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Review

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Guillain-Barré syndrome: old and new concepts

Síndrome de Guillain Barré: viejos y nuevos conceptos

Abstract

Currently, Guillain Barre Syndrome (GBS) is the most frequent cause of acute flaccid paralysis. The classical form of the syndrome has not undergone significant changes in its clinical behavior. However, the spectrum of clinical variants of the syndrome is extensive, and supporting advances in molecular biology and immunology have allowed to better characterize these forms of GBS. The anti-ganglioside antibodies have restructured the criteria because they increase the sensitivity and specificity of diagnosis; because of this, the traditional approaches are inadequate for appropriate classification and discrimination of imitators of the syndrome. The evolution of the criteria should change the way to approach the picture and regulate the therapeutic behavior, without overstepping the clinical judgment of daily medical practice.

Keywords

Guillain Barré, clinical criteria, antibodies.

Resumen

En la actualidad el síndrome de Guillain Barré (SGB) es la causa más frecuente de parálisis flácida aguda12. La forma clásica de síndrome no ha sufrido modificaciones importantes en su comportamiento clínico, sin embargo, el espectro de variantes clínicas del síndrome es extenso, sustentado en los avances de la biología molecular y la inmunología que han permitido caracterizar mejor estas formas del SGB. Los anticuerpos anti-gangliósidos han reestructurado los criterios, ya que aumentan la sensibilidad como la especificidad del diagnóstico; debido a ello, los criterios clásicos son insuficientes para lograr una adecuada clasificación y discriminar los imitadores del síndrome. La evolución de los criterios debe cambiar la perspectiva en el abordaje del cuadro y normar la conducta terapéutica, sin sobrepasar el juicio clínico de la práctica médica diaria.

Palabras clave

Guillain Barré, criterios, variantes.

Introduction

Guillain-Barré syndrome (GBS) is the main cause of acute flaccid paralysis found in first- and second-level hospitals in Mexico. The current conception of this group of autoimmune neuropathies of acute evolution with chronic sequelae has forced to review the basic physiopathogenic, epidemiological, immunological, and clinical mechanisms due to the wide clinical spectrum that they present. The current diagnostic criteria must be based in these areas, forcing the doctor to properly classify the disease, which can have a long-term impact on the patient's overall functionality and allow an adequate discrimination of the overlap effect with other aggregated and/or differential neuropathy causes. Therefore, the objective of this work is to review the basic and phenotypic principles of GBS that support the clinical experience of the doctor, essential at the time of the diagnostic approach.

Historical background

In the first edition of *"Clinical lectures"* in 1848, Robert Graves proposed that in the *"Epidemié du Paris"*, acute flaccid paralysis had its origin in peripheral nerve injury.[1] It was the first occasion in which a paralysis of central origin was distinguished. In 1858, Jean Baptiste Octave Landry de Thézillat formally described the "Ascending paralysis," causing it to be known as Landry's paralysis until 1876. In 1892, Ostler described six types of polyneuropathy and coined the name "acute febrile polyneuritis," pondering that some of Landry's patients probably had an inflammatory process in the spinal cord. The cases described by Ostler are similar to what is now known as Guillain-Barré syndrome (GBS), with the difference that the latter does not strictly present a febrile picture. It was not until 1916 that Guillain, Barré, and Strohl described the characteristics of the classical form of the picture. Miller Fisher contributed in 1958 the description of a consistent variant: ophthalmoplegia, ataxia, and areflexia. Finally, in 1975, Dyck *et al*. described a chronic variant as recurrent polyneuro-radiculopathy.[2-4]

Epidemiology

Two meta-analyses[5,6] carried out in 2011 by the Centers for Disease Control and Prevention of the United States estimated the incidence of GBS worldwide at 0.89-1.89 cases per 100,000 inhabitants/year. There was a male gender predominance of 1.78:1 and 60% of the cases previously presented an infectious episode. This important finding is exemplified by *Campylobacter jejuni*, with 0.25-0.65 case reports per 100,000 inhabitants/year solely attributed to it. It became historically relevant during an outbreak of GBS in the province of Hubei in northern China due to its link with 12 cases confirmed by histopathological diagnosis, supporting the study of antigenic molecular mimicry.[7-9] Since 1967, it was noticed that the subclinical infection by cytomegalovirus produced 0.6-2.2 cases per 100,000 inhabitants/year with predominant cranial nerves affectation and hearing loss, similar to congenital infection. Some European series[10,11] report that 70% are classified as acute inflammatory demyelinating polyneuropathy (AIDP) and 7% as axonal. In Mexico, García Ramos *et al*.[12] described in their 2014 multicenter meta-analysis an incidence at 0.89-1.89/100,000 people per year and a mortality approaching 0.16/100,000 people per year, figures similar to those found in the international literature.

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Characterization of the variants by immunological criteria

The glycosphingolipids are carbohydrate residues bound to a fraction of lipids (mainly sphingolipids and ceramides) by a glycosidic bond. When they present one or more sialic acids (N-acetylneuraminic acid, N-acetylglycolylneuraminic acid) in the carbohydrate fraction, they are known as gangliosides.[13] (Figure 1) Up to 188 types have been characterized in the central nervous system of vertebrates. Their main function is to be part of the cell membranes of the supporting cells (glia) of the central and peripheral nervous system forming myelin, and are classic molecular targets for surface anti-ganglioside antibodies that contribute to the process of inflammation-demyelination of the peripheral nerve in GBS.

The works of Yuki *et al.*[13] have contributed to characterize the variants of GBS based on the antigen of the ganglioside subtype of myelin against which the antibody is formed. This classification attempts to correlate the autoimmune phenomenon with the neurophysiological and neuropathological findings described. (Figure 2) Some vaccines have been associated with a high risk of developing GBS, but not the rabies vaccine made in brain tissue culture. A report showed that vaccines against swine flu and seasonal influenza of 1976 induced the formation of anti-GM1 antibodies in mice, suggesting molecular mimicry in post-vaccination GBS—but this could not be replicated in the murine and human models. In contrast, an anti-rabies vaccine derived from brain cultures of sheep contaminated with gangliosides may trigger GBS associated with anti-GM1 or anti-GD1a IgG antibodies.

In 2013, Uncini and Yuki *et al.*,[14,15] thanks to their clinical-experimental-immunological findings, support the concept of "nodo-paranodopathy" based on the molecular composition of the regions of the Ranvier node (nodal, paranodal, and juxta-paranodal), rich in Na+ and K+ channels, which generate the potential for saltatory conduction. Interestingly, it is also an area full of potential white protein targets (membrane layer components in the Schmidt-Lanterman incisures in Schwann cells), mainly because they are regions within the axon (300% more than the internodal regions) rich in the different varieties of gangliosides, the distribution of which remains uniform in the motor and sensory fibers. This is evidenced by the following experimental observations:

• Titers of anti-ganglioside antigens are higher in the onset of the disease and decrease during its course.

Figure 1. Biochemical structure of ganglioside GMD-1 and the antigenic target of anti-GM1 IgG. Gal: galactosamine, GalNAc: N-acetylgalactosamine, NeuAc: N-acetylneuraminic acid.

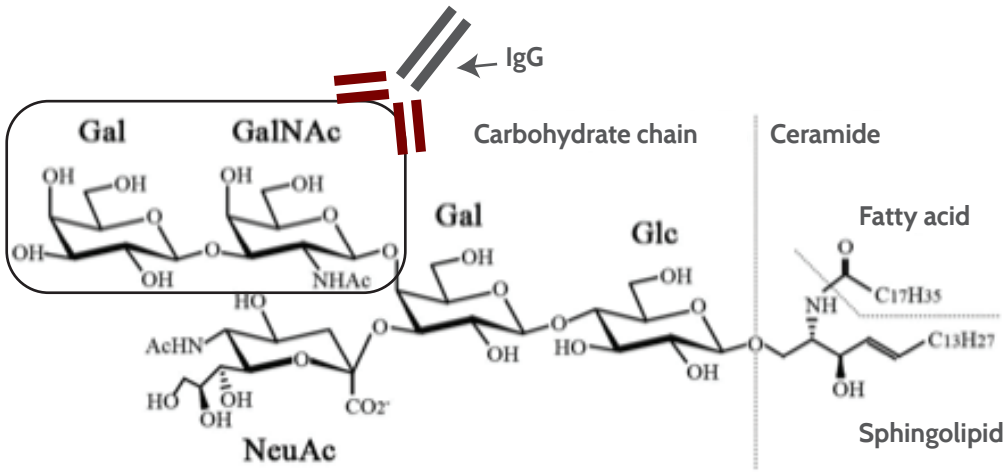
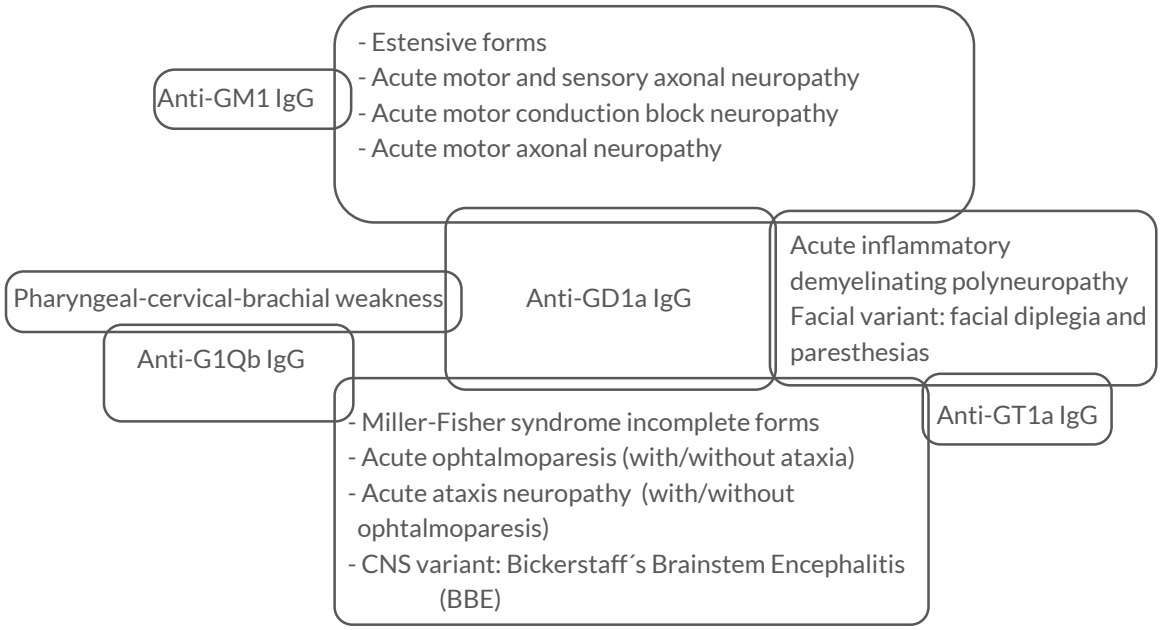


Figure 2. Association of anti-ganglioside antibodies with GBS and MFS. In the experimental models, the immunological superposition of the same antibody has been found in the different phenotypic expressions of Guillain-Barré syndrome—it is not yet clear why they present such a clinical variety.



• Cases of acute motor axonal neuropathy (AMAN) followed by the administration of external antigangliosides by venous injection have been reported.

• Subsequent treatment with melanoma monoclonal antibodies (anti-GD2) can produce sensitive polyneuropathy in some patients and anti-GD2 can produce cross-reactivity by mimicking GBS in severe cases.

• Campylobacter jejuni is the most common agent in cases of GBS and Miller Fisher syndrome (MFS) because it expresses lipopolysaccharides that mimic GM1, GD1a, or GQ1b.

• Sensitization of rabbits with GM1 or GM1-like lipo-oligosaccharides produces a replica of AMAN and sensitization with GD1b induces a model of acute axonal ataxic neuropathy.

• Intraperitoneal injection of anti-GQ1b antibodies and complement produces respiratory paralysis.

• Anti-ganglioside monoclonal antibodies against GD1a block nerve conduction and destroy nerve terminals via complement in murine models.

• In myelinated fibers of rats, the anti-GM1 decrease Na+ currents and induce chronically poor complement-mediated conduction.

Gangliosides are abundant in the peripheral nervous system.[15,16] The composition of the motor and sensory nerves express similar amounts of GM1, GD1a, and GD1b, even though ceramide concentrations in the cell membrane are higher in the motor nerves than in the sensory ones. This data is important because the antibodies recognize the extracellular structure of carbohydrates and not the ceramides immersed in the lipid membrane. GM1, GD1a, and GD1b are found more in the axon than in the myelin fraction, with the motor myelin fraction having larger amounts of GM1 and GD1a than the sensory fraction. The function of gangliosides in the nodal region is still unknown. In the murine mutant models that included GM1 and GD1a, the paranodal structures easily tended towards fragility and disruption, and the K+ channels tended to decrease in the paranodal

regions. These defects were more prevalent in the dorsal and ventral regions of the spinal roots, where the conduction studies revealed that it was slower with reduction of the Na+ channels in the motor nerves. These findings indicate that gangliosides contribute to the stability and maintenance of interactions with glia in the paranodal region and the maintenance of ion channels (mainly Na+) in the nodal region of the motor fibers, mainly.[15,17]

Diagnostic criteria to define gbs

In 1960 Osler *et al.*[18] methodically described in their classic paper 10 cases similar to GBS and variants of the disease, suggesting the need for classification criteria that would cover the broad spectrum to differentiate GBS from other similar pathologies. The diagnostic criteria for GBS based on the 1990 Asbury *et al.*[19] cohort classically include progressive weakness of the pelvic and brachial musculature, ascending, with diminishing or absent muscle stretch reflex. (Table 1)

In 2014, the Dutch group[20] for the study of GBS at the University Medical Center Rotterdam with a cohort that included 567 patients issued the Brighton GBS diagnostic criteria (Table 2), which replaced Asbury because the latter was not very useful in clinical practice. The adapted disability scale of Hughes *et al.*[19] was used to describe the clinical course of GBS, which was useful for observing clinical fluctuations and during treatment. (Table 3) Among the remarkable conclusions, it was found that 97% of patients reached the nadir at four weeks, and during hospital admission, 99% presented symmetric weakness in the extremities and 91%

Table 1. Asbury Criteria.

Characteristics required for the diagnosis	- Progressive weakness in both arms and legs - Areflexia (or hyporeflexia)
Characteristics that support the diagnosis	- The progression of symptoms from days to four weeks - Relative symmetry - Mild sensory signs or symptoms - Impairment of the cranial nerve, facial weakness especially bilateral - Recovery from two to four weeks after the progression ceases - Autonomic dysfunction - Absence of fever at onset - Typical findings in cerebrospinal fluid (Albumin-cytological dissociation) - Electromyography/nerve conduction velocities (characteristic signs of a demyelinating process in the peripheral nerves)
Characteristics that question the diagnosis	- Asymmetric weakness - Persistent bladder and intestinal dysfunction - Initial bladder and bowel dysfunction - >50 cells in the CSF - Presence of sensory level
Characteristics that rule out the diagnosis	- Abuse of hexacarbons (inhaled solvents, N-hexane and N-butyl ketone), includes inhalation of thinner and glue - Abnormal porphyrin metabolism - Recent diphtheria infection - Lead poisoning - Other similar conditions: polio, botulism, hysterical paralysis, toxic neuropathy

Table 2. Brighton criteria diagnosis and definitions for GBS (2014).

Diagnostic criteria	Level of diagnostic certainty			
	1	2	3	4
Bilateral flaccid weakness of limbs	+	+	+	+/-
Decreased or absent deep tendon reflexes in weak limbs	+	+	-	+/-
Monophasic course and time between onset/nadir 12 h to 28 days	+	+/-a	-	+/-
CSF cell count <50/µl	+	+/-a	-	+/-
CSF protein concentration > normal value	+	+/-	-	+/-
Nerve conduction studies findings consistent with one of the subtypes of GBS	+	+	+	+
Absence of alternative diagnosis for weakness	+	+	+	+

Table 3. Disability scale in GBS (Hughes *et al.* 1978).

1. Healthy
2. Minor symptoms and able to run
3. Walks 5 m across an open space without support, but unable to run
4. Walks 5 m across an open space with support
5. Confined to wheelchair or to bed
6. Requires assisted ventilation any part of the day
7. Death

diminished muscle stretch reflex. All patients showed recovery to some extent, and 95% had a monophasic course of the disease, some of them with transient fluctuation during treatment in the acute phase of the picture. Important advantages of the Brighton criteria are the definitions of the explicit cases and the classification into four levels of diagnostic certainty according to the characteristics of the patient and the availability of information. This study highlights the fact that accurate and comprehensive documentation of clinical signs should allow a better classification of Guillain-Barré syndrome in developed countries and in developing countries. Studies are needed in the coming years to validate this premise and demonstrate its usefulness in populations where hospital conditions do not meet all the requirements in the criteria.

In that same year, The GBS Classification Group[21] published in the journal Nature the new criteria for GBS, its subtypes, and MFS (Table 4) based on clinical-serological evidence according to the type of antigen expressed by each nerve. Notable examples are MFS and Bickerstaff Brainstem Encephalitis (BBE) where anti-GQ1b antibodies are predominantly expressed in the abducens, trochlear, and oculomotor nerves, as well as in the muscle spindles of the innervated muscles. GQ1b may possibly also be expressed in the reticular formation, which would explain why patients with BBE present characteristic rostrocaudal deterioration. On the other hand, 18% of patients with acute ataxic sensory neuropathy have anti-GQ1b antibodies and 65% of ataxic GBS also express this antigen. Another important antigen is GT1, which is expressed in the glossopharyngeal and vagus nerves and vagal fibers of the accessory nerve. Incomplete forms of MFS and with pharyngeal-cervical-brachial weakness express both anti-GQ1b and GT1 antibodies in the same way.

In most patients, Guillain-Barré syndrome

Table 4. Diagnostic criteria for GBS, MFS, and the 2014 subtypes by *The GBS Classification Group*.

Classification	Clinical features	Notes	Diagnosis-supporting features
General syndrome			
The whole spectrum of GBS	Symmetric pattern of weakness in the extremities/cranial nerves. Disease of monophasic course with a time interval between onset of weakness and nadir ranging between 12 h and 28 days followed by clinical plateau behavior.	Alternative diagnoses should be excluded.	History of symptoms of an infectious nature. Presence of distal paresthesia before the onset of weakness. Presence of albuminocytologic dissociation in cerebrospinal fluid.
Specific diagnoses			
Classic GBS	Weakness, areflexia/hyporeflexia in the four limbs.	Weakness usually starts in the legs, but can start in the arms. It can be mild, moderate or complete paralysis. Muscles innervated by cranial or respiratory nerves may be affected. Muscle stretch reflex may be normal or increased in 10% of cases.	Electrophysiological evidence of neuropathy.
Pharyngeal-cervical-brachial weakness	Oropharyngeal, neck, and arm weakness, symmetrical or unilateral; with arm areflexia/hyporeflexia. Absence of weakness in the legs.	The absence of certain characteristics indicates incomplete pharyngeal-cervical-brachial weakness: patients without weakness in the arm and neck have acute oropharyngeal paralysis; patients without oropharyngeal paralysis have acute cervicobrachial weakness. In some cases weakness in the legs may be present, but the pharyngeal-cervical-brachial weakness must be prominent. The presence of additional characteristics indicates overlap with other GBS variants: ataxia with ophthalmoplegia suggests overlap with MFS; ataxia without ophthalmoplegia suggests overlap with acute ataxic neuropathy; ataxia, ophthalmoplegia, and deterioration of consciousness suggest overlap with BBE.	Electrophysiological evidence of neuropathy. Presence of anti-GT1a or anti-GQ1b IgG antibodies.

Classification	Clinical features	Notes	Diagnosis-supporting features
Paraparetic GBS	Weakness in the legs/areflexia/hyporeflexia; thoracic limbs respected.	Typically bladder function is preserved and there is no defined sensory level.	Electrophysiological evidence of neuropathy.
Bilateral facial weakness and paresthesias	Facial weakness. Absence of ophthalmoplegia, ataxia, and limb weakness.	In some patients paresthesia of the extremities is absent and the muscle stretch reflex can be normal.	Electrophysiological evidence of neuropathy.
Miller Fisher syndrome (MFS)	Ophthalmoplegia, ataxia, and areflexia/hyporeflexia. Absence of limb weakness and hypersomnolence.	Absences of certain clinical characteristics indicate an incomplete MFS: acute ataxic neuropathy and acute ophthalmoparesis. The presence of a single clinical characteristic indicates an incomplete MFS: acute ptosis, acute mydriasis.	Presence of anti-GQ1b IgG antibodies.
Bickerstaff's brainstem encephalitis (BBE)	Hypersomnolence, ophthalmoplegia, and ataxia. Absence of limb weakness.	Patients without ophthalmoplegia have the incomplete form of BBE known as acute ataxic hypersomnolence.	Presence of anti-GQ1b IgG antibodies.

continues to progress for a maximum of one to three weeks after the onset of symptoms. Two-thirds of patients are not able to walk independently when maximum weakness has been reached. Respiratory failure occurs in 25% of patients, and major complications such as pneumonia, sepsis, pulmonary embolism, and gastrointestinal hemorrhage develop in 60% of intubated patients. Among those severely affected, 20% are still unable to walk six months after the onset of symptoms.[9] Variations in the speed and degrees of recovery from GBS make it difficult to predict a prognosis. The Erasmus GBS Respiratory Insufficiency Score (EGRIS) and Erasmus GBS Outcome Score (EGOS) scales use the number of days between the onset of weakness and hospital admission, the presence/absence of facial or bulbar weakness, and the severity of limb weakness to predict the likelihood of respiratory failure. The Hughes scale is included in the latter. (Table 5) Both scales validated in their respective patient populations (n= 397 and 388 patients followed up in the first four weeks, three and six months), can be useful in the care of patients with GBS.[7,22-25]

Differential diagnosis

The spectrum of diseases that affect the peripheral nerve is extensive. Acute poliomyelitis has historically been the disease on which emphasis is placed when doing a differential diagnosis.[26,28] The symptoms of the minor illness (1-3 days) coincide with the first viremia, resembling a flu-like episode with complete remission of the symptoms—this phase is called abortive polio. If the disease progresses, the symptoms of paralytic polio appear: high fever, intense headache, neck stiffness, back pain, and severe segmental spasm, significantly affecting gait, a prodromal condition lasting 2-3 weeks. Spinal polio itself is characterized by destruction of the anterior horn cells, and, clinically, with asymmetric weakness and areflexia of the pelvic limbs in the following 48 hours until reaching the affected limb, without necessarily involving sphincters (it rarely debuts as a picture of transverse myelitis). A variant is bulbar polio, which does not present limb involvement,

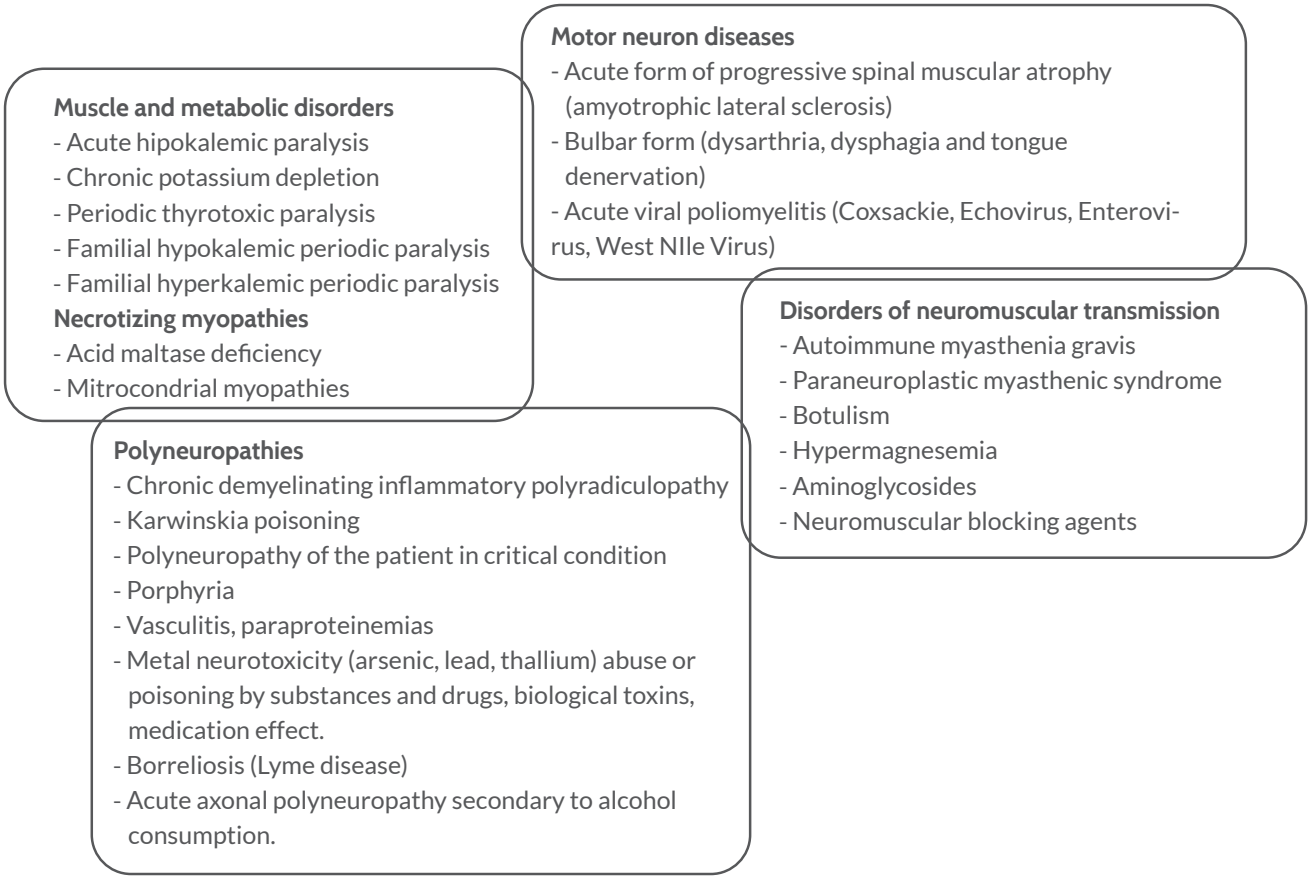
Table 5. *Erasmus GBS Respiratory Insufficiency Score (EGRIS) and Erasmus GBS Outcome Score (EGOS).*

Prognostic factors	Categories	EGRIS	EGOS Modified		EGOS
		Hospital admission	Hospital admission	7 days after admission	14 days after admission
Age of onset	<40		0	0	1
	41-60		1	1	0.5
	>60		2	2	0
Diarrhea in the 4 weeks that preceded the onset of weakness	Absent		0	0	0
	Present		1	1	1
Days between the onset of weakness	>7 days	0			
	4-7 days	1			
	< 3 days	2			
Facial or bulbar weakness	Absent	0			
	Present	1			
Strength scale *Medical Research Council*	60-51	0	0	0	
	50-41	1	2	3	
	40-31	2	4	6	
	30-21	3			
	<20	4			
	<30		6	9	
GBS disability scale	0 o 1				1
	2				2
	3				3

but it does present significant dysautonomia (hypertension, hypotension, neurogenic shock), dysphagia, dysphonia, and respiratory failure, and the development of encephalitis or aseptic polio meningitis is possible. In Mexico the "wild" form of poliovirus has been eradicated thanks to vaccination programs; however, it is important to know its natural history, considering how similar its sudden onset is to GBS.

The flaccid paralysis produced by a toxic plant of the genus Karwinskia (its common name is "cripple"), has been known since colonial times and is continuously reported in Mexico. It manifests as a motor paralysis, initially spastic, subsequent areflexia, ascending, progressive, and symmetric, which can affect the intercostal muscles and lead to acute respiratory failure, and it does not present a sensory involvement. Another invariable and constant sign observed with this poisoning are claw hands. Frequently the picture is confused with GBS and with lesions of the anterior horn of the spinal cord such as poliomyelitis. The toxic substance derived from an anthracene compound (tullidinol toxin T-544) is found in the seeds and dissolves easily in saliva. It links to serum albumin, is gradually released, and its effect can be cumulative; hence, the paralysis may appear after ingestion of the fruit or weeks later. This antecedent is identified in more than 80% of cases. Its toxic mechanism damages primarily the Schwann cells and secondarily the axon. The treatment is symptomatic and depends on the degree of severity. Steroids, immunosuppressants, and intravenous gammaglobulin have been used with partial results. The toxic fraction could be

Figure 3. Differential diagnosis of acute flaccid paralysis.



reduced with plasmapheresis sessions and albumin replacement.[28]

A typical clinical situation is a patient with septic shock, multiple trauma, with acute respiratory distress syndrome, requiring prolonged mechanical ventilation support and multiple organ support, developing severe flaccid weakness in the Intensive Care Unit after several days or weeks upon admission to the ICU. Frequently, this weakness makes it impossible to extubate or remove the mechanical ventilation. Taking into account that one of the etiological antecedents of GBS is infection, the clinical dilemma of differentiating between GBS and the so-called critical illness polyneuropathy (CIP) frequently arise. It is important to remember that the presence of septic encephalopathy may be present before the onset of CIP. Patients with GBS do not have primary alteration in consciousness. CIP is usually associated with the use of muscle relaxants, sedation, corticosteroids, aminoglycoside-type antibiotics, metabolic, nutritional, electrolyte and rhabdomyolysis disorders that aggravate muscle weakness. The axonal variant of GBS and CIP present sensory-motor or purely motor variants; however, severe autonomic alterations are more frequent in the patient with GBS. Finally, plasmapheresis or IgG-IV are not useful in CIP, which has a good prognosis once it's corrected and the issues that require ICU care are stabilized.[28,29] The rest of the causes are summarized in Figure 3.[30,31]

Treatment

In the syndrome of acute flaccid paralysis, GBS is the most frequent and important cause and should be addressed as a medical emergency, which has a natural history in its evolution in an acceptable manner, with a favorable prognosis in the functionality of the patient; however, in those who develop respiratory paralysis, timely detection (the ideal therapeutic window is less than three weeks) allows establishing a diagnosis that significantly influences timely decision-making, such as ventilation assistance, gamma globulin, plasmapheresis, and early support measures.[32]

The current treatments[33,34] have not changed with respect to the previously mentioned measures. Advanced life support in the ICU remains the cornerstone of treatment. The use the EGOS and EGRIS scales have proved to be coadjuvant in the clinical decisions regarding management of treatment and the complications of the syndrome. Regarding the use of intravenous gamma globulin (IVIg), there is still no consensus on the classic use of five days at 0.4 g/kg/day versus the alternative modality of 2 g/kg/day in two days. There is no demonstration that IVIg has proven effective in patients who tend to get worse clinically. Plasmapheresis sessions (five sessions in two weeks as standard) have proven to be as effective as IVIg. However, the majority of studies conducted in the United States and Europe have been carried out in patients with acute inflammatory demyelinating polyneuropathy, so its effectiveness with the rest of the variants is still inconclusive. The effectiveness of IVIg combined with steroids is inferior to the use of IVIg alone. The combination of IVIg followed by plasmapheresis sessions has not been shown to be superior to the administration of each treatment individually. Eculizumab, a humanized monoclonal antibody with a high affinity for complement C5, prevents its activation, the formation of the membrane attack complex (C5b-9), and the subsequent proinflammatory cascade, and it began to be tested in the Inhibition of Complement Activation (Eculizumab) in Guillain-Barré syndrome (ICA-GBS) pilot study.[35]

Something interesting about the development of chronic inflammatory demyelinating polyneuropathy, which 10% of patients with GBS develop eight weeks after onset, is that the use of IVIg 2 gr/kg/day for five days has proved beneficial in these patients, although there are still no studies large enough to determine the impact of this "subacute" therapy in these patients.[35,36]

Conclusions

Each of the GBS subtypes allows establishing other differential diagnoses. The immunological pathophysiology, as well as the measurement of antibodies, generates a greater diagnostic specificity of the syndrome variants, a tool that has been incorporated into the well-known neurometry. The importance of having the necessary elements for molecular diagnosis must be stressed. The norm that the criteria should be reproducible in daily practice often tends to be omitted because of the deficiencies of the institution, so clinical means and a good semiology are still the best tools for an experienced clinician.

Conflicts of interest
The authors declare an absence of conflicts of interest.

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