitation. Pain symptoms should be treated aggressively, and gabapentin is suggested as the first-line treatment of choice for neuropathic pain.[80] Fatigue symptoms can be responsive to physical therapy, exercise, and cognitive behavioral therapy.[81]

Recurrent Guillain-Barré Syndrome and Treatment-Related Fluctuations

Typically, GBS is a monophasic disorder, and recurrent GBS is uncommon, occurring in approximately 5% to 6% of patients.[82–84] Among patients who have recurrent GBS, most patients have 1 recurrence and it is rare for a patient to have more than 2 recurrences.[83] Infection is the most common antecedent event prior to GBS recurrence and the interval between recurrence can range from months to many years.[83,84] Because of the rarity of recurrent GBS, a diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) should be considered in patients whose symptoms continue to worsen beyond 8 weeks or who have relapses within a few months after an episode of GBS. Like GBS, CIDP is an autoimmune demyelinating polyradiculoneuropathy, and the clinical symptoms and findings are similar to GBS.[85] In approximately 16% of CIDP patients, the initial neuropathic symptoms can be rapidly progressive within 4 weeks and may be difficult to distinguish from GBS.[86] The distinction, however, is important because CIDP is a chronic neuropathy with a relapsing course, and CIDP can respond to corticosteroid therapy unlike GBS.[87] Recurrent GBS and CIDP also should be distinguished from treatment-related fluctuations (TRFs), which is a worsening in GBS symptoms after an initial

improvement or stabilization following treatment with IVIG or plasma exchange.[88] TRFs typically occur within a few days after a patient has completed a course of therapy and can be seen in up to 10% of GBS patients.[88–90] Some patients may have 2 episodes of TRFs and in rare patients a third episode can occur.[89,90] Nearly all TRFs occur within 8 weeks from GBS symptom onset, and if a patient has another relapse past this time frame or has more than 3 relapses, a diagnosis of CIDP should be considered.[90,91] In most patients, the relapsing symptoms due to TRFs respond to another course of IVIG or plasma exchange.[88,89] The cause of TRFs is unknown. One hypothesis is that the duration of the treatment effect is shorter than the disease activity, and the immune modulating effect of the therapy dissipates before the autoimmune process resolves.[88]

Prognosis and Long-Term Symptoms

All patients gradually improve over weeks to months, with most improvement in motor function occurring during the first year.[92] A majority of patients can walk independently within 6 months from the time of symptom onset even in patients who required mechanical ventilation, but the time to recovery in older patients may be slower.[2,10,92] Although prognosis tend to be favorable overall, the mortality rate in GBS continues to range from 3% to 6% despite improvements in care in the intensive care setting.[93,94]

Early mobilization with physical and occupational therapy as early as possible is important to minimize complications related to prolonged immobility, such as deconditioning. Inpatient rehabilitation may be considered in the appropriate patient. Physical exercise after acute hospitalization is associated with long-term improved health outcomes in GBS patients. Cycling appears to be the most effective form of exercise.[77] A cautious approach to physical activity should be taken to avoid over exercise that can lead to extreme fatigue.[78]

In addition to motor impairment, many GBS patients have persistent symptoms of pain, fatigue, and mood disorders.[1,95,96] The long-term prevalence of these health-related quality of life determinants in GBS patients is not completely known.[79] Fatigue may be unrelated to persistent motor impairment or the severity of weakness during the acute phase of the GBS.[22,97,98] In these patients, a structured exercise program may be beneficial.[99,100] Chronic pain is another significant source of morbidity. Severe muscular, neuropathic, or joint pain can be present in up to one-third of patients.[22,30,98] Because GBS patients may experience several pain symptoms concurrently caused by different mechanisms, a multidisciplinary approach should be taken to treat the pain syndrome. Although physical therapy may improve pain, many patients require chronic neuropathic pain medications.[101] Depression and/or anxiety triggered by the acute paralytic disorder is not infrequent and may be exacerbated by pain.[22,102] In patients who have symptoms of depression and anxiety, referral to mental health care providers for psychosocial support or to psychiatry for pharmacologic treatment should be considered. Medications with dual effectiveness for both psychiatric and neuropathic pain symptoms should be considered in order to minimize polypharmacy in older patients.

SUMMARY

GBS is a complex autoimmune disorder that can affect multiple organ systems and cause persistent impairment, having an impact on an individual's functional independence. A correct diagnosis leading to early treatments and appropriate interventions can mitigate the risk for poor outcome in geriatric patients diagnosed with GBS.

CLINICS CARE POINTS

- Autonomic dysfunction is common in GBS and it is important to screen for symptoms of dysautonomia.
- Risk factors for respiratory insufficiency requiring mechanical ventilation include duration from symptom onset to hospitalization, facial and/or bulbar weakness, and severity of limb weakness.
- Bedside pulmonary function testing is recommended to screen for impending respiratory failure.
- Normal CSF protein does not exclude a diagnosis of GBS.
- An alternate diagnosis, such as an acute HIV infection, should be considered if there is CSF pleocytosis, especially when more than 50 cells/μL are present.
- IVIG and plasma exchange both are effective treatments of GBS.
- Corticosteroid is not an effective treatment of GBS.
- Sequential use of IVIG and plasma exchange is not recommended.

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DISCLOSURE

The authors have nothing to disclose.

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