Rev Bras Neurol 56(3):15-20, 2020.

Guillain-Barré syndrome: advances and future perspectives

Síndrome de Guillain-Barré: avanços e perspectivas futuras

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ABSTRACT

The first case of Guillain-Barré syndrome was described in 1916. Since then, knowledge about the pathophysiology and immunogenesis of this acquired inflammatory polyradiculoneuropathy has been growing steadily, especially after the advent of nerve conduction studies and the discovery of pathogenic autoantibodies. In the present study, we conducted a review of the main information available in the literature to date about the syndrome, including its diagnosis and management.

Keywords: Guillain-Barré syndrome; polyneuropathies; immunology

RESUMO

A síndrome de Guillain-Barré teve seu primeiro caso descrito em 1916. Desde então, o conhecimento sobre a fisiopatologia e imunogênese dessa polirradiculoneuropatia inflamatória adquirida vem crescendo continuamente, especialmente após o advento dos estudos de condução nervosa e a descoberta de auto-anticorpos patogênicos. No presente estudo, realizamos uma revisão das principais informações disponíveis na literatura até o presente momento sobre a síndrome, incluindo seu diagnóstico e manejo.

Palavras chave: síndrome de Guillain-Barré; polineuropatias; imunologia.

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INTRODUCTION

In 1859, the French physician Octave Landry reported a series of cases of acute ascending paralysis[1], which may correspond to the first sample of cases of Guillain-Barré Syndrome (GBS). At the time, however, the examination of intrinsic muscle reflexes was not regularly documented and a lumbar puncture technique had not yet been described.

In 1916, during the period of the First World War, doctors Georges Guillain, Jean Barré and André Strohl described the case of two soldiers of the French army who suffered weakness with acute progressive evolution related to tingling, diminished reflexes and elevated protein in cerebrospinal fluid, without cell alteration[2]. Subsequently, this disease became known as Guillain-Barré-Strohl syndrome, and then simply GBS.

The standardization of the definition of GBS allowed the disease to be more frequently diagnosed worldwide in the follow decades, being today considered the main cause of acute flaccid paralysis worldwide[3].

GBS is currently considered an acute or subacute immune-mediated inflammatory polyradiculoneuropathy, which classically causes progressive weakness in the limbs associated with hyporeflexia. Sensory changes usually precede or accompany motor symptoms, but they are generally not the most debilitating manifestations[4].

EPIDEMIOLOGY

GBS affects approximately 100 thousand people every year worldwide, has an annual incidence ranging from 0.4 to 4.0 cases/100.000/year, depending on the methodology of the study and the case definition, with the majority of well-designed prospective studies found an average incidence of 2.0 cases/ 100.000 /year[5,6]. The disease affects more frequently men (relative risk 1.5 in relation to women), an unusual characteristic in immune-mediated diseases. It is uncommon in children under 10 years old (incidence 0.34 to 1.34/100.000/ year)[7], and it becomes more common after 50 years of age[8], with peaks between 50-59 and between 60-69 years[9]. The cumulative risk of developing GBS over the course of a lifetime is on the order of 1 for every 1000 people[10].

In up to 76% (approximately three quarters) of the cases immunosensitizing events can be identified, occurring in general from one to four weeks before the onset of symptoms and mainly include: upper airway infection (35%) and gastroenteritis (27%). This pattern is seen in American, European and Asian countries, except Bangladesh, where gastroenteritis is more common (36%)[9]. The etiological agents involved in the pathophysiology of GBS have been mainly the bacteria *Campylobacter jejuni* and *Mycoplasma pneumoniae* and the following viruses: Zika, cytomegalovirus, Epstein-Barr, influenza A and enterovirus D6811. GBS after rabies infection is extremely rare[11].

Since the pandemic by the new coronavirus (COVID-19) was officially recognized by the World Health Organization[12], cases of GBS have been reported within five to ten days after flu-like symptoms in patients with viral infection by COVID-19 in northern Italy[13] and China[14], among other countries, leading to the hypothesis that it is another virus implicated in GBS. Despite the preliminary association, the number of reported cases is still small, therefore, further studies are needed to establish a causal relationship between these two clinical conditions.

GBS has historically been associated with vaccination for A/H1N1 influenza since the epidemic outbreak in the United States in 1976[15]. In the following decades, an effort was made to assess whether the event was a mere temporal coincidence or if there was really a causal relationship between GBS and vaccination. A recent systematic review of the literature by Dudley and collaborators found that, although the literature is conflicting, the influenza vaccine can rarely cause GBS in adults[16]. Taking the risk-benefit into account, the study concludes that there is an excellent general safety profile in recommending vaccination in the general population. Willison and collaborators advice not to vaccinate patients who have had GBS in the last three months or patients who have had post-vaccine GBS[17].

Other immunosensitizing factors that have been associated with GBS are metabolic stressors, such as, for example, surgery (moderate risk, especially bone and gastrointestinal tract surgery)[18]; trauma[19]; gestation; systemic lupus erythematosus[8]; as a paraneoplastic syndrome in patients with malignancy, especially in elderly patients with severe axonal loss and poor response to treatment with immunoglobulin[20].

PATHOPHYSIOLOGY

GBS is probably a disease with a predominance of lesions due to humoral autoimmunity, rather than cellular mediated by T lymphocytes[21]. Although less common, axonal variants have a better understood pathophysiology than the Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP) form. In Acute Motor Axonal Neuropathy (AMAN) or Acute Motor and Sensory Axonal Neuropathy (AMSAN) phenotypes, humoral attack (auto-antibodies) to the peripheral nerve axolema predominates, especially the complement fixators of the IgG1 and IgG33 subclasses.

This aberrant immune response is presumably generated by a mechanism of molecular mimicry between lipo-oligosaccharides (LOS) of infectious agents capable of inducing an immune response (mainly *C. jejuni*) and gangliosides present in the axolema (GM1 and GD1a). These ganglioside-linked autoantibodies induce a cascade with complement fixation, macrophage recruitment and membrane attack complex deposition. A similar phenomenon occurs in Miller Fisher syndrome (MFS), but with anti-GQ1b antibody, which attacks axons that mainly innervate the extraocular muscles, causing the typical ophthalmoplegia[11,22,23].

The cascade of phenomena that lead to demyelinating lesions in patients with AIDP is poorly understood, and appears to involve multiple target antigens in the myelin sheath and in Ranvier's nodules, including gliomedine, contactin, TAG-1, moesin and neurofascin, related to a broader range of immunosensitizing agents, including various infectious agents and vaccines[17]. Another hypothesis is that in AIDP there is the formation of neo-antigens from complexes of glycolipid components of the myelin sheath that may be the target of heteromeric or multimeric anti-complex antibodies that are difficult to be identified by standard techniques[24].

Although not common, rapid recoveries after immunoglobulin administration in axonal GBS are in line with the hypothesis that part of the neurological dysfunction can be attributed to a reversible electrical stunning in the nodal or paranodal region, before the axonal degeneration itself occurs. In AIDP, part of the clinical improvement may occur due to the reversal of nerve conduction blockades after treatment[10].

Diagnose an axonal GBS with or without antibody positivity is a valuable information, because patients generally

have slower and more incomplete neurological recovery than in purely demyelinating form[9]. So far, the detection of autoantibodies among GBS phenotypes is in the field of experimental research and does not yet have specific repercussions on treatment, although there is a prospect in the future for treatments aimed at neutralizing autoantibodies[3].

DIAGNOSIS

The diagnostic criteria for GBS were reviewed by Asbury and Cornblath[25], with the recent additions to the consensus statement published by Leonhard and colleagues in the journal Nature Reviews[26] (Table 1).

Table 1: Diagnostic criteria for GBS.

Characteristics required for the diagnosis of Guillain-Barré Syndrome in clinical practice:
Progressive weakness in the arms and legs [initially only the legs may be involved].
Areflexia [or decreased tendon reflexes] in the affected limbs.
Features that strongly support the diagnosis:
The progressive phase lasts from days to four weeks [often two weeks].
Relative symmetry of signs and symptoms.
Mild sensory symptoms or signs [absent in pure motor variant].
Involvement of cranial nerves, especially bilateral facial paralysis.
Autonomic dysfunction.
Muscle or root pain in the back or limb.
Increased levels of protein in CSF; normal protein levels do not exclude the diagnosis.
Electrodiagnostic characteristics of motor or sensory-motor neuropathy (normal ENMG in the early stages does not exclude the diagnosis).
Features that cast doubt on the diagnosis:
Increase in the number of mononuclear or polymorphonuclear cells in the cerebrospinal fluid (more than 50 cells/mm^3).
Weakness markedly or persistently asymmetric.
Intestinal or bladder dysfunction on presentation or persistent during the course of the disease.
Severe respiratory dysfunction and little limb weakness at presentation.
Sensitive signs with little weakness in presentation.
Fever at onset of symptoms.
Nadir in less than 24 hours.
Well-demarcated sensory level indicating spinal cord injury.
Hyper-reflexia or clonus.
Extensive plantar response [Babinski's sign]
Abdominal pain.
Slow progression with little weakness without respiratory involvement.
Progression continued for more than four weeks after the onset of symptoms.
Change in consciousness (except for Bickerstaff's brainstem encephalitis).

Adapted from Leonhard et al., 2019.

The World Health Organization recommends the wide use of the Brighton Criteria (originally created to assess the relationship between GBS and vaccination) to determine the diagnostic accuracy in epidemiological studies[6,27].
Patients who meet Asbury and Cornblath's diagnostic criteria in general have a classic clinical picture of rapidly progressive bilateral and symmetrical limb weakness (with or without involvement of bulbar and facial muscles, ataxia and ophthalmoplegia) associated with hyporeflexia in the affected limbs. Although hyporeflexia is a cardinal sign of GBS, in extremely rare cases hyperreflexia may occur, probably associated with blocking the activity of medullary inhibitory interneurons[28]. In general, motor involvement is preceded in up to 70% of cases by mild sensory symptoms such as paresthesias and pain[11].

The natural history of GBS occurs with the progression of signs and symptoms until nadir (period in which deterioration stop progressing) which occurs in up to two weeks in 96% of cases and up to 4 weeks in 99.8% of cases. Relapse is rare, occurring in two to five percent of cases[29], and when it does, alternative diagnoses should be investigated, such as Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), which in rare cases may have an acute presentation (A-CIDP) that simulates GBS[30].

Recurrence must, however, be distinguished from treatment-related fluctuations, which actually is a new clinical deterioration that occurs after nadir has been achieved or even a clinical improvement. In the first condition (recurrence) there is no benefit of retreatment, whereas it is common practice to treat again the patient with immunoglobulin after a fluctuation, despite little evidence to support this option[31].

After a variable period of stability, there is usually a gradual recovery of neurological functions, which can be partial or complete. About 80% of patients are able to walk independently without support or help within 12 months of symptom onset. Although neurological recovery is more intense in the first year, there is often an accumulative improvement for more than five years[26]. The prognosis of independent gait with six months of symptoms can be estimated using the Erasmus GBS Outcome Score (EGOS).

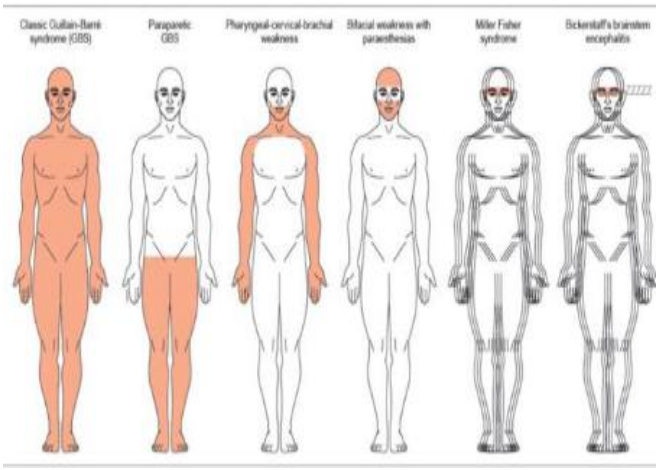
Autonomic dysfunction is common and a sign of poor prognosis, being a manifestation of failure of peripheric nervous system regulation of blood pressure and cardiac function causing orthostatic hypotension, labile blood pressure and cardiac arrhythmias, among others. Bulbar muscle paralysis can cause diaphragmatic involvement and can lead to acute respiratory failure and the need for ventilatory support in approximately 20% of cases[3].

From a clinical point of view, GBS can be classified into classic GBS, which causes weakness and hyporeflexia in the four limbs; pharyngocervic-brachial form, in which there is weakness limited to upper, cervical and bulbar regions; paraparetic GBS, when the weakness is restricted to the lower limbs; bifacial paralysis with distal paresthesia; MFS, characterized by ophthalmoplegia, ataxia and limb areflexia; Bickerstaff's brainstem encephalitis (BBE), considered a central subtype of MFS, because it shares a common pathophysiology of autoantibodies: it is characterized by hypersolence, ophthalmoplegia and ataxia (Figure 1). The clinical classification does not depend on complementary exams and allows the categorization of the main phenotypes presented by the patients, emphasizing the reality observed in clinical practice that there are patients with restricted and incomplete weakness, as well as additional findings, such as hypersolence and ataxia. There are several clinical-physiological and clinical-serological relationships between these variants, which is compatible with the heterogeneity of the syndrome. MFS can occur in isolation or overlap with classic GBS, a phenomenon called overlap GBS-MFS[32,6,26].

Mortality from GBS varies from three to ten percent, with an average of seven percent, and may be higher in some places, such as Bangladesh, where it reaches 17%. This difference can be explained by certain factors, such as difficulty in accessing adequate health care and the presence of an axonal variant with a worse prognosis[9].

The Brazilian National Clinical Protocol and Therapeutic Guidelines for GBS supports professionals to make the suspected diagnosis based primarily on the anamnesis and neurological evaluation and the confirmation of the cases with complementary exams (CSF and nerve conduction study). Its diagnostic criteria are very similar to those of Asbury & Cornblath, except for removing from the criteria suggestive of GBS the recovery of neurological functions between two to four weeks from the onset of symptoms (related to

remyelination) and including the presence of pain among those criteria of diagnostic support[33].



Adapted from Wakerley et al, 2014.
Figure 1. GBS Clinical presentations

Support for the diagnosis of GBS is based, among others, on the finding of albumin-cytological dissociation in the cerebrospinal fluid (less than 10 leukocytes/ml and hyperproteinorrhachia in general greater than 55mg/dl). This finding is present in more than 68% of cases. Less commonly, mild pleocytosis (five to 50 leukocytes/ml) may occur (19%). The presence of pleocytosis greater than 50 leukocytes/ml, associated or not with hyperproteinorrhachia is rare in GBS (up to two percent), and when present, it should be a warning sign for the expansion of the differential diagnosis. The absence of dissociation can occur early (only 50% of patients with GBS have dissociation in the first three days of symptoms), so a viable alternative in patients with suspected GBS and absence of dissociation is to repeat the lumbar puncture, as up to 84% of patients who collect CSF after seven days of symptom presentation presents albumin-cytological dissociation[9].

Another complementary exam that reinforces the diagnosis of GBS is the electroneuromyography (ENMG), whose findings are also highly dependent on the time they are performed. Initial changes include in the early phase (up to three days of symptoms) changes in F-wave and H-reflex responses (prolonged or absent). Then, with evolution of disease, the distal motor latencies are commonly prolonged. Temporal dispersion and focal conduction blocks occurs later (around the third week of symptoms). It has been described that the involvement of sensory potentials in the nerves of the upper limbs and preservation of the potential of the sural nerve is characteristic of GBS, since it is not a length-dependent neuropathy[3].

ENMG can usually be postponed after one week of symptoms, and can optionally be repeated after symptom stabilization (ideally between the third and eighth week of clinical presentation), when there is usually chronic denervation with signs of reinnervation, positive sharp waves, fibrillations and decreased recruitment of motor units[26].

The electrophysiological classification of GBS was proposed by Hadden and collaborators, dividing the findings between five possibilities: normal; primarily demyelinating; primarily axonal; inexcitable and equivocal[34]. However, less common subtypes of GBS have been described in the last thirty years, with the identification of patients with a clinical course other than AIDP and the identification of specific autoantibodies against axonal gangliosides and glycoproteins[32].

This neurophysiological classification was then revised in order to develop a standardized case definition for the purpose of comparability between studies, with the following neurophysiological variants being established: AIDP, AMAN, AMSAN and inexcitable[35,6].

The most common form of GBS (in the Americas, Europe and Asia) is AIDP (demyelinating form), present in up to 85% of cases with a motor-sensitive clinical picture. Axonal variants (AMAN / AMSAN) together account for ten percent of cases, affect younger patients (average 31 years old), cause more weakness (MRC classification), less sensitive symptoms, and have a worse prognosis for recovery (only 62% walk without support within six months of presenting symptoms). In addition, axonal variants are more associated with gastrointestinal infection by *Campylobacter jejuni*. MFS occurs in up to five percent of patients[9].

Another complementary exam of value in patients with GBS is magnetic resonance imaging of the lumbosacral spine, specially to exclude alternative diagnoses such as acute transverse myelitis and compressive/infiltrative myelopathy. The uptake of gadolinium in the nerve roots is a finding that reinforces the diagnosis of GBS[36,37].

MANAGEMENT

The pillars of GBS treatment are general clinical support and immunotherapy. Patients should preferably be admitted to the Intensive Care Center (ICU), especially if they have dysautonomia or have a high risk of progressing to mechanical ventilation (Erasmus GBS Respiratory Insufficency score (EGRIS) greater than or equal to five points)[26] (Table 2).

Table 2. Erasmus GBS Respiratory Insufficency score (EGRIS)

Measure	Category	Pontuation
Number of days between onset of weakness and hospital admission	Greater than seven	0
	Between four and seven	1
	Equal or less than three	2
Facial and/or bulbar weakness at hospital admission	Absent	0
	Present	1
Sum of MRC score* on hospital admission	51-60	0
	41-50	1
	31-40	2
	21-30	3
	Equal or less than 20	4
EGRIS score	**0 a 7**	

Adapted from Walgaard et al., 2010. *Sum of the score in the manual assessment of the strength of 6 muscles of the upper and lower limbs using the Medical Research Council (MRC) score: bilateral adduction of the shoulders (maximum 10 points, five for each shoulder), elbow flexion (up to ten points, five for each upper limb); wrist extension (ten points, five for each wrist); thigh flexion (ten points, five for each thigh); knee extension (ten points, five for each knee) and plantar dorsiflexion (ten points, five for each foot), totaling a maximum of 60 points.

Regular monitoring of respiratory and autonomic function (blood pressure, heart rate and sphincter control), muscle strength and swallowing capacity can be performed more adequately in the ICU than in the infirmary. In addition, the risk of respiratory failure may be present even in the absence of dyspnea, especially if the vital capacity is less than 20ml/kg, the maximum inspiratory pressure is less than 30cmH20 or the maximum expiratory pressure is less than 40cmH20, situations that demand early intubation and mechanical ventilation to avoid neuromuscular fatigue and hypercapnic respiratory failure38. However, if the patient evolves stable and improving, without other signs of severity, he can be admitted to the infirmary and the transfer to ICU be reconsidered in case of complications.

Early physiotherapy rehabilitation is also part of non-pharmacological treatment. Psychological support is important, as the patient with GBS usually has preserved awareness and cognition, and functional limitation in a previously independent patient can be a reason for mental suffering. All procedures must be explained to the patient, who must also be involved in making decisions26.

The Brazilian Clinical Protocol and Therapeutic Guidelines for GBS guides the treatment of GBS with human immunoglobulin 0.4g/kg/day for five consecutive days (total cumulative dose of 2g/kg) in the cases established with moderate-severe GBS (patients that can´t walk without support for more than ten meters) within the 14-day period of symptom presentation33. The degree of neurological disability of the patients must be assessed at admission using the GBS disability score (Table 3).

Table 3. Score GBS of disability.

Grade	Clinical status of the patient
0	Asymptomatic / healthy.
1	With minor / mild signs and symptoms of neuropathy, but able to run and perform manual tasks.
2	Able to walk without a walking stick for at least 10 meters in an open space, but unable to run and perform manual tasks.
3	Able to walk for 10 meters only with a walking stick or support.
4	Confined to bed or wheelchair.
5	Requires assisted ventilation (for any part of the day or night).
6	Death

Adapted from Hughes et al.,2007.

Treatment can also be started early in case of bulbar weakness, respiratory failure, weakness with rapid progression or severe dysautonomia, regardless of gait assessment39. Treatment with immunoglobulin, although it does not alter mortality, decreases the time until maximum neurological recovery40. The treatment of all variants of GBS is the same, but identifying the subtype is essential, because despite being within the same spectrum, different phenotypes have different prognoses and clinical evolution, in addition to different neurophysiological characteristics.

An equally effective option when compared to standard immunoglobulin therapy is plasmapheresis[41], a total of five sessions, on alternate days, with filtration of 200-250ml of plasma/kg of body ideal weight[42]. However, in general, treatment with immunoglobulin has been more widely used for reasons of greater availability in the services and less infrastructure required for its administration. Besides that immunoglobulin is cheaper than plasmapheresis and is associated with shorter hospital time stay3. One of the few advantages of plasmapheresis is that it can be performed in up to four weeks[26]. There is no evidence of an additional benefit in performing a second immunoglobulin pulse in patients with limited prognosis[39] or in performing plasmapheresis followed by immunoglobulin or methylprednisolone[40,42].

CONCLUSIONS

Over a hundred years from the original description of GBS, major scientific advances have occurred in understanding the disease, such as studies of nerve conduction, which have brought insights into the presence of primarily demyelinating or axonal lesions. There was the identification of autoantibodies involved in the immunopathogenesis of some variants of GBS, which represents an advance in the identification of targets for a future specific immunotherapeutic treatment. Despite these advances, the emphasis is still on the importance of early recognition and timely treatment of GBS as a way to accelerate clinical recovery. Multiprofessional treatment is essential in the rehabilitation of patients with GBS, avoiding secondary complications of the disease.

DECLARATIONS OF INTEREST:

None.

FUNDING STATEMENT:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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