GUILLEN-BARRÉ SYNDROME: CAUSES, EPIDEMIOLOGY, IMMUNOPATHOGENIC MECHANISMS, DIAGNOSIS, EVALUATION, DIFFERENTIAL AND TREATMENT

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SUMMARY

Introduction: Guillain-Barré syndrome is an uncommon, yet potentially fatal, immune-mediated disease affecting peripheral nerves and nerve roots that is commonly generated by infections. Recent studies have shown a strong relationship between Guillain-Barré syndrome and SARS-CoV-2, making SARS-CoV-2 a potential trigger for GBS.

Objective: to detail the current information related to Guillain-Barré syndrome, causes, epidemiology, immunopathogenic mechanisms, diagnosis, evaluation, differential and treatment.

Methodology: a total of 42 articles were analyzed in this review, including review and original articles, as well as clinical cases, of which 33 bibliographies were used because the other articles were not relevant for this study. The sources of information were PubMed, Google Scholar and Cochrane; the terms used to search for information in Spanish, Portuguese and English were: Guillain-Barré, peripheral nerves, SARS-CoV-2, nerve roots, epidemics, inflammatory disease of the peripheral nervous system.

Results: Approximately 70% of affected individuals show signs of previous illness 1 to 6 weeks before the debut of Guillain-Barré syndrome. GBS post influenza infection is up to 7 times more likely than post-vaccine GBS. The studies reviewed indicate a strong relationship between Guillain-Barré syndrome and SARS-CoV-2, the latter being a potential trigger for GBS. Cerebrospinal fluid (CSF) shows a classic pattern of albuminocytologic dissociation. Generally, most individuals affected with GBS present good prognosis, and about 85% of those present independent ambulation with recovery; however, significant morbidity is present.
Conclusions: Guillain-Barré syndrome can become difficult to diagnose and treat, as its clinical manifestations are heterogeneous. Treatment of GBS can be challenging during periods of infectious outbreaks, as seen in the Zika virus and SARS-CoV-2 epidemics. Since not all individuals affected by this syndrome are labeled as positive for antiganglioside antibodies, more quality research is needed to clarify the role of antiganglioside antibodies in Guillain-Barré syndrome as a secondary origin or phenomenon. In proportion to the evolution of scientific information and knowledge of Guillain-Barré syndrome, the diagnosis, management, and prognosis are improving all the time.

KEYWORDS: guillain-barré, GBS, neuropathy, immune-mediated, postinfectious.

INTRODUCTION

Guillain-Barré syndrome (GBS) was first discovered more than 100 years ago. Among the advances of the past century have been the recognition of the spectrum of presentations, the advancement of diagnostic modalities, the development of randomized treatment trials to improve outcomes, research into the immune-mediated pathophysiology of the disease, and prognostic models. As a result of the untreated morbidity of this syndrome, all physicians need to increase their knowledge of this rare disease(1-4).

Guillain-Barré syndrome is an uncommon, yet potentially fatal, immune-mediated disease of the peripheral nerves and nerve roots that is commonly caused by infections. It is therefore of utmost importance to understand that the incidence of GBS can increase in infectious disease outbreaks, as presented in the Zika virus epidemics in 2013 in French Polynesia and later in 2015 in Latin America. Recently analyzed studies present a strong relationship between Guillain-Barré syndrome and SARS-CoV-2, thus SARS-CoV-2 is potentially triggering GBS(5,6).

METHODOLOGY

A total of 42 articles were analyzed in this review, including review and original articles, as well as cases and clinical trials, of which 33 bibliographies were used because the information collected was not important enough to be included in this study. The sources of information were Cochrane, PubMed, and Google Scholar; the terms used to search for information in Spanish, Portuguese, and English were: Guillain-Barré, peripheral nerves, SARS-CoV-2, nerve roots, epidemics, inflammatory disease of the peripheral nervous system.

The choice of bibliography exposes elements related to Guillain-Barré syndrome; causes, epidemiology, immunopathogenic mechanisms, diagnosis, evaluation, differential, and treatment.

DEVELOPMENT

Causes

Guillain-Barré syndrome and its variants are considered postinfectious immune-mediated neuropathies, and studies in animal specimens suggest the fundamental role of molecular mimicry. In gastrointestinal infections caused by Campylobacter jejuni, a lipooligosaccharide found in the external membrane of the bacterium is very similar to the gangliosides that are part of the structure of the peripheral nerves; which suggests that when facing an infection the immune system can generate a response or cross-reaction in the nerves of the affected individual. Many infections have been correlated with this syndrome, being more frequent its relation with pulmonary and gastrointestinal infections. Approximately 70% of affected individuals show signs of previous illness 1 to 6 weeks prior to the debut of Guillain-Barré syndrome. In the Zika virus outbreak, several cases identified as GBS occurred. Case studies in particular describe several other possible etiologies that may be linked to the origin of Guillain-Barré syndrome such as medications and surgeries(2,7,8).

In 1976, post-influenza vaccination specifically against the influenza A/H1N1 antigen led to an adequately recorded increase in the incidence of GBS, however, supplemental surveillance data from influenza vaccines in consecutive years have reported only one extra case of GBS per million vaccinations. Shortly thereafter, scientific research determined that developing GBS post-influenza infection is up to 7 times more likely than developing GBS post-vaccination. Multiple trials and reviewed studies indicate a strong relationship between Guillain-Barré syndrome and SARS-CoV-2, the latter being a potential trigger for GBS(5,6,9-11).

Epidemiology

GBS is an inflammatory disease of the peripheral nervous system and is the most common cause of acute flaccid paralysis, with an annual incidence of about 1-2 per 100,000 person-years(5).

Males have a higher incidence than females. Other bibliographies report an incidence of 0.4 to 2 per 100,000, demonstrating that it is an infrequent pathology and that this syndrome has notable effects on the health system, especially on the cost of medical care, since the monetary value for an individual with GBS can be high. Annually, it is assumed that 100,000 individuals will contract GBS worldwide(2,12,13).

Immunopathogenic mechanisms

There are reports of previous infections in about 70% of individuals with Guillain-Barré syndrome, suggesting that molecular mimicry is fundamental in the understanding of the pathology, especially the axonal variant. As previously mentioned, Campylobacter jejuni lipooligosaccharide is very similar to gangliosides of peripheral nerve membranes. Clinical trials have shown that passive immunization of mammalian lagomorphs with these ganglioside-identical lipooligosaccharides have resulted in similar clinical syndromes of flaccid tetraplegia, which is very similar to the acute motor axonal neuropathy variant of GBS. Research has also shown that antibodies to gangliosides target different peripheral nerves. Anti-GD1a antibodies bind to paranodal myelin, nodes of Ranvier and neuromuscular junction. GM1 and GQ1B antibodies bind to a peripheral nerve or
neuromuscular junction. Possibly the different peripheral nerve targets play a role in the heterogeneity of the clinical manifestation of the disease. The complement cascade is activated and has a fundamental role in the pathogenesis of GBS(2,8,14,15).

Some gangliosides are probably related to certain specific manifestations, as is the case of GBS, as is the case of Miller-Fisher syndrome which is closely related to the anti-GQ1B antibody. The pharyngeal/cervical/brachial variant of Guillain-Barré syndrome may be associated with anti-GT1A antibodies and the axonal motor neuropathy variant is suggested to be linked to anti-GM1 antibodies. However, despite the association of Miller-Fisher syndrome with anti-GQ1B antibodies, the specificity and sensitivity of all antibodies for specific subtypes perform minimally to moderately well for clinical use(2,16).

Since not all individuals affected by this syndrome are labeled positive for antiganglioside antibodies, more quality research is needed to clarify the role of antiganglioside antibodies in Guillain-Barré syndrome as a secondary origin or phenomenon. The pathophysiology of the acute inflammatory demyelinating polyneuropathy (AIDP) variant of GBS, which is very common especially in North America, is not well elucidated at the moment(2,15-18).

**Diagnosis**

Guillain-Barré syndrome includes ascending weakness, sensory disturbances that are not length-dependent. By definition, the lowest point is usually reached at 4 weeks. Symmetry is an essential feature of GBS. GBS is usually considered monophasic; therefore, a recurrent or remitting evolution at presentation would be considered out of normality. Previous events or recurrence of GBS is rare, occurring in less than 10% of all affected individuals. If the patient reports progression beyond 8 weeks, other diagnoses should be considered. This syndrome frequently manifests within 1 to 6 weeks of the previous illness. As already mentioned, other related causal factors are a history of vaccination, especially the 1976 swine flu vaccine strain, trauma, other infections and surgery(2,7,19-21).

Originally individuals with GBS will have the pattern of proximal and distal weakness, which is flaccid and, not infrequently, deep. It may be accompanied by significant weakness in neck flexion and which may indicate the need for intubation. In addition there is also areflexia or hyporeflexia, in some uncommon cases there is no hypo-areflexia, especially in the AMAN variant. In addition to flaccid weakness and areflexia, affected individuals often present with sensory symptoms that are not length-dependent; therefore, in contrast to the more common chronic neuropathies, such as diabetic neuropathy, affected individuals may show clinical features of dysesthesias in the hands and later in the feet. Patients often present with facial diplegia due to disruption of the two facial cranial nerves. In addition to that, they may show dysphagia due to involvement of the glossopharyngeal, vagus and hypoglossal cranial nerves. Autonomic nerves can cause relatively significant morbidity. Intermediate or intensive care monitoring is recommended because of possible blood pressure instability and cardiac arrhythmias. Dysautonomia is a primary basis for attributable mortality and morbidity. Nerve impairment of the respiratory muscles may necessitate artificial ventilation. Respiratory failure may be as frequent as in up to 30% of individuals, usually resulting in prolonged hospitalization and recovery(2,7).

Also, multiple variant forms of GBS have been reported, such as the variant with pure motor involvement called "AMAN (acute motor axonal neuropathy)" which is frequently observed in Asian countries. Infrequently, these individuals may have normal reflexes. There is a regional variant that especially affects the pharyngeal, neck and upper extremity muscles called "pharyngeal-cervical-brachial" variant; other variants may involve the central nervous system, called "Bickerstaff's encephalitis". There is another variant that develops paraparesis. The most popular variant is Miller-Fisher syndrome, characterized by the triad of ophthalmoplegia, areflexia and ataxia(2,22).
Figure 1. Ten-step approach to the diagnosis and treatment of Guillain-Barré syndrome.


Evaluation
The diagnosis is clinical. For atypical cases or infrequent subtypes, complementary tests may be helpful. Electromyography and nerve conduction can be used to distinguish GBS from its similar forms. Nerve conduction (NCS) uses technology that allows differentiation between demyelinating and axonal forms of neuropathy. Needle electromyography allows determination of the acuity of a patient's symptoms. These studies can be used to distinguish neuromuscular junction disorders or diabetic neuropathy. Normally, electrodiagnostic studies should be done 10 to 14 days after the onset of symptoms due to the time of Wallerian degeneration of sensory and motor nerve fibers, some trials show that early and non-specific findings can be helpful in the diagnosis of GBS 3 to 7 days after the onset of symptoms(2,23).

The most frequent initial electrodiagnostic findings in this syndrome are absent or prolonged H-reflexes and/or F-wave latencies. The pattern of sural preservation is thought to be specific for GBS as opposed to other polyneuropathies. This pattern would present a preserved sural sensory effect with abnormal sensory disturbances in the upper extremities. Acute
inflammatory demyelinating polyneuropathy presumably presents with partial motor conduction block, temporal dispersion, slow conduction velocities, prolonged-absent F-wave latencies, and prolonged distal latencies. AMAN will usually evidence a pattern of low compound muscle action potential amplitudes or even nonexcitable motor nerves. However, partial motor conduction block or complete conduction block may be seen on the AMAN nerve conduction study. This is due to "reversible conduction failure". Complement is stored in the nodes of Ranvier and in the paranodal regions of the peripheral nerves. After this, the nerves undergo Wallerian degeneration leading to axonal alteration. Acute motor and sensory axonal neuropathy (AMSAN) would present low amplitude motor and sensory potentials. Miller-Fisher syndrome shows diminished or non-existent sensory nerve action potentials (2, 5, 23, 24).

Cerebrospinal fluid (CSF) shows a classic pattern of albuminocytologic dissociation. This term means that the cerebrospinal fluid shows a normal number of white blood cells and a high level of CSF protein. However, this pattern is only present in 80% of individuals 2 weeks after the onset of symptoms. This being so, the absence of this classic finding does not exclude the diagnosis. When the white blood cell count is increased, this should prompt consideration of other agents such as HIV seroconversion (2, 3, 5, 7).

Several ganglioside antibodies have been associated with Guillain-Barré syndrome. Among the antibodies are anti-GM1, anti-GD1A, anti-GT1A and anti-GQ1B. These antibodies vary in sensitivity from 60% in anti-GM1 antibodies in acute motor axonal neuropathy to more than 90% in anti-GQ1B antibodies in Miller Fisher syndrome. Imaging studies, such as magnetic resonance imaging (MRI) of the spine, may show nerve root enhancement, which would be compatible with a breakdown of the blood-nerve barrier due to inflammation in GBS. Currently, MRI in GBS is more useful for differential diagnosis with other entities that may cause tetraparesis or facial diplegia, such as transverse myelitis or intracranial disease, in addition to infection of the brainstem, inflammation of the anterior horn cells or spinal cord, stroke, nerve root compression or leptomeningeal malignancy (2, 8, 20).

It is advisable to perform a negative inspiratory force (NIF) in individuals with suspected GBS. Serial NIF should be maintained in individuals at high risk for respiratory compromise. Those individuals who cannot perform a NIF of -20 to -30 cm H2O should be considered at very high risk. Peripheral nerve ultrasound shows enlarged cervical nerve roots at the onset of the disease, which shows the relevance of spinal root inflammation as an early pathologic form (2, 5).

Differential
Following the elimination of poliovirus, Guillain-Barré syndrome is the most common source of acute or subacute flaccid neuromuscular weakness worldwide; however, other pathologies may resemble GBS. When flaccid weakness is shown in a critically ill individual with multiorgan impairment, neuropathy and critical illness myopathy should be thought of. Among the different etiologies that are similar to GBS are:

➢ Tick paralysis.
➢ Neuromuscular junction disorder.
➢ Spinal cord disorders.
➢ Toxic neuropathies.
➢ Acute intermittent porphyria.
➢ HIV infection.
➢ West Nile virus.
➢ Rabies.

Other infrequent clinical manifestations suggest other diagnoses such as early bowel and bladder involvement, asymmetric features and hyperreflexia or normal reflexes (2).

To differentiate GBS from its look-alikes, a rigorous evaluation of the history, clinical manifestation and complementary data is necessary. Within the clinical manifestations, the presence of dilated pupils leads the diagnosis towards tick paralysis or botulism. Complementary tests, such as electromyography and nerve conduction studies, differentiate GBS from critical illness neuropathy-myopathy, in addition to the patient’s clinical manifestations. Cerebrospinal fluid tests with pleocytosis instead of classical albuminocytologic dissociation suggest the possibility of infectious diseases such as HIV or West Nile virus (2).

Patients with Guillain-Barré syndrome usually present a series of complications which are described in Table 1.
Table 1. Important complications of Guillain–Barré syndrome.

<table>
<thead>
<tr>
<th>Complication</th>
<th>When to be alert</th>
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<tbody>
<tr>
<td>Choking</td>
<td>Bulbar palsy</td>
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<tr>
<td>Cardiac arrhythmias</td>
<td>All patients</td>
</tr>
<tr>
<td>Hospital-acquired infections (e.g., pneumonia, sepsis or urinary tract infection)</td>
<td>Bulbar and facial palsy; immobility, bladder dysfunction, mechanical ventilation</td>
</tr>
<tr>
<td>Pain and tactile allodynia</td>
<td>Limited communication</td>
</tr>
<tr>
<td>Delirium</td>
<td>Limited communication</td>
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<tr>
<td>Depression</td>
<td>All patients</td>
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<tr>
<td>Constipation</td>
<td>Immobility</td>
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<tr>
<td>Corneal ulceration</td>
<td>Facial palsy</td>
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<tr>
<td>Dietary deficiency</td>
<td>Bulbar and facial palsy</td>
</tr>
<tr>
<td>Hypoalbuminaemia</td>
<td>Immobility</td>
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<tr>
<td>Pressure ulcers</td>
<td>Immobility</td>
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<tr>
<td>Compression neuropathy</td>
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<td>Limb contractures and osifications</td>
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Treatment
The literature reports 2 types of treatment that are currently considered the gold standard for individuals with Guillain-Barré syndrome, these are:

➢ Intravenous immunoglobulin (IVIG): thought to exhibit an immunomodulatory action; however, the exact mechanism is not yet clear. Generally, 2 grams/kilogram is administered over 5 days.

➢ Plasmapheresis: It is thought to act by eliminating pathogenic antibodies, humoral mediators and complement proteins involved in the pathogenesis of GBS. Like IVIG, its precise mechanism of action is not clearly proven. It is usually administered as an exchange volume over five sessions.

Results from randomized clinical trials demonstrate that plasmapheresis and IVIG are similar in efficacy. Results are present when either of these treatments is given in the first 4 weeks, however the most potent result may be shown if therapy is given in the first 2 weeks. Interestingly, corticosteroids such as oral prednisone and venous methylprednisolone have not shown improvement compared to placebo or in combination with IVIG and plasmapheresis in any of the individual categories. Treatment is commonly thought to decrease the recovery period for GBS. Some studies show that properly managed individuals had earlier ambulation compared to those who did not receive treatment, approximately 32 days faster(2,25-28).

Generally, most of the individuals affected with GBS have a good prognosis, and about 85% of them have independent ambulation with recovery; however, there is significant morbidity. Other studies present the same results previously cited, finding that plasmapheresis followed by IVIG and IVIG together with steroids have not presented a significant improvement. At the moment there are ongoing trials of complement inhibitors in individuals with refractory GBS(2,29-32).

CONCLUSIONS
Guillain-Barré syndrome can become difficult to diagnose and treat, as its clinical manifestations are heterogeneous. Treatment of GBS can be challenging in periods of infectious outbreaks, as observed in the Zika virus and SARS-CoV-2 epidemics. Since not all individuals affected by this syndrome are labeled as positive for antiganglioside antibodies, more quality research is needed to clarify the role of antiganglioside antibodies in Guillain-Barré syndrome as a secondary origin or phenomenon. In proportion to the evolution of scientific information and knowledge of Guillain-Barré syndrome, the diagnosis, management and prognosis are improving all the time.

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