

Guillain-Barré Syndrome

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ABSTRACT

Purpose of Review: This article reviews the current state of Guillain-Barré syndrome (GBS), including its clinical presentation, evaluation, pathophysiology, and treatment.

Recent Findings: GBS is an acute/subacute-onset polyradiculoneuropathy typically presenting with sensory symptoms and weakness over several days, often leading to quadriparesis. Approximately 70% of patients report a recent preceding upper or lower respiratory tract infection or gastrointestinal illness. Approximately 30% of patients require intubation and ventilation because of respiratory failure. Nerve conduction studies in the acute inflammatory demyelinating polyradiculoneuropathy (AIDP) form of GBS typically show evidence for a multifocal demyelinating process, including conduction block or temporal dispersion in motor nerves. Sural sparing is a common phenomenon when testing sensory nerves. CSF analysis commonly shows an elevated protein, but this elevation may not be present until the third week of the illness. Patients with AIDP are treated with best medical management and either IV immunoglobulin (IVIg) or plasma exchange.

Summary: GBS is a common form of acute quadriparesis; a high level of suspicion is needed for early diagnosis. With appropriate therapy, most patients make a very good to complete recovery.

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INTRODUCTION

The clinical presentation of Guillain-Barré syndrome (GBS) was first described by Landry in 1859. He reported five patients with an ascending post-infectious polyneuropathy and all the features of GBS except for areflexia. The illness has been recognized as GBS since 1916, when Guillain, Barré, and Strohl described two French soldiers who contracted the illness during World War I. They described the clinical features we now recognize, including elevation of CSF protein. For unclear reasons, Strohl's name was dropped from the term GBS beginning in the early 20th century.

Since the eradication of polio, GBS has become the most frequent cause of acute or subacute flaccid weakness worldwide.^{1,2} GBS typically occurs in patients who were previously healthy and not burdened by prior autoim-

mune or systemic illnesses. The incidence of GBS is 0.5 per 100,000 to 2 per 100,000, and it affects men slightly more than women.^{1,2} It occurs during all seasons. The risk of developing GBS over the lifetime of an individual has been estimated to be less than 1 in 1000.¹

GBS is an acute- or subacute-onset polyradiculoneuropathy that often follows an upper or lower respiratory illness or gastroenteritis by 10 to 14 days. Approximately 70% of patients can identify a preceding illness, although it is often benign and may be minimized or forgotten by the patient.^{1–3} Many infections have been associated with GBS, including Cytomegalovirus, *Mycoplasma pneumoniae*, Epstein-Barr virus, influenza A, *Haemophilus influenzae*, Enterovirus, and *Campylobacter jejuni*.^{4,5} In approximately 40% of patients, antibodies will be found

KEY POINTS

- Guillain-Barré syndrome is the most frequent cause of acute or subacute flaccid weakness worldwide.
- *Campylobacter jejuni* is the most commonly identified organism associated with Guillain-Barré syndrome.
- Approximately 50% of patients with Guillain-Barré syndrome achieve maximum weakness by 2 weeks, 80% by 3 weeks, and 90% by 4 weeks.
- Thirty percent of patients with Guillain-Barré syndrome develop respiratory failure from phrenic nerve disease, requiring intubation and ventilation.

against the *Campylobacter* antigen, thus making it the most commonly identified organism associated with GBS.¹⁻³ GBS appears to be more common after infection with the Zika virus, and the onset of weakness follows within a few days after infection.⁶ Other authors have challenged this relationship, citing the inability to satisfy strict criteria for GBS.⁷ Other less common precipitants are surgery, pregnancy, cancer, and vaccinations.

During the 1976 flu vaccination period with the influenza A/H1N1 antigen, the incidence of GBS rose 9.5-fold.⁸ Epidemiologic studies of GBS after flu vaccinations in subsequent years have found very small or no increase in GBS. Some studies have shown a protective effect from the flu vaccination in preventing GBS.⁹ When one considers the effectiveness of the flu vaccination in preventing disease (60% in most years) and the high incidence of the natural influenza infection (5%) for a worldwide population, the importance of the flu vaccination for public health reasons cannot be overstated.⁹

DIAGNOSIS

GBS evolves over days, often beginning with numbness in the lower limbs and weakness in the same distribution. The progression of symptoms, particularly weakness, can be rapid, resulting in quadriplegia within a few days. Approximately 50% of patients achieve maximum weakness by 2 weeks, 80% by 3 weeks, and 90% by 4 weeks.¹⁰ Progression beyond 4 weeks is unusual and should raise concern for other illnesses, particularly chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Neuropathic pain is observed in up to 66% of patients and is often localized to the lower back and thighs.¹¹ Determining the cause of the pain can be challenging

before the diagnosis of GBS is established. Since GBS is a polyradiculoneuropathy, weakness may be more proximal than distal, but in most patients, the weakness begins distally and spreads proximally. In rare cases, the weakness may be localized to the legs only (giving the appearance of paraplegia), but absent or reduced reflexes or electrodiagnostic findings in the arms betray upper limb involvement. The sensory examination may be normal or show minor deficiencies in vibration and proprioception, abnormalities expected in patients with large myelinated fiber involvement. Essentially all patients have areflexia or at least hyporeflexia at some time in the illness (**Case 4-1**). Approximately 50% of patients develop some degree of facial weakness, and other cranial nerves may be affected during the height of illness.^{3,10,12} Weakness attributed to cranial nerves includes ocular dysmotility, pupillary changes, and ptosis. Ophthalmoparesis has been reported in approximately 20% of patients with GBS.^{3,10,12} Thirty percent of patients with GBS develop respiratory failure from phrenic nerve disease, requiring intubation and ventilation.¹⁻³ Many progress to tracheostomy until the acute phase of the illness resolves. Autonomic involvement is common in GBS, with the most common manifestations being tachycardia, bradycardia, hypertension and hypotension, gastric hypomotility, and urinary retention.¹⁻³ Autonomic involvement may be the cause of death in some patients with GBS. **Table 4-2** lists diagnostic criteria for GBS.

Brighton Collaboration

In 2009 and 2011, the Brighton Collaboration published case definitions and guidelines for the collection, analysis, and presentation of immunization safety data for making the

Case 4-1

A 35-year-old man experienced 3 days of progressive numbness and weakness after exposure to his daughter's viral illness. Neurologic examination was notable for weakness of eye closure on both sides. He was weak proximally and distally in the upper extremities and proximally more than distally in the lower extremities. He had diffuse areflexia; plantar responses were mute. Sensation was decreased in the arms to the mid clavicle and in the legs to the groin.

Nerve conduction studies showed findings consistent with a multifocal demyelinating polyneuropathy (Table 4-1). The sural response was normal; the ulnar sensory response was absent. The fibular (peroneal) and tibial motor distal latencies were prolonged. Conduction slowing was recorded in all but one motor nerve. All F-wave latencies were markedly prolonged. Conduction block was recorded along all motor nerves (Figure 4-1).

TABLE 4-1 Nerve Conduction Study Results for the Patient in Case 4-1

Nerve and Site	Latency (Milliseconds)	Amplitude (Millivolts)	Conduction Velocity (Meters per Second)
Right median motor wrist	4.4	2.8 mV	
Right median motor elbow	10.3	1.7 mV ^a	41
Right ulnar motor wrist	3.2	9.8 mV	
Right ulnar motor below elbow	6.7	7.9 mV	59
Right ulnar motor above elbow	8.6	7.1 mV	47
Right tibial motor ankle	8.1	3.2 mV	
Right tibial motor popliteal fossa	18.1	1.4 mV ^a	39
Right fibular (peroneal) motor ankle	10.0	2.3 mV	
Right fibular (peroneal) motor below knee	20.7	0.9 mV ^a	29
Right fibular (peroneal) motor above knee	23.0	0.8 mV	38
Left fibular (peroneal) motor ankle	7.1	2.8 mV ^a	
Left fibular (peroneal) motor below knee	16.3	1.3 mV	33
Left fibular (peroneal) motor above knee	18.4	1.2 mV	43
Left tibial motor ankle	7.0	6.6 mV	
Left tibial motor popliteal fossa	17.4	1.8 mV ^a	37
Right ulnar sensory	No response	No response	
Right sural sensory	3.1	29 μ V	

^a Conduction block observed.

The patient was diagnosed as having acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and treated with a 5-day course of IV immunoglobulin (IVIg). Lumbar puncture was normal except for a CSF protein of 80 mg/dL. His condition was complicated by burning pain in the hips and thighs, for which he was treated with gabapentin and opioids. He was transferred to rehabilitation after 9 days in the hospital.

When evaluated 2 months after hospitalization, the patient had regained most of his strength. He admitted to occasional tingling in the feet. He was able to return to his work as an airplane mechanic.

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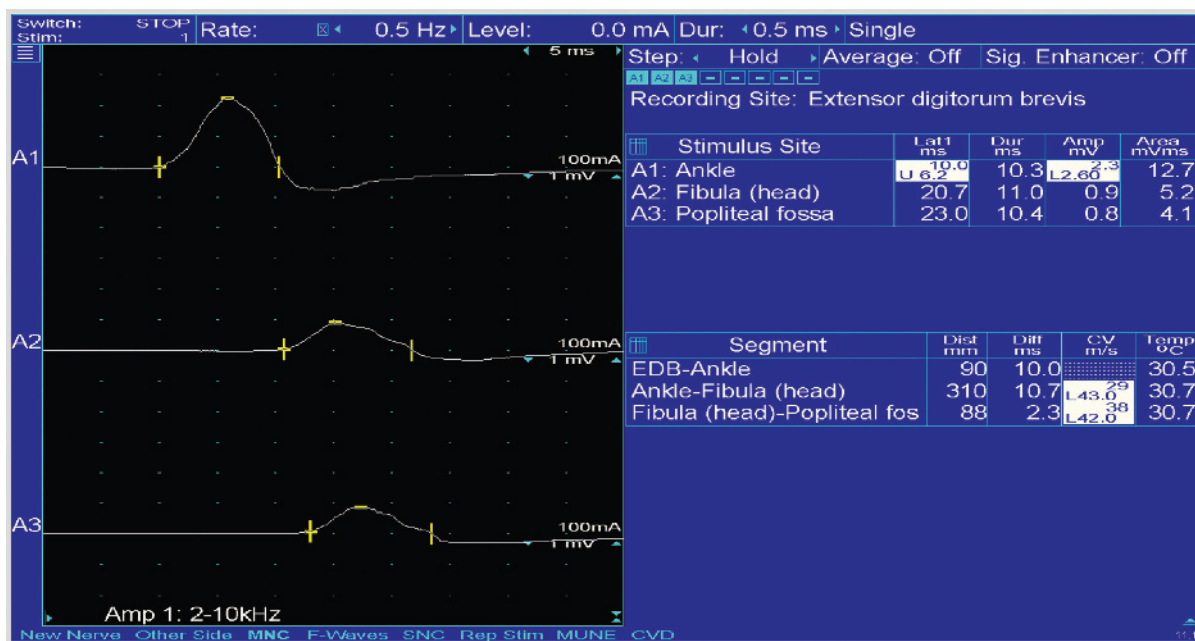


FIGURE 4-1 Fibular (peroneal) motor nerve conduction study of the patient in Case 4-1 recorded from the extensor digitorum brevis (EDB) muscle showing a markedly prolonged distal latency, conduction block below and above the knee, and slowing of conduction velocity.

Neurologic examination revealed normal strength in the upper extremities and mild weakness of hip flexion and ankle flexion and extension. Muscle stretch reflexes were absent. Sensation was normal to pinprick and light touch. Routine gait was normal.

When assessed 5 months later, he had made a complete recovery except for mild leg weakness and tingling in the feet. On examination, facial strength was normal. Strength was normal in the upper extremities and mildly reduced at the hips and ankles. Reflexes were 1+ in the upper extremities, 2+ at the knees, and 1+ at the ankles. Tandem gait was performed without difficulty.

Comment. The patient achieved an excellent recovery 7 months after the onset of AIDP. At onset, he showed both proximal and distal weakness in the lower extremities, a clinical feature of a polyradiculoneuropathy. He regained almost all his strength, sensation, reflexes, and gait. He continued to have reduced reflexes at the ankles. Over time, he is likely to make a complete recovery.

diagnosis of GBS.¹³ For GBS and Miller Fisher syndrome (also referred to by some neurologists as Fisher syndrome), the collaboration developed three levels of diagnostic certainty useful to determine the likelihood of the diagnosis. Achieving level 1 is the strongest argument for the diagnosis of GBS and level 3 the weakest (Table 4-3). Clinical case definitions have also been created for three levels of certainty for

Miller Fisher syndrome. Although not developed to assess the certainty of GBS in patients who have not received a recent vaccination, the criteria create a yardstick for determining the likelihood of GBS. Not all patients initially thought to have GBS have the diagnosis confirmed. Asbury and Cornblath¹⁰ have published features that raise doubt or eliminate the diagnosis of GBS (Table 4-4).

TABLE 4-2 Diagnostic Criteria for Guillain-Barré Syndrome^a

- ▶ Progressive weakness in the legs and arms^b
- ▶ Areflexia or hyporeflexia^b
- ▶ Progression of symptoms lasting up to 4 weeks
- ▶ Relative symmetry of weakness and sensory loss
- ▶ Sensory symptoms and signs, if present, less impressive than weakness
- ▶ Pain is common, often in the back and legs
- ▶ Autonomic dysfunction common
- ▶ Absence of fever
- ▶ Albuminocytologic dissociation in the CSF by 3 weeks
- ▶ Postgadolinium enhancement of peripheral nerve roots and cauda equina

^a Data from Willison HJ, et al, *Lancet*,¹ [thelancet.com/journals/lancet/article/PIIS0140-6736\(16\)00339-1/fulltext](http://thelancet.com/journals/lancet/article/PIIS0140-6736(16)00339-1/fulltext); Esposito S, Longo MR, *Autoimmun Rev*,² sciencedirect.com/science/article/pii/S1568997216302178; and Asbury AK, Cornblath DR, *Ann Neurol*,¹⁰ onlinelibrary.wiley.com/doi/10.1002/ana.410270707/abstract.

^b Required for the diagnosis.

Variants of Guillain-Barré Syndrome

Since the initial reports of GBS, variants have been identified that differ from the AIDP presentation of GBS that is the most common form of the illness. Variants of GBS include acute motor axonal neuropathy (AMAN), acute motor-sensory axonal neuropathy (AMSAN), Miller Fisher syndrome, a paraplegic form of GBS, and the pharyngeal-cervical-brachial presentation. Rare and poorly defined forms of GBS are acute autonomic neuropathy

and acute sensory neuropathies that follow viral illnesses.

AMAN is more common in children during the summer and much more common in northern China than the United States, Europe, and other areas of Asia.¹⁴ The illness is purely motor without sensory symptoms and signs. Nerve conduction studies show reduced compound muscle action potential (CMAP) amplitudes, normal latencies and conduction velocities, and normal sensory studies. AMSAN is similar to AMAN except for the addition of sensory involvement.¹⁵ It differs greatly from AMAN in the later age of onset, involvement of sensory fibers clinically and on nerve conduction studies, broader geographic distribution, a more protracted course, and slower and incomplete improvement (Case 4-2).¹⁵

Miller Fisher syndrome is classified as an acute or subacute demyelinating polyradiculoneuropathy, but its clinical presentation differs markedly from typical GBS.¹⁻³ Patients with Miller Fisher syndrome present with the triad of ophthalmoparesis or ophthalmoplegia, areflexia, and ataxia. Some patients have lower brainstem involvement, such as facial and pharyngeal weakness. The illness is often grouped with Bickerstaff brainstem encephalitis, which has a similar presentation plus usually an encephalopathy and corticospinal tract dysfunction.¹⁶ Patients with Bickerstaff brainstem encephalitis commonly have abnormal imaging studies of the brainstem, as expected in a brainstem encephalitis.¹⁶ Patients with either condition often have anti-GQ1b antibodies found in their serum. The prognosis in both Miller Fisher syndrome and Bickerstaff brainstem encephalitis is favorable. Most patients improve within 1 to 2 months and make a complete recovery in 6 months without specific treatment.

KEY POINT

- Patients with Miller Fisher syndrome present with the triad of ophthalmoparesis or ophthalmoplegia, areflexia, and ataxia.

TABLE 4-3 Brighton Collaboration Diagnostic Criteria for Guillain-Barré Syndrome^a**► Level 1 of Diagnostic Certainty**

Bilateral *AND* flaccid weakness of the limbs

AND

Decreased or absent deep tendon reflexes in weak limbs

AND

Monophasic illness pattern *AND* interval between onset and nadir of weakness between 12 hours and 28 days *AND* subsequent clinical plateau

AND

Electrophysiologic findings consistent with Guillain-Barré syndrome (GBS)

AND

Albuminocytologic dissociation (ie, elevation of CSF protein level above laboratory normal value and CSF total white blood cell count less than 50 cells/ μ L)

AND

Absence of an identified alternative diagnosis for weakness

► Level 2 of Diagnostic Certainty

Bilateral *AND* flaccid weakness of the limbs

AND

Decreased or absent deep tendon reflexes in weak limbs

AND

Monophasic illness pattern *AND* interval between onset and nadir of weakness between 12 hours and 28 days *AND* subsequent clinical plateau

AND

CSF total white blood cell count less than 50 cells/ μ L (with or without CSF protein elevation above laboratory normal value)

OR

If CSF not collected or results not available, electrophysiologic studies consistent with GBS

AND

Absence of identified alternative diagnosis for weakness

► Level 3 of Diagnostic Certainty

Bilateral *AND* flaccid weakness of the limbs

AND

Decreased or absent deep tendon reflexes in weak limbs

AND

Monophasic illness pattern *AND* interval between onset and nadir of weakness between 12 hours and 28 days *AND* subsequent clinical plateau

AND

Absence of identified alternative diagnosis for weakness

CSF = cerebrospinal fluid.

^a Modified with permission from Sejvar JJ, et al, *Vaccine*.¹³ © 2010 Elsevier. sciencedirect.com/science/article/pii/S0264410X1000798X.

TABLE 4-4 Features Casting Doubt or Eliminating a Diagnosis of Guillain-Barré Syndrome^a

► **Features That Cast Doubt on a Diagnosis of Guillain-Barré Syndrome**

- Marked persistent asymmetry of weakness
- Bowel or bladder dysfunction at onset
- Presence of greater than 50 polymorphonuclear leukocytes in CSF
- Sharp sensory level
- Severe pulmonary dysfunction with little or no limb weakness at onset
- Fever at onset
- Slow progression of weakness more than 4 weeks

► **Features That Eliminate the Diagnosis of Guillain-Barré Syndrome**

- Current history of hexacarbon abuse
- Abnormal porphyrin metabolism, particularly acute intermittent porphyria
- Recent diphtheric infection
- Exposure to lead
- A purely sensory presentation

CSF = cerebrospinal fluid.

^a Data from Esposito S, Longo MR, Autoimmun Rev,² *sciencedirect.com/science/article/pii/S1568997216302178*, and Asbury AK, Cornblath DR, Ann Neurol,¹⁰ *onlinelibrary.wiley.com/doi/10.1002/ana.410270707/abstract*.

Case 4-2

A 44-year-old man was in good health until he developed an eye infection. Several days later, he experienced numbness in the lower extremities that quickly progressed to the upper extremities. This was followed by weakness and eventually quadriplegia. Lumbar puncture revealed an elevated protein. Nerve conduction studies showed evidence for a severe motor greater than sensory axon loss neuropathy. He was diagnosed as having the acute motor-sensory axonal neuropathy (AMSAN) form of Guillain-Barré syndrome (GBS). Over several days, he developed respiratory failure requiring intubation, subsequent tracheostomy, and feeding tube placement for nutrition. Hospitalization was complicated by pneumonia and bilateral lower extremity deep venous thromboses. He was treated with plasma exchange. He was eventually extubated and transferred to rehabilitation.

When assessed 4 months after the onset of the illness, his primary symptom was severe neuropathic pain in the feet. Examination showed bifacial weakness, mild weakness proximally in the arms and legs, and little movement of the toes and ankles. He was areflexic. Light touch was diminished from the toes to the mid shins. He could not tolerate stroking the bottom of his foot or the application of the tuning fork to his toes. He could walk with a walker. When reevaluated 7 months later, the pain in his feet was improved on a regimen of methadone, pregabalin, and α -lipoic acid. There was no improvement in facial motor function. He showed improved strength at the ankles bilaterally. He was able to return to work as an electrician wearing ankle-foot orthoses and boots to stabilize his ankles.

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KEY POINTS

- No biomarkers exist in the blood, urine, or CSF that confirm the diagnosis of Guillain-Barré syndrome.
- In the first few days after onset of Guillain-Barré syndrome, nerve conduction studies may be normal or only show subtle changes of demyelination, such as prolonged or absent F waves and H reflexes and patchy changes in distal latencies.

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Comment. This case demonstrates the AMSAN form of GBS. Patients are often left with severe deficits, particularly in distal strength, but this patient also showed bifacial weakness. IV immunoglobulin (IVIg) was not prescribed because of deep vein thromboses, a relative contraindication for its use. The patient also demonstrated the persistence of neuropathic pain in GBS, often requiring several agents for management. The presence of severe weakness approximately 1 year after the onset of illness portends the likelihood of significant permanent ankle and bifacial weakness.

Laboratory Testing

At present, no biomarkers exist in the blood, urine, or CSF that confirm the diagnosis of GBS. Most patients with GBS will have an elevated CSF protein, but this laboratory finding may not be present until 3 weeks after the onset of the illness. A pleocytosis (greater than 5 white blood cells) is usually not present in patients with GBS, but approximately 15% of patients have a CSF white blood cell count of 10 to 50 cells per high-power field.²

If a pleocytosis is present, it raises suspicion for an infectious process such as human immunodeficiency virus (HIV), cytomegalovirus, or Lyme disease; sarcoidosis; or carcinomatous or lymphomatous meningitis. For this reason, any patient with presumed GBS and an elevated CSF white blood cell count must be assessed for an infectious or neoplastic etiology. It has become commonplace for neurologists to omit performing a CSF analysis when the clinical presentation and electrophysiology strongly support the diagnosis of GBS. Although an increasingly accepted practice, it lessens the certainty of the diagnosis and opens the possibility of misdiagnosis.

Electrodiagnosis

Nerve conduction studies and EMG are performed in patients with GBS to support the diagnosis and to eliminate mimicking illnesses. Nerve conduction studies are not required to diagnose

GBS but are necessary to differentiate AIDP from AMAN and AMSAN and consequently provide data for prognostic determination.¹⁻³ In the first few days of the illness, nerve conduction studies may be normal or only show subtle changes of demyelination, such as prolonged or absent F waves and H reflexes, and patchy changes in distal latencies in patients with AIDP.^{17,18} As the disease evolves, the classic features of a multifocal demyelinating polyradiculoneuropathy evolve, showing conduction block, temporal dispersion, and prolonged distal and F-wave latencies.¹⁷ Nerve conduction slowing, a feature many physicians associate with GBS, may not be recorded until several weeks into the illness.¹⁷ Sensory nerve conduction studies may show a characteristic sural nerve sparing, a term used to describe the presence of normal sural responses in the setting of abnormal upper limb sensory results.^{17,18} When noted, this finding lends strong consideration for the diagnosis of GBS in the proper clinical setting, as sural sparing is not commonly observed in length-dependent neuropathies. The degree of prolongation of distal latencies and F waves, the severity of slowing of conduction velocity, and the amount of conduction block and temporal dispersion necessary to verify a demyelinating neuropathy differ among laboratories and electromyographers. The needle examination in GBS is often deferred until the fourth week of the

illness or later, when the likelihood of finding active denervation is the strongest. In this setting, one would find positive sharp waves, fibrillation potentials, and reduced recruitment of motor units of normal amplitude and duration. Abnormalities might be found in proximal and distal muscles and in the paraspinous muscles since GBS is a multifocal polyradiculoneuropathy. Features of chronic denervation and reinnervation will be recorded months after the onset of the illness in clinically weak muscles. The results of nerve conduction studies can be used to predict prognosis. Markedly reduced CMAP amplitudes are associated with a protracted hospitalization and recovery.

A confounding problem when performing serial nerve conduction studies in patients with GBS is the difficulty in determining a pattern of improvement or worsening from one study to the next.^{1,18} The electrophysiologic characteristics and pattern can change in an individual. What appears to be AIDP in the initial study may evolve into a pattern more consistent with AMAN as conduction block and temporal dispersion are reversed by myelin repair and secondary axonal loss becomes the predominant pathology. Compounding the problem is the difficulty of performing nerve conduction studies in patients who are critically ill in the intensive care unit (ICU) setting, where warm temperatures can be challenging to maintain and electrical and mechanical interference may preclude a thorough and interpretable study. Comparing a follow-up study performed in the comfortable setting of a warm EMG laboratory to the results from a prior study recorded in a cold ICU can be frustrating.

Imaging Studies

In recent years, MRI scanning of the brain and spine has been commonly

performed to assess for gadolinium enhancement of nerve roots and to eliminate other causes of quadriplegia, particularly transverse myelitis, subacute compressive myelopathy, and infiltrating illnesses of the roots and the spinal cord. As many as 95% of children with GBS show enhancement of the lumbar roots secondary to the inflammatory process; this finding adds confidence to the diagnosis of GBS.^{19,20}

DISORDERS MIMICKING GULLAIN-BARRÉ SYNDROME

Many disorders may appear to resemble GBS in the first few days of presentation and should be considered in the differential diagnosis of GBS (Table 4-5).^{10,21,22} The most common of the group are critical illness neuropathy and myopathy, tick paralysis, acute intermittent porphyria, and HIV infection. Consideration for GBS often arises in patients who have been critically ill with sepsis for several days to weeks, are quadriplegic, and are difficult to wean from the ventilator.²³ The presence of fever and multiorgan failure favors critical illness neuropathy. Most of these patients eventually are diagnosed with critical illness neuropathy or myopathy.²³

Tick paralysis is seen in children during tick season.²⁴ Differentiating it from GBS are the presence of diplopia, pupillary changes (dilated pupils), the lack of sensory symptoms and sensory examination findings, and normal CSF results.²⁴ On nerve conduction studies, children with tick paralysis have low CMAP potentials and normal sensory results. The tick is commonly located on the nape of the neck or scalp. Its removal results in rapid improvement of weakness.

Acute intermittent porphyria may closely resemble GBS, particularly if autonomic dysfunction is present.²⁵ Differentiating points are the presence

KEY POINT

- Markedly reduced compound muscle action potential amplitudes are associated with a protracted hospitalization and recovery.

KEY POINTS

- Guillain-Barré syndrome is more common in patients with human immunodeficiency virus and may occur before or at the time of seroconversion.
- Patients with botulism often have ptosis, dilated and unresponsive pupils, and paralyzed extraocular movements, findings rare in Guillain-Barré syndrome.

TABLE 4-5 Disorders That Mimic Guillain-Barré Syndrome^a

- ▶ Critical illness neuropathy and myopathy
- ▶ Neurotoxin poisoning: tick paralysis, snake bite, marine toxins, buckthorn, pyrinuron, organophosphates, *n*-hexane
- ▶ Acute intermittent porphyria, hepatic porphyrias
- ▶ Heavy metal poisoning, particularly arsenic
- ▶ Infectious: poliomyelitis, West Nile encephalomyelitis, human immunodeficiency virus (HIV), cytomegalovirus, Lyme disease, diphtheria, botulism
- ▶ Myasthenia gravis
- ▶ Amyotrophic lateral sclerosis
- ▶ Transverse myelitis
- ▶ Wernicke encephalopathy
- ▶ Vitamin B₁₂ deficiency (severe)
- ▶ Acute/subacute compressive myelopathy
- ▶ Metabolic abnormalities: hypermagnesemia, hypophosphatemia
- ▶ Drug adverse effect: amiodarone, cytarabine, streptokinase, suramin
- ▶ Vasculitis

^a Data from Asbury AK, Cornblath DR, *Ann Neurol*,¹⁰ onlinelibrary.wiley.com/doi/10.1002/ana.410270707/abstract; Sciacca G, et al, *Neurol Sci*,²¹ link.springer.com/article/10.1007/s10072-015-2450-4?no-access=true; and Levin KH, *Neurologist*,²² journals.lww.com/theneurologist/Abstract/2004/03000/Variants_and_Mimics_of_Guillain-Barre_Syndrome.1.aspx.

of psychiatric disease, prior attacks, and a potential precipitating medication in acute intermittent porphyria.

GBS is more common in patients with HIV and may occur before or at

the time of seroconversion.²⁶ Nerve conduction studies are identical to those in non-HIV-associated GBS. A helpful differentiating point is the presence of a pleocytosis on CSF analysis in patients with HIV.^{1-3,26}

Acute arsenic poisoning may resemble GBS except for the multiorgan involvement that typically is associated with arsenic intoxication.²⁷ The preceding nausea and vomiting of acute arsenic poisoning may be misinterpreted as a gastroenteritis preceding GBS and may strengthen the impression that the patient has GBS.

Poliomyelitis is usually seen in the setting of prior meningitis, and the weakness is usually asymmetric and associated with pain. The patient with polio should not have sensory symptoms or signs. In most patients, it should not be difficult to exclude myasthenia gravis, an acute presentation of amyotrophic lateral sclerosis, or a cervical form of transverse myelitis from GBS. Patients with West Nile encephalomyelitis typically have a fever, rash, asymmetric weakness, back pain, normal sensation, and a CSF pleocytosis.²⁸

Botulism begins after exposure to tainted food or in patients with infected wounds.²⁹ Profound autonomic dysfunction in patients who are quadriplegic is often the key to diagnosis (dilated pupils, blurring of vision, urinary retention, constipation). Patients with botulism often have ptosis, dilated and unresponsive pupils, and paralyzed extraocular movements, findings rare in GBS.²⁹

IMMUNOPATHOGENESIS

Until the clinical presentations of AMAN and AMSAN were reported, GBS was considered a multifocal demyelinating polyneuropathy that led to secondary axonal loss. Recent data suggest that Guillain-Barré syndrome is primarily an antibody-mediated disorder rather than

a T-cell-mediated disorder.^{1-3,30} With the description of AMAN came the realization that the axons could be the primary focus of injury by the autoimmune process. Antibody biomarkers have been identified against neuronal membrane gangliosides GM1 and GD1a in patients with AMAN.² The antibodies arise as a result of molecular mimicry between the lipooligosaccharides of infective organisms and the surface molecules on the motor axons. IgG1 and IgG3 subclass immunoglobulins are thought to bind with GM1 and GD1a gangliosides and to induce axon injury by complement fixation, attracting macrophages and depositing membrane attack complexes on the axolemma.² Rapid repair of nodal and paranodal conduction block has been used to explain the quick recovery of children with AMAN.

Despite our understanding of the pathology and electrodiagnosis of AIDP and its much greater prevalence than AMAN and AMSAN, the immunologic sequence causing AIDP is less understood. Since a wide range of viruses and bacterial agents can incite an antibody in AIDP, it has been difficult to find a common antigenic stimulus for the illness. Equally difficult has been the identification of specific antibody biomarkers in myelin.

MANAGEMENT

Comprehensive treatment of GBS requires close attention to general medical care and immunologic treatment.^{1,2} Early in the illness, patients must be monitored carefully for respiratory failure, cardiac arrhythmias, dysphagia, ileus, and potential hypotension and hypertension. Frequent measurements of respiratory reserve, such as forced vital capacity and maximal expiratory pressure, should be ordered, particularly for patients who are markedly weak. It is often

advisable to admit the patient to the ICU prematurely if one suspects a high probability for respiratory failure. This is especially true when the patient is admitted to a regular hospital floor where nursing care may be less available, particularly at night. Prophylaxis for deep vein thrombosis and decubitus ulcers is important. Surveillance for pulmonary and urinary bladder infections prevents further complications. Autonomic dysfunction may cause bladder retention and constipation. Early physical therapy and occupational therapy are advisable to maintain range of motion, prevent contractures, and begin the rehabilitation process. Pain should be managed using pharmacologic agents that are effective for neuropathic pain.¹¹ Popular agents are gabapentin, pregabalin, and low doses of tricyclic antidepressants. Opioids can be used for short-term treatment of pain but should be avoided for long-term pain management.

Evidence-based research supports the use of immunotherapy for GBS; proven therapies are IV immunoglobulin (IVIg) and plasma exchange, which have been shown to be equally efficacious in the management of GBS.³¹⁻³⁵ One or the other should be started as soon as possible once the diagnosis of GBS has been considered. A common dosing schedule for IVIg is 0.4 g/kg/d for 5 days. It is not known whether this treatment schedule is superior to administering the same total dose over 2 or 3 days. As early as the mid-1980s, plasma exchange was shown to be superior to best medical management of GBS.³¹ For safety reasons, to prevent major shifts in fluid balance, it is advisable to perform plasma exchange every other day. Over time, IVIg has become the preferred treatment for GBS because of its widespread availability, fewer

KEY POINTS

- Early in the illness, patients with Guillain-Barré syndrome must be monitored carefully for respiratory failure, cardiac arrhythmias, dysphagia, and potential hypotension and hypertension.
- It is often advisable to admit patients with Guillain-Barré syndrome to the intensive care unit prematurely if one suspects a high probability for respiratory failure.
- Intravenous immunoglobulin and plasma exchange have been shown to be equally efficacious as immunotherapy for the treatment of Guillain-Barré syndrome.

KEY POINT

■ Over time, IV immunoglobulin has become the preferred treatment for Guillain-Barré syndrome because of its widespread availability, fewer associated complications, peripheral vein access, and convenience of infusing at night and on weekends.

associated complications, peripheral vein access, and convenience of infusing at night and on weekends. In most medical centers, the cost of IVIg and plasma exchange is comparable. No published evidence suggests that a second course of IVIg is superior to a single course. In one large study, plasma exchange followed by IVIg was not shown to be superior to either treatment alone.³⁵

Oral and IV corticosteroids have not shown efficacy in the treatment of GBS used alone or in combination with IVIg or plasma exchange.³⁶ Weak evidence exists that patients with GBS treated with steroids fared worse than those receiving best medical management.³⁶ **Table 4-6** summarizes the management approach for GBS, including best medical care and immunotherapy.

Treatment-related Fluctuations

Treatment-related fluctuations are defined as worsening of weakness after an initial improvement or after stabilization following treatment with IVIg or plasma exchange.³⁷ Treatment-related fluctuations occur in approximately 10% of patients with GBS.³⁷ They usually take place within the first 2 months after treatment is initiated and are thought to relate to continuation of an active immune attack on the peripheral nervous system.³⁷ Treatment-related fluctuations are usually treated with another course of IVIg or plasma exchange, and the treatment is often beneficial.

Approximately 5% to 16% of patients with CIDP present acutely,³⁷ and the worsening after initial treatment and improvement is considered a treatment-related fluctuation. The initial phase of the illness is almost always diagnosed as GBS. Over time, the question of CIDP arises if the patient has a long protracted course of weakness, particularly if progression occurs after the first 4 weeks. If

TABLE 4-6 Management of Guillain-Barré Syndrome^a

- ▶ Frequent monitoring of respiratory function
- ▶ Monitoring for autonomic dysfunction
- ▶ Deep venous thrombosis prophylaxis
- ▶ Treatment of constipation/ileus
- ▶ Nonopioid management of neuropathic pain
- ▶ Psychosocial support
- ▶ Physical, occupational, and speech therapy
- ▶ Immunologic treatment with IV immunoglobulin (IVIg) or plasma exchange
- ▶ Corticosteroid treatment not indicated

^a Data from Willison HJ, et al, *Lancet*,¹ [thelancet.com/journals/lancet/article/PIIS0140-6736\(16\)00339-1/fulltext](http://thelancet.com/journals/lancet/article/PIIS0140-6736(16)00339-1/fulltext); Esposito S, Longo MR, *Autoimmune Rev*,² sciencedirect.com/science/article/pii/S1568997216302178; and van den Berg B, et al, *Nat Rev Neurol*,³ nature.com/nrneuro/journal/v10/n8/full/nrneuro.2014.121.html.

the patient experiences more than one treatment-related fluctuation, and particularly if it occurs 2 months or more after the onset of the illness, then the diagnosis of CIDP becomes a strong consideration.³⁷

PROGNOSIS

The prognosis for most patients with GBS is for good to excellent recovery. Approximately 87% experience full recovery or minor deficits.³⁸ Some patients do not regain full strength in the hands or movement of the ankles. Residual bilateral footdrop is a not uncommon sequela of GBS requiring ankle-foot orthoses and light boots to promote ambulation. Numbness and

pain are also common residuals. Many patients experiencing a relatively complete recovery from GBS describe persistent fatigue, particularly in the afternoon and evening.^{39,40} Most of the improvement in GBS occurs within the first year, but patients may continue to improve for up to 3 years or longer.^{1,2} Features of GBS that predict a poor prognosis are late age of onset, preceding diarrhea or *C. jejuni* infection, the need for intubation and ventilator support within the first week of illness, and severe weakness.¹⁻³ Mortality in GBS is 3% to 7% and is most often attributable to respiratory failure, infection, or uncontrollable autonomic dysfunction.¹⁻³

CONCLUSION

GBS has become the most frequent cause of acute or subacute flaccid weakness worldwide.^{1,2} The illness presents with ascending weakness and areflexia over several days to weeks. The diagnosis requires high diagnostic suspicion and is usually substantiated by nerve conduction study abnormalities and elevated CSF protein. The illness is treated with IVIg or plasma exchange. Patients with GBS should receive best medical management, including physical and occupational therapy, and should be watched closely for respiratory decompensation, deep venous thromboses, and decubitus ulcers. Most patients with GBS recover, many making a complete recovery.

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KEY POINT

- Features of Guillain-Barré syndrome that predict a poor prognosis are late age of onset, preceding diarrhea or *Campylobacter jejuni* infection, the need for intubation and ventilator support within the first week of illness, and severe weakness.

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