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REVIEW

Guillain-Barré syndrome: causes, immunopathogenic mechanisms and treatment

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ABSTRACT

Introduction: Guillain-Barrè syndrome is a rare disease representing the most frequent cause of acute flaccid symmetrical weakness of the limbs and areflexia usually reaching its peak within a month. The etiology and pathogenesis remain largely enigmatic and the syndrome results in death or severe disability in 9–17% of cases despite immunotherapy.

Areas covered: In terms of etiology, Guillain-Barrè syndrome is linked to *Campylobacter* infection but less than 0.1% of infections result in the syndrome. In terms of pathogenesis, activated macrophages and T cells and serum antibodies against gangliosides are observed but their significance is unclear.

Expert commentary: Guillain-Barrè syndrome is a heterogeneous condition with numerous subtypes and recent data point towards the role of ganglioside epitopes by immunohistochemical methods. Ultimately, we are convinced that the syndrome results from a permissive genetic background on which environmental factors, including infections, vaccination and the influence of aging, lead to disease.

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1. Introduction

Guillain–Barré syndrome (GBS) represents the most common cause of acute flaccid symmetrical weakness of the limbs and areflexia in the post-polio era. In general terms, GBS encompasses a wide range of clinical syndromes with an acute inflammatory polyradiculoneuropathy, muscle weakness, and reduced reflexes. It was first described almost 100 years ago by three French neurologists Georges Guillain, Jean-Alexandre Barré, and Andre Strohl in two soldiers with elevated protein concentration and a normal cell count in the cerebrospinal fluid (CSF). In 1949, Haymaker and colleagues described the clinicopathologic features of 50 fatal GBS cases and noted axonal degeneration, myelin breakdown, and nerve edema [1]. In 1986, Feasby and colleagues further described a GBS variant with predominant direct axonal damage rather than demyelination [2], which was later coined acute motor axonal neuropathy (AMAN) or acute motor sensory neuropathy (AMSAN), secondary to the molecular mimicry between bacterial lipooligosaccharide and the human GM1 ganglioside [3–5]. Based on these observations and the proposed role for autoimmunity, intravenous immunoglobulin (IVIg) and plasma exchange are utilized in GBS [6], without impacting on the risk of death or severe disability which ensues in 9–17% of cases [7].

Along with enormous progress made in the understanding of immune-mediated neurological disorders [8,9], particularly multiple sclerosis [10–13], the past 10 years have witnessed substantial advancements in the epidemiology, immunopathogenesis, clinical features, and clinical management of GBS, and this manuscript will provide a comprehensive overview of the past and recent lines of evidence. This is well illustrated by the fact of serum antiganglioside antibodies, often detected although their levels decrease over time [14], which may represent a good candidate biomarker in this complex condition, despite their limited sensitivity particularly in patients with AMAN and virtual absence in acute inflammatory demyelinating polyradiculoneuropathy (AIDP) [15].

2. Epidemiology

The term GBS can be used to denote a syndrome that includes the aforementioned AMAN, the AIDP and other variants such as AMSAN, and the Miller-Fisher syndrome (MFS), which is characterized by ataxia, ophthalmoplegia, and areflexia. Overall, the clinical course, severity, and outcomes of GBS are highly variable. However, with the identification of several new phenotypes in the past years, the conceptual framework of GBS has become increasingly complex.

The incidence of typical GBS ranges between 0.81 and 1.89 (median 1.11) cases per 100,000 person-years, being more common in men than women (sex ratio 1.5:1), and available data are illustrated in Table 1. The prevalence and incidence of GBS increase with age, and age-specific GBS rates are 0.62 cases per 100,000 person-years among 0–9-year-old subjects versus 2.66 cases per 100,000 person-years in the 80–89-year-

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Table 1. Reported incidence rates of Guillain–Barré syndrome in different Countries [16].

Author	Reference	N	Yearly incidence (/100,000)	Country
Deceuninck	[23]	33	0.81	Canada
Winner and Evans	[24]	72	1.1	England
Govoni	[25]	69	1.89	Italy
Bogliun and Beghi	[26]	138	1.55	Italy
Chiò	[27]	126	1.44	Italy
Sedano	[28]	63	1.03	Spain
Aladro-Benito	[29]	81	1.04	Spain
Cuadrado	[30]	337	0.85	Spain
Cuadrado	[31]	98	1.25	Spain
Cheng	[32]	73	1.63	Sweden
Beghi	[33]	48	1.68	USA
Schonberger	[34]	418	0.94	USA

old population [16]. The crude incidence rate of GBS in Bangladesh was highest (2.5 per 100,000 person-years) with seasonal fluctuation and a peak in May [17] and lowest (0.40 per 100,000 person-years) in Brazil [18]. The epidemiology of the AMAN subphenotype of GBS is limited, and the reported frequency using electrodiagnostic criteria is highest (65%) in Chinese patients [19] compared to 6–7% in North American and European series [20,21]. It has been hypothesized that AMAN is more prevalent with poor hygiene infrastructures and higher incidence of diarrhea [22]. The severity of GBS cases also manifests different prevalence rates in different areas being highest in China compared to Europe and the USA, particularly in cases of AMAN group and Bickerstaff's brain stem encephalitis requiring mechanical ventilation with the former representing 4% of GBS cases in Japan, 6% in India, and 11% in Bangladesh [22].

3. Prior infections

Over two-thirds of patients with GBS refer symptoms of respiratory or digestive infections within 6 weeks of onset [22,35]. In 30–40% of GBS cases, *Campylobacter* is the infecting agent, and it has been estimated that 1/1058 infections results in GBS [36]. The association between GBS and *Campylobacter jejuni* was first described around 1982 in clinical anecdotes by Rhodes and Tatterfield [37]. Other infections preceding GBS may derive from *Mycoplasma pneumoniae, Haemophilus influenzae, Salmonella* species, *Mycobacterium bovis, Brucella, Orientia tsutsugamushi, Legionella pneumophila, Bartonella henselae, Helicobacter pylori, Francisella tularensis, Borrelia*, cytomegalovirus, Epstein–Barr virus, varicella-zoster virus, influenza virus, human immunodeficiency virus, parainfluenza virus type 1, adenovirus, herpes simplex virus, hepatitis (A, B, and E), Japanese encephalitis virus, West Nile virus, enterovirus (D68, 71), Hantavirus, measles, Parvovirus B19, Norovirus, parechovirus, Coxsackieviruses, Echovirus, mumps, rubella, polio (wild-type 3), dengue, chikungunya, and Zika viruses [37–41] (for details, see Table 2). Several vaccines, including influenza A H1N1, rabies, meningococcal, live-attenuated yellow fever, hepatitis A and B, smallpox, polio, MMR, tetanus–diphtheria, and *H. influenzae* type B, have also been considered as a possible trigger of GBS [42,43].

The *Zika virus* is a mosquito-borne flavivirus [140] that was first observed in 1947 and was demonstrated in numerous cases since 2007 [141] with a most recent outbreak in numerous countries worldwide [142]. *Zika virus* infection has been linked to GBS as cases have been reported within a Zika and Dengue fever epidemics in French Polynesia [127], but it remains unclear which infection was related to the neurological manifestations, as previous reports suggested a connection with Dengue fever. The mechanisms involved would be that of molecular mimicry, which can exist on a primary amino acid basis, secondary, or even tertiary structure [128].

Molecular mimicry is an important mechanism that can lead to autoimmune responses, and further data on not only vaccination but also infection will require the ability to do detailed analysis of the structural homologies and the individual host immune response. Certain criteria need to be met before attributing disease causation to molecular mimicry. These include epidemiological evidence linking the suspected infectious agent or exogenous substance with the autoimmune disease; identification of T-cell responses or specific antibodies against the target autoantigen; identification of structural homology between the infectious agent or exogenous substance and the target autoantigen; and finally, reproduction of the autoimmune disease following immunization with the infectious agent or exogenous substance in an animal model [143]. The axonal subphenotype of GBS is the only autoimmune disease at present that fulfills all four criteria for molecular mimicry [144]. Other mechanisms explaining the relationship between infection and GBS may include epitope spreading, bystander activation, the production of superantigens, and aberrant activation of the immune response [145].

4. Pathogenesis

Different mechanisms are proposed for AIDP and AMAN. In the former case, Asbury et al. in 1969 first reported the segmental demyelination restricted to nerve regions infiltrated by T cells and macrophages in four patients who died from GBS [146]. This led to the understanding that myelin damage is caused predominantly by activated macrophages which penetrate the basement membrane around nerve fibers ultimately leading to demyelination [147]. Furthermore, patients with acute GBS have lower peripheral CD4+ CD25+ T-cell count compared to controls, thus also supporting the role of T cells in pathogenesis of GBS [148]. The demonstration of complement activation products on the surface of Schwann cells and the identification of vesicular myelin degeneration led to hypothesis that complement activation on Schwann cell surface led to demyelination. The complement activation was mediated by the binding of specific antibodies to epitopes on the Schwann cell surface followed by vesiculation of myelin before invasion of macrophages [149]. The invasion of Schwann cell basement membrane was hypothesized to be a consequence of the increased matrix metalloproteinase 9 (MMP9) observed in patients with GBS [44]. Macrophages target antigens on the surface of Schwann cells or myelin sheath via activated T cells and MMP9 along with toxic nitric oxide radicals released by activated macrophages lead to Schwann cell injury and subsequent invasion of the peripheral nerve [150]. Furthermore, the inflammatory mediators and cells may induce axonal damage in severe cases of AIDP in a process referred to as secondary degeneration [150]. Nonetheless, we should also

Table 2. The proposed links between Guillain–Barré syndrome and infection, from *C. jejuni* to *Zika virus*.

Agent	Epidemiology	Subphenotype(s) association	Physiopathological mechanism	Pathogen characteristics	Anti-gangliosides antibodies	References
Bacterial						
Campylobacter jejuni	*C. jejuni* has consistently been identified as the most frequent antecedent infection in GBS, appearing in approximately a quarter of patients	Predominantly, but not exclusively, related to AMAN	Molecular mimicry: cross-reactivity between epitopes on *C. jejuni* and peripheral nerve gangliosides	*C. jejuni* epitopes: surface LOS, subtyping into seven classes (A–G) based on the presence of specific LOS loci	AMAN: anti-GM1a, GM1b, GD1a, and GalNAc-GD1a gangliosides	[6,44–52]
		GBS following *C. jejuni* infection may be more severe than that caused by other infectious agents	Ganglioside expression is tissue-specific and anti-ganglioside profiles, therefore determine patterns of neurological involvement	Class A (GBS) and B (MFS) locus	MFS or MFS–GBS overlap syndrome: anti-GD1b, GD3, GT1a, and GQ1b gangliosides	
				Polymorphisms: *cstII* gene, Thr51 variant (GBS), Asn51 variant (MFS), TNF, and *MBL2* gene	MFS and BBE: anti-GT1a and GQ1b	
	Approximately 1 in 1000 patients with *C. jejuni* goes on to develop GBS		Complement activation seems to contribute to nerve degeneration in GBS	*C. jejuni* serotypes O:19 (GBS), O:2 (FS)	Antibodies against combinations of epitopes from ganglioside complexes	
			C. jejuni LPO bind to siglec-7 (sialic acid binding immunoglobulin-like lectin 7) and activate dendritic cells via Toll-like receptor 4 and CD14. These dendritic cells produce type 1 interferon and TNF, which induce proliferation of B cells	*C. jejuni* subspecies jejuni HS:41 strains RM3196 (233.94) and RM3197 (308.95)		
Mycoplasma pneumoniae	*M. pneumoniae* seropositivity in GBS patients ranges significantly (1–25%)	AIDP, BBE, MFS	Molecular mimicry	Presence of GM1 epitope in *M. pneumoniae*.	Anti-GM1 (pathogenic), Gal-C (possible epiphenomenon), and GA1	[53–56]
Haemophilus influenzae	*H. influenzae* is a normal constituent of upper respiratory tract flora in 80% of humans, and isolation may occur in conjunction with other infectious triggers of GBS	MFS and AIDP	Molecular mimicry GBS following immunization with the *H. influenzae* type b conjugate vaccine	Of the six serotypes (a–f) of capsular strains of *H. influenzae*, type b causes serious chest infections and appears to be associated with GBS	Anti-GM1 (AMAN) and GQ1b (MFS)	[42,57–62]
				LOS from some type b strains have been shown to bear ganglioside-like molecules		
Salmonella species	1% of patients with typhoid fever developed GBS	AIDP, MFS, and BBE	It is unclear whether molecular mimicry plays a role in *Salmonella*-related GBS	GBS related to enteric fever caused by *Salmonella* Typhi (typhoid fever) or *Salmonella* Paratyphi (paratyphoid fever)	Anti-GQ1b (BBE)	[63–67]
Viral						
CMV	0.6–2.2 cases per 1000 persons	AIDP (up to 70%), AMSAN, AMAN (7%), and MFS (6%)	The roles of anti-ganglioside antibodies, cellular immune responses, and viral replication are not yet established	Serological evidence of primary CMV infection	Anti-GM2 (IgM), more closely associated with primary CMV infection than with GBS	[57,68–75]
		Younger, female, sensory symptoms, and facial palsy	T cell-mediated immune response to neural antigens		Anti-GalNAc-GD1a, GM1, GM3, GD2, GD3, GT1b, and GT1a	

(*Continued*)

Table 2. (Continued).

Agent	Epidemiology	Subphenotype(s) association	Physiopathological mechanism	Pathogen characteristics	Anti-gangliosides antibodies	References
		GBS associated with CMV infection after transplantation	Possible association between viral replication and sensory defects Molecular mimicry		Antibodies against moesin, a component of the ezrin–radixin–moesin cytoplasmic complex in Schwann cell microvilli that surround the nodal axolemma (not replicated)	
EBV	Large population studies on the incidence of EBV reactivation and GBS are lacking	AIDP, AMSAN, AMAN, and BBE	Immunological (anti-GQ1b antibodies) mechanism induced by infection	Acute EBV infection: IgM and IgG antibodies against VCA and the absence of antibodies to EBNA	Anti-GQ1b, GM1, and GM3	[37,68,75–79]
		GBS associated with EBV infection after transplantation	Disturb the regulatory mechanisms that normally inhibit latent autoimmunity against peripheral nerve antigens rather than providing a specific autoimmune antigenic stimulus			
VZV	Risk of developing GBS 18.7-times greater	GBS Mainly in the case of latent infection reactivation	Molecular mimicry: scarce data regarding possible structural mimicry between VZV and the molecules of human peripheral nerves	More likely to have had a recent infectious event	Anti-GM1 (IgM) and GD-1 (IgM)	[37,80,[81]
	Only 1% of antecedent infections	Short latency period between rash onset and the development of neurological symptoms	HZ could play a pathogenic role in triggering GBS	GBS might be associated with recent infectious events of pathogens other than VZV		
	Fewer than 50 cases reported	Poor clinical prognosis	Directly related to autoimmune-mediated responses initiated by the VZV reactivation Aberrant immunological status of the host Imbalance of helper and suppressor lymphocytes	Coinfection with different strains of pathogen can be found		
Influenza virus	Four to seven cases per 100,000 cases of influenza	AMAN, AMSAN, AIDP, and MFS	Influenza virus does not share structural homologies with known gangliosides	Influenza A (H1N1), influenza B virus	Anti-GD1b, GM1, GD1a, Gal-C, GM3 (H1N1 vaccination), GQ1b (MFS)	[68,82–91]
	15-fold increased risk of developing GBS		The mechanisms linking influenza virus and GBS are poorly understood and probably relate to increased risk of secondary infection			
	18% had antecedent influenza-like illness and 3.5% had serological evidence of recent infection		GBS after seasonal and 2009 H1N1 monovalent influenza vaccines[a]			
HIV	GBS is a well known but rare complication of primary HIV infection	AIDP, AMAN and MFS	Immune mechanisms poorly understood	GBS often develops in early HIV and	Anti-GM1	[92–102]
			Increased susceptibility to infection, direct action of HIV on nerves, and generation of myelin-specific antibodies	sometimes at the time of seroconversion and is only rarely seen in full-blown AIDS	Elevated titers of IgG antibodies against sulfatide, which is a major glycosphingolipid in the myelin sheath (significance in disease pathogenesis questionable)	

(*Continued*)

Table 2. (Continued).

Agent	Epidemiology	Subphenotype(s) association	Physiopathological mechanism	Pathogen characteristics	Anti-gangliosides antibodies	References
			$CD4^+$ T cell-mediated cellular immunity appears to play a role in the pathogenesis of GBS	GBS has also been reported during immune reconstitution following highly active antiretroviral therapy		
DENV	Largest GBS-DENV outbreak ever reported: New Caledonia (2012–2013)	AMAN, AIDP, AMSAN, and MFS	Molecular mimicry	Serotypes (DENV 1–4)	Anti-GD1b	[103–118]
		GBS is reported during the recovery phase of illness	T cells produce cytokines and chemokines which open the BBB allowing antibodies to enter and Schwann cells to attack	Dengue nonstructural protein 1 antibody (anti-NS1) produced after dengue infection could be responsible for the cross-reactivity to endothelial cell		
	There are a few cases of GBS following dengue infection (about 20 cases)	Oligosymptomatic dengue infection (underestimates prevalence of GBS)	Activated T cells could cross the vascular endothelium (BBB) and recognize an antigen in the endoneural compartment			
	GBS accounted for 30% of the neurological manifestations of dengue infection		Proinflammatory substances that participate in immune response to DENV such as TNF, complement, interleukins may have important role in the pathogenesis			
CHIKV	Incidence per 10^6: up 22% from baseline (3.3), Réunion Island	AIDP GBS associated with CHIKV infection has been rarely reported yet	Tropism for brain tissue has been validated in several mouse models of CHIK neuroinfection	The presence of CSF abnormalities and CHIK-specific IgM intrathecal synthesis was highly suggestive of CHIK-induced pathology in the nervous system	Not reported	[119–126]
	The incidence rate of GBS increased 22% in 2006 (26/787,000, persons)	Neurological symptoms started during the invasion phase prior to seroconversion	Disseminated acute CHIKV infection previous to GBS development	Genomic products of CHIKV in serum and CSF are negative		
	GBS incidence was increased four- to ninefold during 2014–2015 (French Polynesia), suggesting a link to CHIKV infection					
ZIKV	2.4/10,000 ZIKV infections Incidence was 20-fold higher than expected during the time coinciding with the ZIKV epidemic in French Polynesia	AMAN	A causal relationship between ZIKV and neurological complications is very likely due to molecular mimicry mechanism	Neutralizing antibodies against ZIKV	Anti-glycolipid antibodies: anti-GA1, GM1, GM2, GD1a, GD1b, and GQ1b	[41,127–139]

[a]The estimated attributable risk of vaccine-related GBS in the adult population was just under one case per 100,000 vaccinations. Major nervous system gangliosides include GM1, GM2, GD1a, GD1b, GT1a, GT1b, and GQ1b.

AIDP: acute inflammatory demyelinating polyneuropathy; AMAN: acute motor axonal neuropathy; AMSAN: acute motor sensory axonal neuropathy; BBB: blood–brain barrier; BBE: Bickerstaff brain stem encephalitis; CSF: cerebrospinal fluid; EBNA: antibodies against the EBV nuclear antigen complex; Gal-C: galactocerebroside; GBS: Guillain–Barré syndrome; LOS: lipooligosaccharide; MFS: Miller-Fisher syndrome; VCA: viral capsid antigen; EBV: Epstein–Barr virus; VZV: varicella-zoster virus; HIV: human immunodeficiency virus; DENV: dengue virus; CHIKV: chikungunya virus; ZIKV: *Zika virus*; CMV: cytomegalovirus; TNF: tumor necrosis factor; Ig: immunoglobulin.

note that AIDP-associated Wallerian-like degeneration occurs mainly in the epiperinerium of nerve trunks, as is the case in P2-induced EAN, thus suggesting a pathogenic role for transperineurial blood flow dysfunction in endoneurial ischemia [151].

C. jejuni induces the unbalance of Th1/Th2/Th17/Treg and cytokines that is crucial for the development of GBS [14]. Upregulation of Th1 cytokines in the early disease course may be associated with immune-mediated disease progression due to neuronal inflammation, but upregulation of Th2

immune response during the later phase aids recovery from the disease [152]. In addition, Th17 also plays a pathogenic role, and elevated circulating Th22 cells are correlated with severity of disease, but not with GBS subphenotypes [153]. Th17 and Th22 cells of GBS patients at acute phase could express an appropriate cytokine profile, like interleukin (IL)-17, IL-22, and others (IL-6 and tumor necrosis factor-α), which can enhance the inflammatory and autoimmune response and conduce to the development of GBS [153].

In the pathogenesis of AMAN, the early changes include the lengthening of the node of Ranvier with myelin distortion while overlying macrophages invade the space between Schwann cell and the axon leaving the internodal myelin sheath and Schwann cytoplasm intact. These changes may be initially reversible, thus explaining the rapid recovery of some patients [44]. The more rapid recovery observed in some cases suggested that AMAN is associated with a block of axonal conduction or axon terminal degeneration [154]. This assumption has been challenged by the experimental evidence shown by the preserved neuromuscular transmission at axonal-stimulating single-fiber electromyography in AMAN, thus supporting that transmission may be impaired in the motor terminal axons proximal to the neuromuscular junction [155]. Patients with AMAN manifest little demyelination or lymphocytic inflammation but demonstrate the presence of immunoglobulin G (IgG) and the complement activation product C3d bound to the axolemma of motor fibers, and in severe cases, IgG and C3d were found within periaxonal space of the myelinated internodes [149].

Serum antiganglioside antibodies represent a major player in the induction and perpetuation of GBS pathology. Gangliosides are sialic acid containing subgroup of glycosphingolipids with *N*-acetylneuraminic acid linked to an oligosaccharide core portion which is expressed on cell surface [156]. Major nervous system gangliosides include GM1, GM2, GD1a, GD1b, GT1a, GT1b, and GQlb, with specific localizations at immunohistochemistry of peripheral nerves, as in the case of GD1a in motor fibers and GD1b in large dorsal root ganglia [154] and are illustrated in Table 3. Conversely, the GQ1b epitope is predominant in oculomotor, trochlear, and *abducens* nerves [156], and Kusunoki and colleagues demonstrated that large neurons in dorsal ganglia had localization of GQ1b epitope which could explain ataxia associated with opthalmoplegia seen in MFS [157]. GQ1b, GT1a, and GD1b mainly localize in the extraocular muscles and limb muscle spindles but are scarcely represented in the limb and axial muscle neuromuscular junctions [157,158]. Anti-GQ1b antibodies cross-react with GT1a and GD1b, thus explaining the paralytic effects observed in the MFS in limited groups of muscles. Kaida et al. described antibodies that are specific for a new conformational epitope formed by two gangliosides such as GD1a/GD1b or GQlb/GM1 ganglioside complexes with antibodies associated with severe GBS requiring artificial ventilation [159]. Bickerstaff's brain stem encephalitis, characterized by acute ophthalmoplegia, ataxia, and drowsiness, shares some similar features with MFS including a prior *C. jejuni* infection and positive serum anti-GQ1b IgG antibody [160]. The pharyngeal–cervical–brachial weakness is associated with anti-GT1a IgG with or without GQ1b reactivity [161]. Authors from Japan reported the molecular mimicry of the lipopolysaccharide of *C. jejuni* with the GM1 ganglioside from a patient with GBS and with GQ1b from patients with MFS [148]. The AMAN subphenotype of GBS is associated with serum antibody to ganglioside GM1 in 64%, GM1b in 66%, GD1a in 45%, and GalNac-GD1a in 33% of cases. Furthermore, 90% of patients with MFS have serum antibodies to GQ1b, while the AIDP subphenotype is frequently seronegative [4,150,162]. *C. jejuni* isolated from patients with GBS and MFS frequently express ganglioside mimics in their lipopolysaccharides, thus possibly inducing antiganglioside antibodies and neurological symptoms, while the heterogeneity in the LPS structure also determines the specificity of the anti-glycolipid response [149]. Specific *C. jejuni* strains have a set of polymorphic genes and enzymes that can alter ganglioside-mimicking lipooligosaccharide outer core [44], and only a subset of *C. jejuni* strains contain lipopolysaccharide that mimic gangliosides in peripheral nerves.

Table 3. Serum antibodies directed against specific gangliosides and the localization of the antigens in Guillain–Barré syndrome and subphenotypes [154–158].

Ganglioside	Localization	Clinical association
GQ1b	Oculomotor nerve	Miller-Fisher syndrome
	Trochlear nerve	Bickerstaff's brain stem encephalitis
	Abducens nerve	Acute ataxic neuropathy (without opthalmoplegia)
	Dorsal root ganglion	Acute ophthalmoparesis (without ataxia)
	Muscle spindle	
GD1b	Dorsal root ganglion	Sensory ataxic GBS
	Muscle spindle	
GM1, GD1a,	Myelinated axons in both motor	AMAN
GalNac-GD1a, Gm1b	and sensory nerves	AMSAN
GT1a,	Glossopharyngeal nerve	Pharyngeal–cervical–brachial weakness
GQ1b	Vagus nerve	

GBS: Guillain–Barré syndrome; AMAN: acute motor axonal neuropathy; AMSAN: acute motor sensory axonal neuropathy.

5. Clinical subphenotypes

The clinical array of GBS varies widely from pure sensory [163] to autonomic variants [164], but these classifications have been challenged by recent reports, as will be discussed in detail. AIDP and AMAN are the most common GBS subphenotypes. Other variants include MFS, AMSAN, Bickerstaff brain stem encephalitis, and pharyngeal–cervical–brachial weakness (the main characteristics are listed in Table 4). AIDP is sometimes mistaken for AMAN if conventional electrodiagnostic data are applied as patients with AMAN have a rapidly reversible conduction block or slowing evident on sequential studies, but numerous issues remain open, suggesting that AIDP may be overestimated and AMAN underestimated. Such conduction blocks disappear with no electrophysiologic evidence of remyelination in patients with AMAN [45]. Cranial nerve involvement is less frequent in AMAN compared to AIDP [165]. The disease progression in terms of muscle weakness differs between AMAN and AIDP, being more rapid and with an earlier peak in AMAN with a variable recovery pattern [166].

Table 4. Clinical subphenotypes and major features in Guillain–Barré syndrome (GBS) [45–168].

GBS subphenotype	Clinical features	Notes
AIDP	Multifocal patchy Demyelination Secondary axonal degeneration in small percentage of patients Autonomic dysfunction Common including HTN, hyperhidrosis, and blood pressure fluctuation. Cranial nerve palsy Frequent sensory loss	Most common in Europe/USA 85–90% of cases Association with CMV and EBV infections. No AB association
AMAN	Cranial nerves rarely affected Tendon reflexes might be preserved or exaggerated in 20% of patients. Progression more rapid and recovery longer compared to AIDP	Ab to GM1a, GD1a Preceding infection is *C. jejuni* 5–10% of GBS in USA 30–65% of GBS patients in Asia, South America, and Central America
Acute motor and sensory axonal neuropathy	Severe form of AMAN	Antibody to GM 1a and GD1a ganglioside
MFS	Ophthalmoplegia, ataxia, areflexia No impaired consciousness Incomplete MFS Acute ophthalmoparesis without ataxia Acute ataxic neuropathy (no ophthalmoparesis)	Anti-GQ1b, anti-GT1a Antibodies in 90% of patients. Preceding infections include *C. jejuni*, *Haemophilus influenzae*
Bickerstaff brain stem encephalitis	Ophthalmoplegic ataxia Areflexia Absence of limb Weakness Impaired consciousness	GQ1b antibodies GT 1a antibodies
Pharyngeal–cervical–brachial weakness	Oropharyngeal neck and arm weakness Absence of leg weakness	Anti-GT1a antibodies Anti-GQ 1b IgG antibodies

CMV: cytomegalovirus; EBV: Epstein–Barr virus; Ab: antibody; AIDP: acute inflammatory demyelinating polyradiculoneuropathy; AMAN: acute motor axonal neuropathy; MFS: Miller-Fisher syndrome.

An irreversible conduction block is associated with slow recovery and extensive axonal degeneration at the nerve roots with poor recovery.

AIDP is characterized by autonomic dysfunction such as hyperhidrosis and fluctuations in blood pressure; autonomic dysfunction is uncommon in AMAN [167]. In general terms, AMAN has been classically addressed as the pure motor form of GBS with no sensory deficits and the acute motor sensory axonal neuropathy is the most severe variant [168], but more recent pathology reported that pure motor GBS is associated with primary demyelination mainly involving the ventral roots [169,170], while 11% of patients with AIDP manifest a pure motor GBS [21].

The MFS is associated with ophthalmoplegia, ataxia, and areflexia in its classical form but may present in a limited form with bilateral internal ophthalmoplegia or bilateral abducent nerve palsies. In the majority (up to 76%) of patients, MFS is anticipated by an upper respiratory tract infection [171] and associated with serum GQ1b antibody in approximately 90% of cases. Patients with pharyngeal–cervical–brachial weakness manifest with symptoms affecting the oropharyngeal, neck, and shoulder muscles and have detectable serum anti-GT1a antibody as GT1a is expressed predominantly in the glossopharyngeal nerve and vagal nerves [172].

6. Diagnosis

Diagnostic criteria for GBS were first published in 1981 and later modified in 1990 [173,174] to include features that make the diagnosis more or less likely (Table 5) and to verify the proposed rise in the frequency of GBS following vaccination for swine influenza virus. New diagnostic classification has been recently published in order to enable neurologists and non-neurologists to diagnose GBS and all its variants using a simple yet all-inclusive classification system [175]. The typical onset of GBS is characterized by the rapidly progressive, symmetrical weakness of limbs usually reaching its maximum severity within 4 weeks [150]. In a large cohort of patients, a monophasic course was observed in 95% of patients, and 97% of patients had reached the clinical nadir by 4 weeks and 80% by 2 weeks [176]. An atypical presentation of GBS, such as paraparesis, is seen in approximately 8% of patients which can persist up to 6 months, while 9% of patients have normal tendon reflexes in the weak arms and 2% in the weak legs

Table 5. Diagnostic criteria for Guillain–Barré syndrome [174–175].

Features necessary for the diagnosis of GBS:

- Progressive weakness in both arms and both legs
- Areflexia

Features strongly supporting the diagnosis of GBS:

- Progression of symptoms over days to 4 weeks
- Relative symmetry of symptoms
- Mild sensory symptoms or signs
- Autonomic dysfunction
- Cranial nerve involvement, especially bilateral weakness of facial muscles
- Absence of fever at onset
- Typical electrodiagnostic features
- High concentration of protein in cerebrospinal fluid, with fewer cells than 10 × 10/l
- Recovery beginning 2–4 weeks after progression ceases

Features making the diagnosis of GBS less likely:

- Bladder or bowel dysfunction at onset
- Persistent bladder or bowel dysfunction
- Sharp spinal cord sensory level
- Marked persistent asymmetry of weakness
- Increased number of mononuclear cells in CSF (>50 cells/μl)
- Severe pulmonary dysfunction with limited limb weakness at onset
- Fever at onset of neurological symptoms
- Polymorphonuclear cells in CSF

CSF: cerebrospinal fluid; GBS: Guillain–Barré syndrome.

at presentation [176]. Severe respiratory muscle weakness necessitating ventilatory support develops in 10–30% of patients.

MFS is diagnosed in patients with opthalmoplegia, ataxia, and areflexia but may also present with incomplete forms without ataxia and in association with serum anti-GQ1b antibody. Different incomplete forms of MFS are known as ataxic GBS to include ataxia without opthalmoplegia and negative Romberg test and acute sensory ataxic neuropathy with ataxia and a positive Romberg test but no opthalmoplegia. Paraparetic GBS is another uncommon and localized variant in which patients develop isolated flaccid lower limb weakness and absent deep tendon reflexes in lower limbs but without neurological findings in the upper limbs [176]. The facial muscle weakness with paresthesias may also appear as a GBS variant coined in the absence of opthalmoplegia or limb weakness, to be distinguished from Lyme disease, sarcoidosis, and bilateral Bell palsy by the presence of serum antiganglioside antibodies. In general terms, atypical and incomplete presentations of GBS should be included in the diagnostic work-up of patients with new onset peripheral symptoms and addressed with a careful history and serological panel.

A CSF analysis is frequently obtained in the differential diagnosis of GBS, and the Brighton Collaboration criteria for GBS and MFS include a cell count in the CSF lower than 50 cells/μl [177]. The albumin-cytological dissociation is a combination of elevated protein level and normal CSF cell count and is observed in only two-thirds of cases, as elevated protein concentration is dependent on the timing of the lumbar puncture. One large Dutch cohort of patients manifested elevated CSF protein in 53% of cases when puncture was performed in the first 3 days after onset of weakness and increased to 80% after 7 days. A CSF cell count between 5 and 50 cells/μl was found in 15% of patients [177]. In an Asian cohort, there was a lower prevalence of elevated CSF protein concentration (55%) and a higher proportion of mild pleocytosis up to 26% [178]. Therefore, normal CSF protein concentration in the first week of weakness does not rule out GBS as the sensitivity is as low as 50%. Only in a subgroup of cases, CSF cell count is higher than 50 cells/μl, and differential diagnoses include Lyme disease or human immunodeficiency virus (HIV)-related radiculitis [178].

Neurophysiological studies are frequently used in the diagnostic process of suspect GBS cases, and nerve conduction studies are helpful to identify the subphenotype of GBS type and exclude disorders that may mimic GBS. AIDP, AMAN, and AMSAN are difficult to distinguish based only on clinical grounds; electrophysiology is the key test. Nerve conduction studies can be normal in nearly one-third of patients when done during the first 4 days, but the absence of F waves or a prolonged F wave latency is frequently observed, especially in the lower limbs. Selective lesions in proximal nerve trunks may explain the discrepancy between nerve conduction and the established paralysis, as elegantly illustrated in electrophysiological [179] and ultrasonographic [180,181] studies of the ventral spinal nerves in AIDP and AMAN/AMSAN. The sensory nerve conduction study of sural nerve is normal in greater proportion of patients [182]. Nerve conduction studies suggestive of demyelination in early AIDP are nonspecific and may occur in disorders that mimic the acute-stage GBS, including acute myelopathy or critical illness polyneuropathy, but more specific finding suggestive of early demyelinating GBS is the presence of a spared normal sural sensory nerve action potential with abnormal ulnar sensory nerve action potential in one retrospective study [183]. Patients with normal EMG have significantly milder weakness at the lowest peak of disease progression compared to patients with abnormal nerve conduction study [176]. Almost 85% of patients with GBS have abnormal nerve conduction studies after 3 weeks and including additional nerves in the study improves sensitivity. Motor conduction slowing exceeding 30% below the lower limit of normal, prolongation of motor distal latency of >150% of upper limit of normal, and prolongation of F wave latency over 120% in two nerves are specific for primary demyelination [184]. The compound muscle action potential is reduced <80% of the lower limit of the normal range in at least two nerves without signs of demyelination in AMAN. However, patients with AMAN may present reversible conduction failure likely derived from an impaired conduction at the nodes of Ranvier due to antibodies to gangliosides and can be falsely diagnosed as having AIDP instead of AMAN due to nerve conduction features suggesting demyelination [185]. Nerve conduction studies need to be interpreted with caution especially when performed early in the disease course, and sometimes, serial studies need to be performed to improve sensitivity, and reversible conduction failure has to be taken into account and most importantly should not delay treatment. Almost 40% of GBS cases did not meet criteria for one of the defined subphenotypes of GBS [176].

7. Differential diagnosis

Careful history, physical examination, CSF analysis, nerve conduction studies, and imaging studies help differentiate GBS and its subphenotypes from other mimics. These include infectious causes, leptomeningeal malignancy, and disorders of the neuromuscular junction (Table 6). GBS manifests a monophasic course in 90% of cases, but 10% of patients develop recurrent or relapsing form. A course not showing improvements after 8 weeks is not typical for GBS, and chronic inflammatory demyelinating neuropathy needs to be ruled out, particularly since patients with this latter condition may mimic GBS at the early stages of progression [186]. Poliomyelitis should be considered in unvaccinated individuals with travel to endemic areas, and non-polio enteroviruses may cause acute flaccid paraparesis with high mortality. West Nile virus and herpes simplex virus can cause extensive necrotizing myelopathy [187]. Herpes, hepatitis A, and rabies viruses may cause transverse myelitis manifesting with back pain with sharp sensory disturbances and changes at MRI based. Elevated CSF lymphocytes with painful asymmetric polyradiculoneuropathy that occurs several months after a tick bite could be due to Lyme disease. Gadolinium MRI allows to discriminate the paraparetic variants of GBS from *cauda equina* syndrome and lumbosacral plexopathy. Findings of nerve root enhancement support a diagnosis of GBS. Diphtheria can cause neuropathy involving either cranial or peripheral nerves, which is demyelinating in nature as opposed to other acute peripheral neuropathies

Table 6. Conditions mimicking Guillain–Barré syndrome to be included in the differential diagnosis.

Peripheral neuropathy
• Chronic inflammatory demyelinating polyneuropathy
• Lead, thallium, and arsenic poisoning
• Acute intermittent porphyria
• Critical illness polyneuropathy (associated with use of high-dose intravenous steroids)
• Tick paralysis
• Metabolic disturbances of serum potassium, phosphate, magnesium, and glucose
• Severe vitamin B1 deficiency
• Puffer fish poisoning
Neuromuscular junction disorders
• Myasthenia gravis
• Lambert–Eaton myasthenic syndrome
• Botulism
Spinal cord involvement
• Transverse myelitis (CMV, herpes simplex virus, Epstein–Barr virus, and varicella-zoster virus)
• Anterior spinal artery occlusion
• Epidural abscess
Anterior horn cell involvement
• Poliomyelitis and non-polio enterovirus (enterovirus 71)
• West Nile virus, herpes simplex virus, CMV, and varicella-zoster virus
• Rabies virus and HIV
Muscle disorders
• Acute myositis (postinfectious can be sec to influenza A)
• Acute hypokalemic periodic paralysis (often familial)
• Thyrotoxic periodic paralysis (more common in Asians and Hispanics)
Brain stem stroke
Brain stem encephalitis
• Listeriosis, tuberculosis, brucellosis, JC virus, and toxoplasmosis
• Multiple sclerosis, sarcoidosis, and systemic lupus erythematosus
Wernicke encephalopathy

Adapted from Ref. [187].
CMV: cytomegalovirus; HIV: human immunodeficiency virus.

which are of axonal type [187]. Different from virus-induced transverse myelitis, Listeria, Mycobacteria, and Lyme disease may associate with brain stem encephalitis that, however, may also be based on autoimmune mechanisms and mimic MFS and Bickerstaff brain stem encephalitis. The Bickerstaff brain stem encephalitis may mimic Wernicke's encephalopathy from thiamine deficiency in alcoholism or other causes of dietary imbalance such as major gastrointestinal surgery [188]. HIV infection may directly involve spinal cord, nerve root, and peripheral nerves, and opportunistic infections with cytomegalovirus, Epstein–Barr virus, and varicella-zoster virus can cause acute flaccid paralysis.

8. Treatment

Patients with GBS need a multidisciplinary approach, which includes careful monitoring of vital capacity, prevention of infections, monitoring for possible autonomic dysfunction, physical therapy, and rehabilitation.

Approximately one-third of patients with GBS need to be admitted to the intensive care unit because of respiratory failure, dysautonomia, or medical complications [189]. Adequate ventilation relies on the triad of adequate inspiratory effort, effective expiratory force, and ability to protect the airway. The decision to intubate the patient with GBS is based on clinical and paraclinical evidence of impending or overt respiratory failure, including impaired mentation, air hunger, increased respiratory rate, the inability to count on one breath to 20, forehead sweating, staccato speech, paradoxical respiration, inability to lift the head from the bed, shoulder weakness, and signs of bulbar muscle weakness [189]. Chronic ventilatory failure should be suspected by a history of fatigue, lethargy, difficulty concentrating, poor sleep and daytime somnolence, and morning headache (indicating hypercapnia) [190].

Prednisolone or intravenous methylprednisolone treatment in GBS patients did not improve patient outcomes [191,192]. Plasmapheresis and IVIg are the only known effective treatments for GBS. Plasmapheresis was found to be most effective in GBS cases who received treatment within the first 2 weeks of disease onset and who are unable to walk [193]. Two plasma exchanges were found to ameliorate mildly affected GBS cases who were able to walk. Patients with severe GBS who need mechanical ventilator had to undergo at least four plasma exchange sessions to improve outcomes [194]. In a randomized controlled trial, IVIg given daily for 5 consecutive days were as effective as five sessions of plasma exchange started within 14 days [195]. IVIg inhibits the binding of autoantibodies to GQ1b and also complement activation by anti-GQ1b in a mouse model [196]. IVIg is preferred in young children over plasma exchange where it can be technically difficult and also patients with cardiovascular instability, given large volume shifts that occur with plasma exchange. Patients with GBS who received IVIg showed significant pharmacokinetic variation, and patients with low rise in serum IgG 2 weeks after treatment have a more severe clinical course and poor outcomes at 6 months after standard-dose treatment independent of other prognostic factors [197]. IVIg therapy did not affect recovery outcomes in patients with MFS, and excellent recovery from ophthalmoplegia and ataxia was noted in patients who did not receive plasmapheresis or IVIg treatment at the end of 1 year [198]. A double-blind, placebo-controlled randomized trial showed no additional benefit when combining methylprednisolone and IVIg [199]. Adverse prognostic indicators include previous diarrhea, older age, disease severity, and rapid disease onset [7].

Pain is a common symptom in GBS patients, occurring in up to 50% of all GBS patients, and should be diagnosed and treated promptly [200]. Another priority to consider is monitoring nutritional status.

Death or severe residual disability has varied widely with rates between 1% and 18% despite immunotherapy [7,201]. Death results from pneumonia, sepsis, adult respiratory distress syndrome, and autonomic dysfunction [201], and data are awaited from an ongoing prospective international multicenter observational trial assessed whether a second dose of IVIg (I-SID-GBS) improved outcomes in poor-prognosis cases. Erythropoietin has been associated with the amelioration of nerve regeneration/repair with reversal of inhibitory effects of anti-ganglioside antibodies on nerve repair in an animal model [191]. Eculizumab is a humanized monoclonal antibody against the complement protein C5 which appeared protective against complement-mediated motor neuropathy and respiratory paralysis in a mouse model [192], and phase II clinical trials are currently recruiting patients in Scotland and Japan. Clinical studies are still lacking on the use of

erythropoietin or eculizumab. New and more effective treatments are required to improve the prognosis.

9. Expert commentary

GBS encompasses numerous common paradigms of autoimmune and chronic inflammatory diseases, including but not limited to the specific serum autoantibodies, the infectious trigger, and the response to immunosuppressants, similar to other conditions [202]. First described almost a century ago by three French neurologists, GBS is an uncommon disease (with incidence rates ranging between 0.81 and 1.89 [median 1.11] cases per 100,000 person-years) but is the most frequent cause of acute flaccid symmetrical weakness of the limbs and areflexia following the polio era. Different from other autoimmune or chronic inflammatory diseases, GBS is more prevalent in men (male to female ratio of 1:5). The syndrome typically appears with a rapidly progressive, symmetrical weakness of limbs usually reaching its peak within a month and respiratory or gastrointestinal infections precede the symptoms within 6 weeks in the majority of patients [203,204]. GBS is strongly linked to *Campylobacter* infection, but less than 0.1% of infections result in the syndrome. The most recent outbreak of *Zika virus* infection raises concerns also for GBS as cases have been reported within a Zika and Dengue fever epidemics in French Polynesia and South America. Diagnostic criteria include features that make the diagnosis more or less likely and were first published in 1981 to be modified recently, but clinical suspicion and physician awareness remain the limiting factors of the diagnostic approach. The AMAN and the AIDP represent the most common clinical subphenotypes along with the more rare MFS, AMSAN, Bickerstaff brain stem encephalitis, and pharyngeal–cervical–brachial weakness. Besides the activation of macrophages and T cells, serum antibodies are associated with GBS being directed at gangliosides, sialic acid containing subgroup of glycosphingolipids with *N*-acetylneuraminic acid linked to an oligosaccharide core portion. Nervous system gangliosides include GM1, GM2, GD1a, GD1b, GT1a, GT1b, and GQlb, with specific localizations by immunohistochemistry possibly predicting the associated clinical phenotype. GBS results in death or severe disability in near 20% of cases despite immunotherapy, which is represented by plasmapheresis and IVIgs which remain the cornerstone of the medical management. Cumulatively, GBS is a heterogeneous condition with numerous subphenotypes, and advances have been made over the past 20 years on the understanding of GBS immunopathogenesis and localization of ganglioside epitopes by immunohistochemical methods. Ultimately, we are convinced that GBS, similar to other inflammatory diseases, is the result of a permissive genetic background on which environmental factors, including infections, vaccination, and the influence of aging, lead to disease onset and the natural history of disease [203–210].

10. Five-year view

Further research efforts are needed to identify GBS biomarkers to help in the early diagnosis, predict progression, and initiate adequate treatment. Similar to what observed in other autoimmune conditions [202,211], serum autoantibodies currently represent the only option for diagnostic and prognostic purposes, but our understanding is limited by the relative rarity of the disease. New powerful tools should be used in GBS to determine additional serum autoantibodies, including protein and RNA immunoprecipitation. Alternative research directions should be sought for a better understanding of GBS pathogenesis, including the collection of large multicenter series of patients, including twins [212], or the study of sex-related factors [213] via epigenetics [214–217]. Ultimately, we are convinced that the enormous number of biotechnological drugs, i.e., monoclonal antibodies and small molecules, may prove useful also in GBS by tackling pivotal pathogenesis of effector inflammatory mechanisms [218,219].

Key issues

- Guillain-Barré syndrome was first described almost a century ago by three French neurologists and remains the most frequent cause of acute flaccid symmetrical weakness of the limbs and areflexia;
- Guillain-Barré syndrome yearly incidence ranges between 0.81 and 1.89 (median 1.11) cases per 100,000 person;
- Guillain-Barré syndrome is more prevalent in men by 50%;
- Guillain-Barré syndrome onset is observed with a rapidly progressive, symmetrical weakness of limbs;
- Guillain-Barré syndrome follows respiratory or gastrointestinal infections within 6 weeks in the majority of patients, often by *Campylobacter*;
- The most recent outbreak of Zika virus infection raises concerns also for Guillain-Barré syndrome as cases have been reported within Zika and Dengue fever epidemics;
- Most frequently observed subphenotypes include the acute motor axonal neuropathy (AMAN) and the acute inflammatory demyelinating polyradiculoneuropathy (AIDP);
- Rare forms are represented by Miller-Fisher syndrome (MFS), acute motor and sensory axonal neuropathy (AMSAN), Bickerstaff brain stem encephalitis, and pharyngeal-cervical-brachial weakness;
- Serum autoantibodies are detected against gangliosides mainly GM1, GM2, GD1a, GD1b, GT1a, GT1b and GQlb;
- Despite treatment, Guillain-Barré syndrome mortality or severe disability occur in near 20%;
- Immunotherapy includes high-dose steroids, plasmapheresis, and intravenous immunoglobulins.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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