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A CLOSER LOOK AT GUILLAIN-BARRE SYNDROME AND ITS VARIANTS

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Abstract

The name "Guillain-Barré Syndrome" (GBS) is used to refer to a group of clinically and electrophysiologically diverse illnesses that are all characterized by acute onset regional or widespread flaccid paralysis, either with or without sensory loss. Clinically, GBS can manifest as circumscribed involvement, generalized weakness, or the uncommon central nervous system involvement known as Bickerstaff Brainstem Encephalitis. Axonal or demyelinating characteristics may exist electrophysiologically, and these characteristics can impact a patient's prognosis. It's critical to distinguish GBS from other mimics by understanding its variations. Differentiating between GBS variations may be aided by nerve conduction testing and anti-ganglioside antibodies. New therapeutic approaches are being developed based on the pathophysiology of GBS variations, even though existing treatment guidelines are comparable for different subtypes. This article provides an overview of our current knowledge regarding the etiology and clinical characteristics of GBS and its variations.

Keywords: Guillain-Barré syndrome (GBS), Acute inflammatory demyelinating polyradiculoneuropathy (AIDP), Miller Fisher syndrome.

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Introduction

The clinical journey through Guillain-Barre syndrome follows a typical pattern that can be readily divided into its constituent phases and components.(1) Demyelinating and axonal forms of the syndrome occur in varying proportions across different geographical regions, and clinical variants, such as Miller-Fisher syndrome, are readily definable. (2) Within the typical disease course are many less well-understood biological variations, which are considered chronologically in this Seminar. First, Guillain-Barré syndrome is usually preceded by infection or other immune stimulation that induces an aberrant autoimmune response targeting peripheral nerves and their spinal roots. Molecular mimicry between microbial and nerve antigens is a major driving force behind the development of the disorder, at least in the case of Campylobacter jejuni infection. However, the interplay between microbial and host factors that dictate if and how the immune response is shifted towards unwanted autoreactivity is still not well understood. (3) Furthermore, genetic and environmental factors that affect an individual's susceptibility to developing the disease are unknown. Unwanted autoimmunity does not arise in most individuals (>99%) exposed to an immune stimulus as a result of Guillain-Barré syndrome associated infections such as C jejuni. (4)

It has been more than 100 years since Guillain-Barré and Strohl reported two cases of acute flaccid paralysis with albumin-cytological dissociation that has come to be known as Guillain- Barré syndrome. (5) Guillain-Barré syndrome (GBS) is now considered a heterogeneous group of related disorders, that includes Miller-Fisher syndrome and various GBS subtypes. Even before the time of the original description by Guillain-Barré and Strohl, French neurologist Landre had described 10 cases with remarkable similarity to the clinical description of Guillain, Barré, and
Strohl's cases. (6)

Causes of Guillain-Barre Syndrome:

Around 75% of patients have a history of preceding infection, usually of the respiratory and gastrointestinal tract. A large (7) number of infections have been linked to the onset of the syndrome, but only a few associations have been established. Infections that have been linked to Guillain-Barré syndrome,

- Campylobacter jejune.
- Epstein Barr virus.
- Cytomegalovirus.
- Mycoplasma.
- Human immunodeficiency virus.

Epidemiology and Preceding Infections:

Most studies that estimate incidence rates of Guillain-Barré syndrome were done in Europe and North America, and showed a similar range of 0·8–1·9 (median 1·1) cases per 100000 people per year.(8) The annual incidence rate (see figure 1) of Guillain-Barré syndrome increases with age (0·6 per 100000 per year in children and 2·7 per 100000 per year in elderly people aged 80 years and over) and the disease is slightly more frequent in males than in females. Seasonal fluctuations, presumably related to variations in infectious antecedents, have been reported, but these observations are rarely statistically significant.(9)

Guillain-Barré syndrome is a typical post-infectious disorder, as shown by the rapidly progressive, monophasic disease course (< 1 month) shortly after infection, usually without relapse. An emerging relationship between Guillain-Barré syndrome and acute arbovirus infection including Zika and chikungunya is being closely monitored and is the subject of major interest as the global epidemic spreads. As further information emerges from epidemiological monitoring in case-control studies, the precise incidence data for arbovirus-associated Guillain- Barré syndrome will become clear.(16)

Variants of GBS:

As mentioned, GBS is an umbrella term that describes many clinically and electro physiologically heterogeneous disorders that share the common feature of acute onset symmetric paralysis with or without sensory loss. GBS can be classified based on clinical features depending on topographic involvement or based on electrophysiological features. Clinically, GBS has one important variant – the Miller Fisher syndrome (MFS) and both GBS and MFS have various forms of frustes leading to a very heterogenous clinical picture. [19] Electro physiologically GBS can have a demyelinating pattern – acute inflammatory, demyelinating polyradiculoneuropathy (AIDP) or an axonal pattern – acute motor axonal neuropathy (AMAN) and acute motor sensory axonal neuropathy (AMSAN)

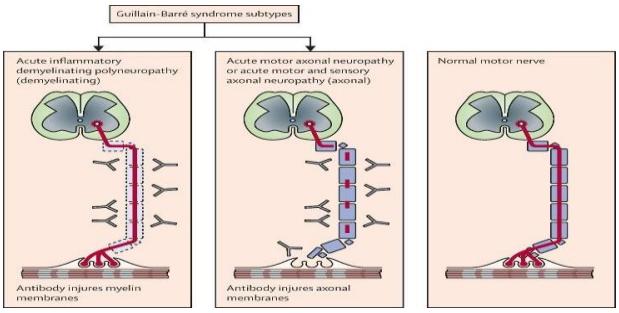

Figure 1: Major Guillain-Barré syndrome subtypes in which antibody-mediated effector pathways

including complement activation, cause glial or axonal membrane injury with consequent conduction failure. Typical GBS is often preceded by a viral-like prodrome that may occur between 3 days to 6 weeks before the onset of neurological symptoms. Besides this viral prodrome, several other triggers also have been noted including bacterial (particularly Campylobacter jejuni) and parasitic infections, surgery, vaccination, malignancy, pregnancy, and bone marrow transplantation. Neurological symptoms usually begin abruptly with a distal, relatively symmetrical onset of paraesthesia (acral paraesthesia) with little objective sensory loss often associated with severe radicular back pain (related to nerve root inflammation) or neuropathic pain. (20) This is an important symptom because the absence of sensory phenomenon points to an alternative diagnosis such as poliomyelitis, myasthenia gravis, electrolyte disturbance, or botulism.

Pathophysiology and Immunopathology:

Until 20 years ago Guillain-Barré syndrome was regarded as a homogeneous disorder, the outcome of which varied according to severity. This variation was believed to be largely caused by the extent of bystander axonal injury arising secondarily to adjacent demyelination, rather than fundamental pathophysiological differences in the types of Guillain-Barré syndrome between individuals. (20) Peripheral nerve remyelination is a functionally effective, natural repair process, whereas axonal regeneration is slow, and can be irreversible if widespread along the whole length of a nerve Fiber. The advance in understanding that changed this viewpoint was the appreciation that distinct, clinical, pathological phenotypes could be delineated within the Guillain-Barré syndrome spectrum, the main phenotypes of which are termed acute inflammatory demyelinating polyneuropathy and acute motor axonal neuropathy. Although this distinction of Guillain-Barré syndrome phenotypes does not negate the idea of bystander axonal injury, it does clarify the point that axons themselves can be the primary target for autoimmune injury, rather than being injured as a secondary phenomenon. (12)

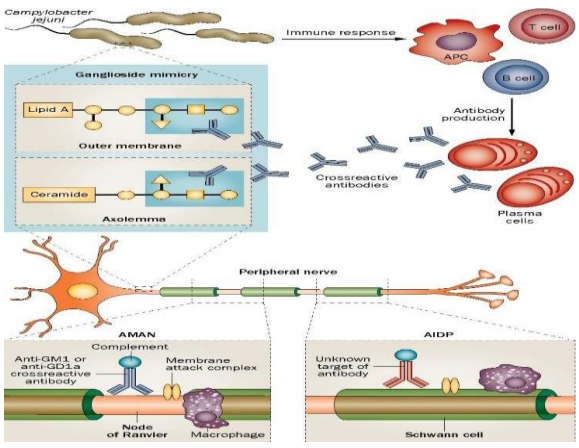

Figure no: 2

In animal models, they induce axonal injury by fixing complement, recruiting macrophages, and depositing membrane attack complex in the axolemmal membrane. (19) This immunological cascade disrupts the anatomical and physiological integrity of exposed nerve membranes in nerve terminals and nodes of Ranvier, causing a nerve conduction blockade that is either reversible or, in severe cases, results in severe, widespread axonal degeneration with poor recovery.

Diagnostic Criteria for Guillain-Barre Syndrome and its Variants:

(i) Features needed for diagnosis of Guillain-Barré syndrome in clinical practice

- Progressive weakness in legs and arms (sometimes initially only in legs).
- Areflexia (or decreased tendon reflexes) in weak limbs.

(ii) Additional symptoms

- Progressive phase lasts days to 4 weeks (often 2 weeks).
- Relative symmetry.
- Mild sensory symptoms or signs (not present in acute motor axonal neuropathy).
- Cranial nerve involvement, especially bilateral weakness of facial muscles.
- Autonomic dysfunction.
- Pain (common).

(iii) Features that should raise doubt about the diagnosis of Guillain-Barré syndrome

- CSF: increased number of mononuclear cells or polymorphonuclear cells (>50 cells per μL).
- Severe pulmonary dysfunction with little or no limb weakness at onset.
- Severe sensory signs with little or no weakness at onset.
- Bladder or bowel dysfunction at onset.
- Fever at onset.
- Sharp spinal cord sensory level.
- Marked, persistent asymmetry of weakness.
- Persistent bladder or bowel dysfunction.

Criteria for its Variants:

Pharyngeal cervical brachial (PCB):

The Pharyngeal cervical brachial (PCB) variant is a regional variant of GBS that typically presents with rapidly progressive oropharyngeal and cervicobrachial weakness associated with areflexia in the upper limbs. Mild ptosis and facial weakness along with mild sensory symptoms in upper limbs may be present and do not refute a diagnosis of PCB. Weakness in the lower limbs is variable; but much less prominent than the upper limbs and neck muscles. If the leg weakness is severe and extensive, current nosology is to consider it as extensive PCB rather than an overlap with GBS. DTRs may be preserved in about 5 - 10% of the patients. Patients with pharyngeal-cervical-brachial weakness often carry antiganglioside T1a (GT1a) IgG antibodies, some of which might cross-react with anti-ganglioside Q1b (GQ1b).

Core features

- Relatively symmetric oropharyngeal weakness AND neck weakness AND arm weakness AND arm areflexia/ hyporeflexia
- Absence of ataxia AND disturbed consciousness AND prominent leg weakness
- Monophasic illness pattern AND interval between onset and nadir of oropharyngeal or arm weakness between 12 h and 28 days AND subsequent clinical plateau

Bifacial weakness with paraesthesia (BFP):

Bifacial weakness with paraesthesia (BFP) is characterized by rapidly progressive bilateral facial weakness with or without loss of taste, paraesthesia in the distal limbs, hyporeflexia, nadir within 4 weeks of onset(5), and subsequent recovery that accounts for < 1% of GBS. Distal paraesthesia usually precedes facial weakness by 7 - 10 days. Facial weakness can be simultaneous or sequential with asymmetry. Although there is no limb weakness or sensory loss, DTRs may be decreased and there is electrophysiological evidence of demyelination on Nerve Conduction Studies (NCS) in the limbs. The condition has an excellent prognosis irrespective of treatment with Intravenous Immunoglobulin (IVIG)/Plasma Exchange (PE). (13) Diagnostic criteria for bilateral facial palsy with paraesthesia are listed in Table II. (16) It is important to be aware of this diagnosis and differentiate it from the other common cause of facial palsy – Bell's Palsy. BFP usually does not progress to tetra paresis, though facial weakness can occur in MFS and PCB, which can then cause tetra paresis. No treatment is required unless ophthalmoplegia or pharyngeal weakness is present.

Core features

- Facial weakness and limb areflexia/hyporeflexia
- Absence of ophthalmoplegia, ataxia, and limb or neck weakness
- Monophasic disease course with an interval between onset and nadir of the weakness of 12 hours to 28 days, followed by a clinical plateau

Supportive features

- Antecedent infectious symptoms
- Presence of distal paraesthesia at or before the onset of weakness
- Electrophysiological evidence of neuropathy
- Cerebrospinal fluid albuminocytological dissociation

Paraparetic GBS:

Paraparetic GBS is another regional variant of GBS that is characterized by isolated flaccid lower limb weakness without neurological findings in the upper limbs. Symptoms usually begin with a severe bilateral 'sciatic-like' leg pain that contributes to loss of leg function and a positive Lasègue's sign that can be misdiagnosed as an orthopaedic disorder. Deep tendon reflexes are absent in

the lower and variable in the upper limbs. There is no sensory level though bladder dysfunction may be present in 14% of cases. (14) MRI of symptoms. CSF is essential to rule out infectious causes of lumbosacral radiculopathy such as tuberculosis and cytomegalovirus. Diagnostic criteria are enlisted in Table III. (17)

- Leg weakness (may be asymmetric or unilateral) and leg areflexia/ hyporeflexia
- Absence of arm weakness Supportive features
- Electrophysiological evidence of neuropathy

Diagnosis of GBS:

GBS is a rare disorder that can be difficult to accurately diagnose. Weakness of the limbs and areflexia, the most common symptoms experienced in GBS, are often attributed to other diseases due to the infrequent diagnosis of GBS. This along with a wide range of diversity in other symptoms can be problematic when identifying the cause of a patient's symptoms. In
children, GBS is even more difficult to recognize, resulting in only one-third receiving a correct diagnosis at admission. (18) Currently, only two diagnostic tools are used to diagnose GBS:

Electromyography:

Electromyography is a diagnostic tool that uses probes, either attached to the skin or inserted into the muscle, that send out electrical impulses to detect nerve activity in potential GBS cases. In GBS patients the electrical impulses being sent may show signs of slowed nerve conduction or conduction being blocked completely. These findings indicate that the patient's paralysis can be attributed to nerve damage in the limbs.

Treatment:

Treatment options for GBS are dependent on the severity of the disease. Currently, in mild cases, there is typically no prescribed treatment. A mild case is defined as an individual who is still able to walk with or without assistance. In these cases, however, physical therapy may be beneficial. For more severe cases there are two treatment options,

Plasma Exchange:

Plasma exchange is a procedure in which the patient's blood is removed from their body and filtered before being returned to the body system. The goal of this treatment is to remove the harmful, soluble antibodies that are causing damage to the nerves from the blood. However, the timing of this treatment plays a key role in determining how effective it is. A study conducted in North America showed that plasma exchange had the greatest improvement when given within
two weeks of the onset of symptoms.

Intravenous Immunoglobulin:

Intravenous immunoglobulin is another treatment for GBS and is more commonly used than plasma exchange. For this treatment, donated blood is processed and separated such that the immunoglobulin is isolated. The antibodies, which are in the immunoglobulin, are then given to the patient through an IV to help stop the harmful, cross-reacting antibodies from damaging the nerves. Several mechanisms have been suggested as to how this treatment is beneficial. These mechanisms include a blockage of receptors found on macrophages which prevents the harmful antibodies from attacking the myelin and the donor antibodies help to regulate the antiganglioside antibodies or cytokines.

Conclusion

More than a century has passed since the initial description of GBS. Since then, a number of developments have been made in our comprehension of the pathophysiology of GBS, and many variances in clinical presentation have been identified. It is important to understand that GBS can show in a variety of regional or localized ways, not just the characteristic quickly increasing quadriparesis, and that it can even include the central nervous system in the form of BBE. This will assist in differentiating between variations and starting therapy early to avoid problems.

Author contributions

All authors are contributed equally.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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