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Guillain-Barré Syndrome and its Variants

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Abstract

Guillain-Barré Syndrome (GBS) is an umbrella term that describes several clinically and electrophysiologically heterogenous disorders that share the common feature of acute onset regional or generalised flaccid paralysis with or without sensory loss. Clinically, GBS may have generalised weakness or there may be restricted involvement and rare central nervous system involvement in the form of Bickerstaff Brainstem Encephalitis. Electrophysiologically, there may be demyelinating or axonal features, which can determine the prognosis in an individual patient. A knowledge of variants of GBS is important in differentiating GBS from other mimics. Nerve conduction studies and anti-ganglioside antibodies may be helpful in further classifying various GBS variants. Although current treatment guidelines are similar for various subtypes, novel treatment strategies are in development depending on the pathophysiology of GBS variants. In this article we review the current understanding of pathophysiology and clinical features of GBS and its variants.

Key words: Guillain-Barré syndrome (GBS), acute inflammatory demyelinating polyradiculoneuropathy (AIDP), Miller Fisher syndrome.

Introduction

It has been more than 100 years when Guillain-Barré and Strohl, reported two cases of acute flaccid paralysis with albumino-cytological dissociation that has come to be known as Guillain-Barré syndrome[1]. 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 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[2].The cases described by Guillain-Barré and Strohl had a relatively benign course with spontaneous remission in contrast to fatal course of Landre ascending paralysis which along with lack of CSF findings in Landre's cases led Guillain to conclude that these 2 were different conditions. Since then we have come to know that GBS has an extended spectrum ranging from isolated cranial nerve palsies to rapidly developing acute flaccid paralysis leading to respiratory failure. In this review we discuss the clinical features and management of various variants of GBS.

Variants of GBS

As mentioned, GBS is an umbrella term that describes a number of clinically and electrophysiologically heterogenous disorders that share the common feature of acute onset symmetric paralysis with or without sensory loss. GBS can be classified on the basis of clinical features – depending on topographic involvement or on the basis of electrophysiological features (Fig. 1). Clinically, GBS has one important variant – the Miller Fisher syndrome (MFS) and both GBS and MFS have various forme frustes leading to a very heterogenous clinical picture[3]. Electrophysiologically 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).

Classical/Typical GBS: 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 that include bacterial (particularly *Campylobacter jejuni*) and parasitic infections, surgery, vaccination, malignancy, pregnancy, and bone marrow transplantation. Neurological symptoms usually begin abruptly with distal, relatively symmetrical onset of paraesthesias (acral paraesthesias) with little objective sensory loss often associated with severe radicular back pain (related to nerve root inflammation) or neuropathic pain[4].This is an important symptom because absence of sensory phenomenon points to an alternative diagnosis such as poliomyelitis, myasthenia gravis, electrolyte disturbance, or botulism. This is followed by a symmetric ascending paralysis that begins in the lower limbs

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Figure 1

Classification of GBS

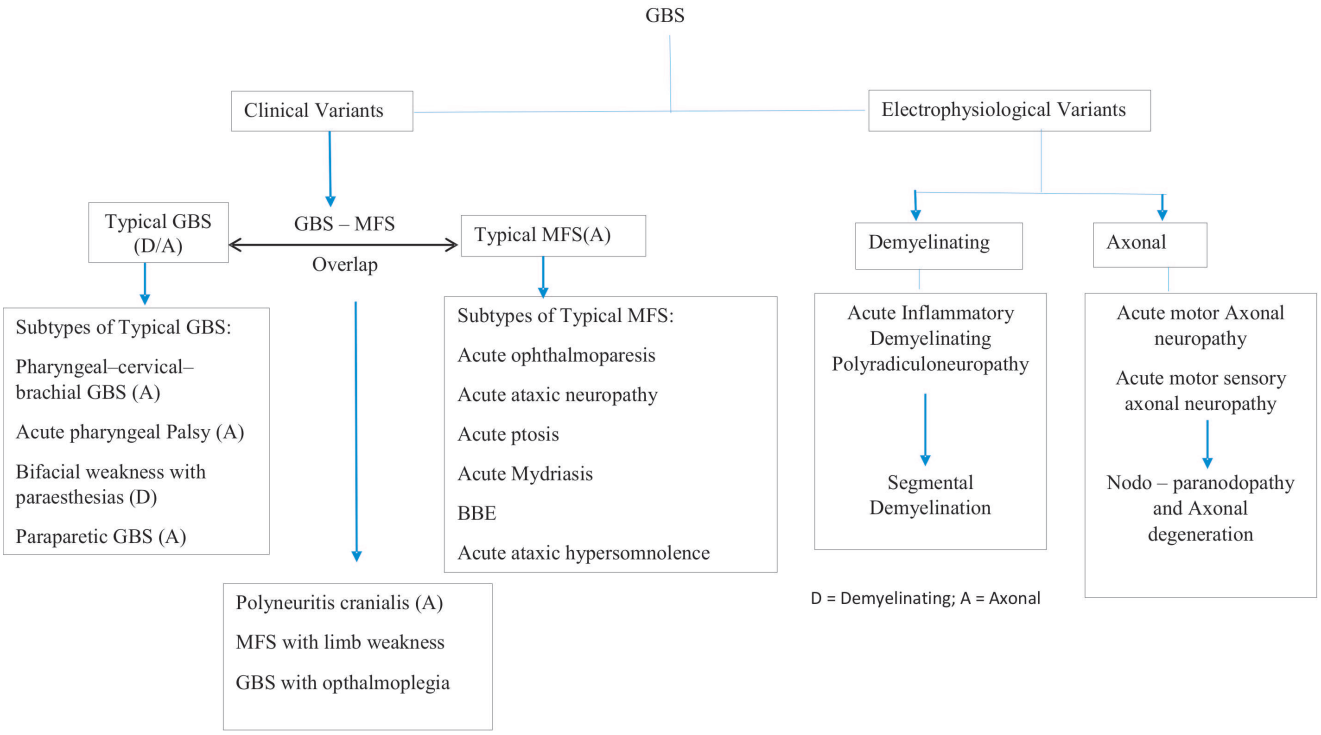


Fig. 1: *Phenotypic and electrophysiological classification of GBS.*

ascending to the upper limbs, may or may not involve the respiratory muscles and cranial nerves. The ascending pattern of weakness is only seen in ~50% of cases and in 32% cases weakness may begin simultancously in arms and legs, and in another 12% it may begin in the upper limbs[5]. Additionally, weakness may not be distal predominant and may start proximally and may be more prominent in the proximal muscles of the arms and legs – giving rise to diagnostic confusion with a pyramidal lesion. This proximal and distal weakness occurs because of a more proximal focal conduction block at the level of the lumbar and/or cervical nerve roots, rather than distally in the nerves[6].The weakness reaches nadir in 2 to 4 weeks after symptom onset, with progressive recovery over weeks to months. If the weakness progresses for more than 4 weeks, a diagnosis of subacute onset demyelinating radiculoneuropathy (subacute GBS) is made[6,7]. Facial nerve involvement occurs in up to 70% of cases, is usually bilateral and accentuated peri-orally; dysphagia occurs in 40%; and rarely (5%) patients may develop ophthalmoplegia, ptosis, or both[8]. Respiratory failure occurs in 25% of patients and is more likely in cases with rapid progression, bulbar palsy, upper limb involvement, and autonomic dysfunction[9]. Deep tendon reflexes (DTR) are usually lost especially in functionally weak muscles within a week of onset of weakness. Rarely DTRs may be preserved in about 10% of patients, more likely in cranial nerve variants or in patients with pure motor limb weakness and were more likely to have anti-ganglioside M1 (GM1) or anti-ganglioside D1a (GD1a) antibodies, as well as neurophysiological features consistent with acute motor axonal neuropathy.The most plausible mechanism for preserved or exaggerated DTRs is disruption of intramedullary inhibitory interneurons, which could occur if antiganglioside antibodies crossed the blood-brain barrier[10]. Despite preserved DTRs, the tone in the paralysed limb is always decreased. Dysautonomia occurs in 15% of patients[11]with bladder-bowel disturbances in approximately 9% of patients causing diagnostic difficulties with a spinal cord lesion[12]. Inspite of prominent sensory symptoms, sensory signs are mild in typical GBS, often limited to distal impairment of vibration sense. Eventually, patients begin to recover, though recovery may be delayed and leave a substantial neurological deficit in some patients. Diagnostic criteria

for classical GBS are enlisted in Table I.

Table I: Diagnostic criteria for classical GBs.

Brighton criteria for diagnosis of classical GBS				
	Criterion	**Level of diagnostic certainty**		
		1	2	3
1.	Bilateral and flaccid weakness of limbs	+	+	+
2.	Decreased or absent DTRs	+	+	+
3.	Monophasic pattern of illness	+	+	+
4.	Onset to nadir of illness – 12 hours to 28 days followed by subsequent plateau	+	+	+
5.	Albuminocytological dissociation: CSF protein > 45 mg/dl and cells < 50 cells/mm^3	+	Either of 2 are positive	–
6.	NCS consistent with GBS	+		–
7.	Alternative diagnosis of weakness have been excluded	+		+

GBS subtypes

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. Diagnostic criteria for PCB are enlisted in Table II. Patients with pharyngeal-cervical-brachial weakness often carry anti-ganglioside T1a (GT1a) IgG antibodies, some of which might cross-react with anti-ganglioside Q1b (GQ1b). The selective involvement of pharyngeal, cervical, and brachial segments is probably explained by dense expression of GT1a in the human glossopharyngeal and vagal nerves. Incomplete forms include acute oro-pharyngeal palsy (without cervical and brachial weakness) and overlaps with MFS (ophthalmoplegia + ataxia) and Bickerstaff Brainstem Encephalitis (BBE) (+ altered consciousness) may be seen[13]. Ophthalmoplegia in association with oropharyngeal palsy denotes an interface of MFS and GBS-Polyneuritis Cranialis (discussed later). Electrophysiology shows axonal features. It is essential to be aware of this diagnosis because patients with PCB can deteriorate rapidly and timely intervention can prevent morbidity and mortality. Treatment is on the usual lines of GBS (discussed below).

Table II: Diagnostic criteria for pharyngeal cervical brachial variant of GBS.

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
- Absence of identified alternative diagnosis

Supportive criteria

- Antecedent infectious symptoms
- Cerebrospinal fluid albuminocytological dissociation
- Neurophysiological evidence of neuropathy
- Presence of IgG anti-GT1a or anti-GQ1b antibodies

Bifacial weakness with paraesthesias (BFP) is characterised by rapidly progressive bilateral facial weakness with or without loss of taste, paraesthesias in the distal limbs, hyporeflexia, nadir within 4 weeks of onset, and subsequent recovery that accounts for < 1% of GBS. Distal paraesthesias usually precede 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)[14]. Diagnostic criteria for bilateral facial palsy with paraesthesias are enlisted in Table III[14]. 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 tetraparesis, though facial weakness can occur in MFS and PCB, which can then cause tetraparesis. No treatment is required unless ophthalmoplegia or pharyngeal weakness is present.

Paraparetic GBS is another regional variant of GBS, that is characterised 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 orthopedic disorder. Deep tendon reflexes are absent in the lower and variable in upper limbs. There is no sensory level though bladder dysfunction may be present in 14% of cases[15]. MRI, which is necessary to rule-out spinal causes of paraparesis is often unremarkable, though gadolinium enhancement of nerve roots may be present. NCS shows

an axonal pattern and may be abnormal in upper limbs also despite paucity of symptoms. CSF is essential to rule-out infectious causes of lumbosacral radiculopathy such as tuberculosis and cytomegalovirus. Diagnostic criteria are enlisted in Table IV[15].

Table III: Diagnostic criteria for bilateral facial palsy with paraesthesias.

Core features

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

Supportive features

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

Table IV: Diagnostic criteria for paraparetic GBS.

Core features

- Leg weakness (may be asymmetric or unilateral) and leg areflexia/ hyporeflexia
- Absence of arm weakness

Supportive features

- Electrophysiological evidence of neuropathy

Miller Fisher Syndrome

Although Miller Fisher Syndrome is phenotypically different from GBS, it shares a number of clinical features with GBS such as presence of antecedent infection, a monophasic disease course, areflexia, distal paraesthesias, CSF albuminocytological dissociation, and nerve conduction abnormalities. MFS accounts for ~ 5% of cases of GBS and is the most common variant of GBS after AIDP and is characterised by the classical triad of ophthalmoplegia, ataxia, and areflexia[3]. Besides the classical MFS, there can be forme fruste and more extensive forms with central nervous system involvement in the form of hypersomnolence; together these are clubbed as MFS subtypes (discussed below).

Classical MFS usually presents with diplopia resulting from asymmetric ocular motor weakness that may progress to complete ophthalmoplegia. Sixth cranial nerve is the first nerve to be involved and downgaze is often preserved till late. Ptosis is common, and pupils are rarely involved, though variable pupillary involvement may be seen. There may be associated nystagmus in the form of gaze-evoked, dissociated abducting, and convergence-retraction nystagmus. The onset of ataxia, usually truncal or gait ataxia with minimal limb ataxia often occurs within 1 - 2 days of diplopia though it may be the presenting symptom in 1/3 of cases[16]. The pathogenesis of ataxia is controversial, and it has been postulated to be due to cerebellar dysfunction or more likely due to selective involvement of muscle spindle afferents by anti GQ1b antibodies that result in a cerebellar type ataxia without significant sensory loss[16]. Almost 50% of patients complain of distal paresthesias but there is no objective sensory loss. Additionally, upto 43% of patients who present with MFS may go on to develop limb weakness in a descending fashion; usually within the first week: MFS – GBS overlap. Since there are no clinical or electrophysiological features that may differentiate MFS – GBS overlap patients from classical MFS, it is worthwhile to clinically observe all patients with MFS for at least 1 week to look for any progression[17]. CSF albuminocytological dissociation is seen in 59% of patients during the first 3 weeks of illness[16]. High titres of anti-GQ1b IgG antibodies are present in 80 - 100% of patients who have MFS, which usually peak during the first week. Nerve conduction studies in MFS may be normal in 1/3 of patients, though it may reveal axonal sensory abnormalities, more prominent in the upper limbs in some and demyelinating features in other patients[16]. MRI of the brain may demonstrate cranial nerve enhancement (e.g., oculomotor nerves) in MFS but is usually normal. Diagnostic criteria for MFS have been enlisted in Table V[3]. MFS has a favourable prognosis, with recovery within 2 - 3 months and a corresponding reduction in the antibody titers. Ataxia usually improves first followed by ophthalmoplegia, and reflexes return last but may remain undetectable for a long time. Because prognosis of MFS is good, it is reasonable to manage uncomplicated MFS conservatively, though IVIG has been found to hasten recovery. However, patients with complicated MFS (Bickerstaff Brainstem Encephalitis, MFS – GBS overlap, MFS – Pharyngeal cervical brachial variant overlap) should be treated with IVIG/PE as for typical GBS which is discussed in the treatment section.

MFS subtypes: The term 'MFS subtypes' encompass both more-extensive forms (with additional features, such as hypersomnolence) and less-extensive (incomplete or forme - fruste) forms of MFS[3].

Bickerstaff Brainstem Encephalitis: Bickerstaff's Brainstem Encephalitis (BBE) is a rare neurological condition classically characterised by a constellation of signs and symptoms including acute ophthalmoplegia, ataxia, and altered sensorium or hypersomnolence. The neurological features are typically preceded by an antecedent infection. Neurological symptoms include altered sensorium, ranging from drowsiness, stupor, or in the most severe cases to coma and is due to involvement of brain-stem reticular

activating system. In addition to ophthalmoplegia, there may be associated involvement of motor part of fifth cranial nerve, seventh nerve and bulbar involvement and cerebellar ataxia. Reflexes are variable (absent in 60%), and plantars are extensor in 40%[18]. Again, like MFS, BBE can also overlap with GBS resulting in variable limb weakness.The frequency of CSF albuminocytological dissociation is lower in BBE, with a greater tendency towards CSF pleocytosis probably reflecting a more severe breakdown in the blood-CSF barrier. Anti-GQ1b IgG antibodies are seen in 68% of patients with BBE and together MFS, BBE, acute opthalmoplegia and acute ataxic neuropathy all fall within the spectrum of anti-GQ1b syndrome[19]. Diagnostic criteria for BBE are listed in Table VI[18]. A forme fruste of BBE would be acute ataxic hypersomnolence which is ataxia + hypersomnolence without opthalmoplegia.

Table V: Diagnostic criteria for MFS.

Core clinical features

- Ophthalmoplegia (may be asymmetric or unilateral), ataxia and areflexia/ hyporeflexia.
  - Clinical severity of each component may vary from partial to complete
  - Absence of certain features indicates incomplete MFS: patients without ataxia have 'acute ophthalmoparesis'; patients without ophthalmoplegia have 'acute ataxic neuropathy'
  - Presence of a single feature indicates incomplete MFS: ptosis suggests 'acute ptosis'; mydriasis suggests ' acute mydriasis'
- Absence of limb weakness and hypersomnolence

Supportive criteria

- Presence of anti-GQ1b IgG antibodies

Acute ophthalmoparesis, acute ptosis, and acute mydriasis: These are incomplete forms of MFS, that constitute isolated eye signs in association with anti-GQ1b antibodies, but without ataxia.The usual picture is similar to MFS without ataxia or areflexia following an antecedent illness who are seropositive for the anti-GQ1b antibodies. However, case reports of unilateral or isolated presentations of ocular neuropathies, highlighting the importance of testing for GQ1b antibodies in cases of isolated 3rd, 4th, or 6th nerve palsy once other causes have been ruled-out. In one study, 25% of 100 patients presenting with acute abducens palsy had anti-GQ1b antibodies[20]. Patients may go on to develop facial weakness or bulbar weakness indicating overlap with GBS.

Acute Ataxic Neuropathy: There has been a lot of confusion regarding the terminology of sensory variants of GBS (Fig. 2)[21]. Ataxic GBS was the term used for acute onset of profound ataxia with negative Romberg sign and no (or minimal) ophthalmoplegia and albuminocytological dissociation and positive GQ1b antibodies[3]. Acute sensory ataxic neuropathy on the other hand presents with distal paraesthesias, sensory loss, with rapidly progressive gait ataxia, positive Romberg sign and positive Anti GD1b antibodies[3]. Recent studies have shown that these 2 conditions are a continuous spectrum; patients with both these conditions had either GQ1b or GD1b antibodies and the collective term acute ataxic neuropathy has been coined for this irrespective of presence or absence of Romberg sign[22]. The clinical features differ because targets of GQ1b (muscle spindle afferents) and GD1b (paranodal myelin of sensory and motor neurons) are different. This is to be differentiated from sensory GBS, which is characterised by sensory loss with or without ataxia and demyelinating features on NCS[21].

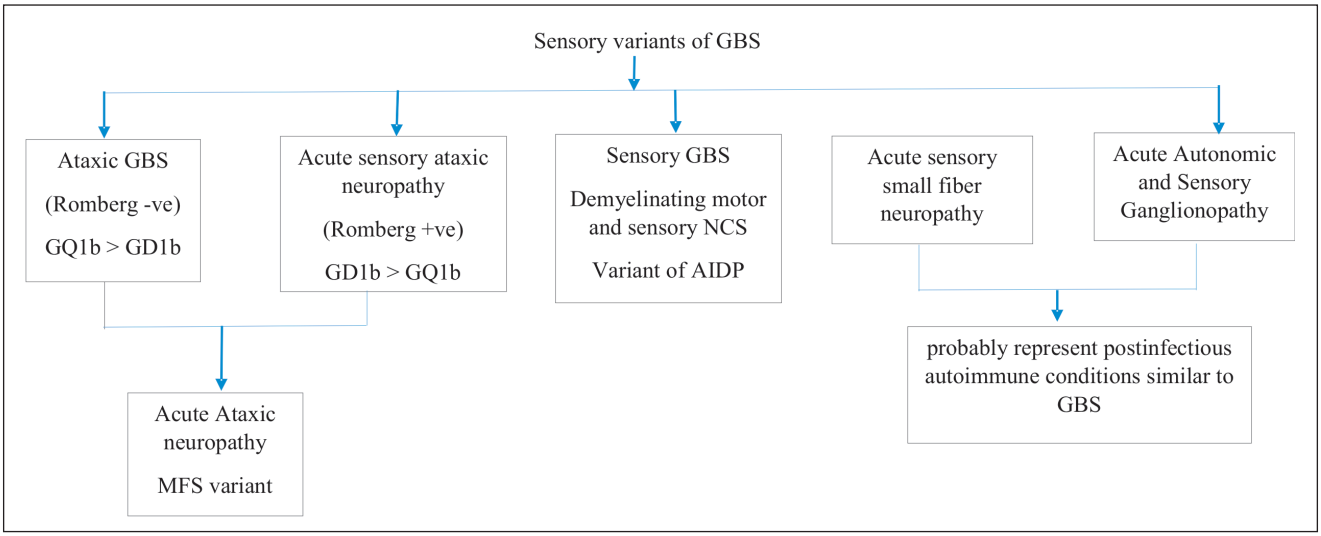


Fig. 2: *Classification of sensory variants of GBS.*

Table VI: Diagnostic criteria for Bickerstaff Brainstem Encephalitis.

Probable Bickerstaff's brainstem encephalitis - Diagnosis can be made when both of the following criteria have been met:

1. Subacute onset (rapid progression of less than 4 weeks) of all the following symptoms:
   - Decreased level of consciousness
   - Bilateral external ophthalmoplegia
   - Ataxia
2. Reasonable exclusion of alternative causes

Definite Bickerstaff's brainstem encephalitis: diagnosis can be made in the presence of positive IgG anti-GQ1b antibodies even if bilateral external ophthalmoplegia is not complete or ataxia cannot be assessed, or if recovery has occurred within 12 weeks after onset.

Polyneuritis Cranialis: Oculopharyngeal subtype of Guillain-Barré syndrome – GBS-MFS interface:

Polyneuritis cranialis is a term used for multiple cranial nerve palsies from various etiologies. It has long been recognised that GBS could be one of the causes of Polyneuritis Cranialis. A recent review found 15 cases displaying a combination of ocular signs (ophthalmoplegia, ptosis or pupillary changes) and bulbar signs (dysarthria or dysphagia), which were often associated with facial weakness. The involvement may be asymmetric, and a substantial proportion of patients also displayed asymmetrical neuropathy[23]. The diagnostic criteria of oculopharyngeal subtype of Guillain-Barré syndrome are enlisted in Table VII.

Table VII: Diagnostic criteria for Polyneuritis Cranialis variant of GBS

Core features

- Unilateral or bilateral oculomotor (cranial nerves III, IV or VI) AND oropharyngeal weakness (cranial nerves IX, X, XI or XII)
  - Involvement of other cranial nerves (VII[[V[VIII) may also be present. Typically, cranial nerves I and II are spared.
- Absence of ataxia AND disturbed consciousness AND prominent limb weakness
- Monophasic illness pattern AND interval between onset and nadir of cranial nerve involvement between 12 h and 28 days AND subsequent clinical plateau
- Absence of identified alternative diagnosis

Supportive features

- Antecedent infectious symptoms
- Hyporeflexia
- Cerebrospinal fluid albuminocytological dissociation
- Neurophysiological evidence of neuropathy

Presence of anti-GQ1b or anti-GT1a IgG antibodies

Acute motor axonal neuropathy (AMAN) and Acute motor sensory axonal neuropathy (AMSAN)

Initially thought to be a pure demyelinating illness, an axonal motor variant of GBS termed "acute motor axonal neuropathy" (AMAN) was reported in 1993 from Northern China, (Chinese paralytic illness). Clinically, patients with AMAN present with acute onset flaccid symmetric paralysis (limbs; cranial, including facial and pharyngeal muscles; respiratory muscles) without clinical or electrophysiologic sensory involvement. DTRs may be preserved or even hyperreflexic in 10% of patients particularly early in the disease or during recovery[24]. Tongue weakness is more likely in AMAN, as compared to AIDP, but autonomic features are less likely. Table VII enlists the clinical and electrophysiological differences between AIDP and AMAN[24]. AMSAN also presents with acute, severe ascending quadraparesis with sensory loss that reaches a nadir in ~1 week and recovery may take longer time and is often incomplete compared to AIDP. In India AIDP is the predominant variant accounting for 48.8 to 85.2 per cent of cases with AMAN accounting for remaining of the cases[25,26,27].

Other variants

Some other variants that are not mentioned in the classification criteria but are often mentioned include: acute sensory small fibre neuropathy, autoimmune autonomic neuropathy and ganglionopathy (AAG) and GBS mimicking cerebral death. Acute small fibre sensory neuropathy presents with acute onset of numbness and/or burning sensation and pain in the extremities usually after an infection or vaccination and has a self-limiting course. AAG is characterised by the rapid onset of combined sympathetic and parasympathetic failure with autoantibodies to nicotine ganglionic acetylcholine receptors. GBS mimicking cerebral death is a rare, devastating variant of GBS that presents as an acute onset, symmetric, rapidly progressive polyneuropathy that is followed by a comatose state occurring within days of symptom onset[28]. Other rare variants reported in literature include bilateral foot-drop with upper limb paresthesias and acral paresthesias with diminished reflexes in either arms or legs.

Pathophysiology

GBS is an immune-mediated attack against various parts of the peripheral nerve – myelin or axon as a result of molecular mimicry following an antecedent infection[6]. The pathogenesis of AMAN is closely linked to molecular mimicry as a result of *Campylobacter jejuni* diarrhoeal infection that

results in formation of antiganglioside antibodies that cause nodal and paranodal pathology resulting in a reversible conduction failure or axonal degeneration in contrast to segmental demyelination seen in AIDP (Fig. 3). If reversal of nodal pathology occurs early in AMAN, quick recovery can be seen clinically and electrophysiologically with improvement in reversible conduction failure; however, over time, lengthened nodal and paranodal disruption can lead to degeneration of the axon and poor outcomes. On the other hand, in AIDP; immune reactions directed against epitopes in Schwann cell surface membrane or myelin can cause multifocal inflammatory demyelination starting at the level of the nerve roots (Fig.3). The antibodies that are responsible for AIDP have not yet been identified.

Table VIII[24]: Clinical and electrophysiological features of demyelinating and axonal variants of GBS.

Feature	AIDP	AMAN
Preceding infection	Cytomegalovirus, Epstein – Barr virus	Campylobacter jejuni
Course of illness	Progression over weeks	Progression over days with nadir in 7 days
Cranial nerve palsy	Frequent	Less common
Sensory loss	Common – often distal	None (only in AMSAN variant)
Pain	Common	Less common
Autonomic involvement	Common	Rare
Deep tendon reflexes	Absent or hyporeflexic (exaggerated or normal in 5%)	Absent or hyporeflexic (exaggerated or normal in 20%)
Electrophysiology	Decreased conduction Velocity and increased Distal latency with relative preservation of amplitudes Conduction block ± Temporal dispersion ±	Decreased amplitudes with normal conduction velocity and distal latency Reversible conduction block
Target molecule	Unknown	Anti-ganglioside antibody
Prognosis	Slow uniform recovery	2 patterns: Rapid or poor and slow recovery

AIDP: Acute inflammatory demyelinating polyradiculoneuropathy; AMAN: Acute motor axonal neuropathy; AMSAN: Acute motor sensory axonal neuropathy.

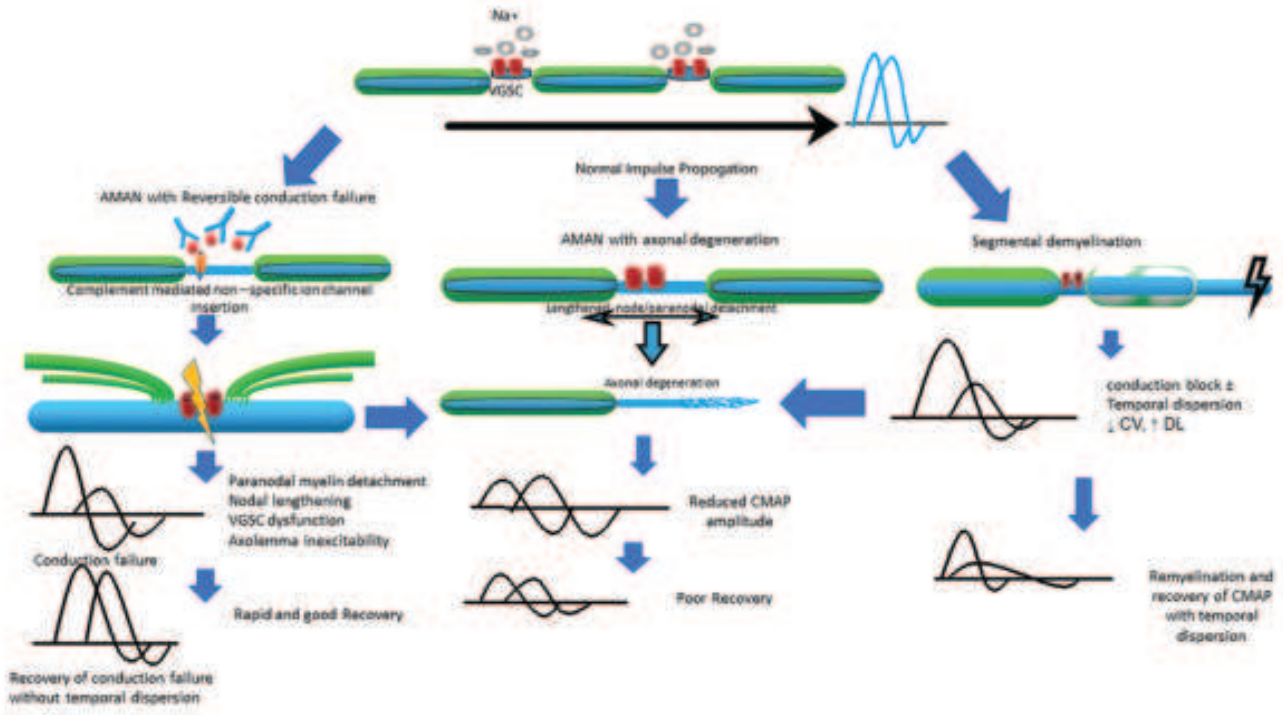


Fig. 3: *Pathophysiology of GBS and its electrophysiological correlation. Electrophysiologically GBS can have an axonal or demyelinating pathology. In Axonal GBS, weakness can occur because of reversible conduction failure secondary to complement mediated non-specific ion channel insertion in the Nodes of Ranvier that causes nodal lengthening and voltage gated sodium channel (VGSC) dysfunction. The resulting conduction failure recovers rapidly without temporal dispersion and has a good prognosis. Alternatively, in other cases of AMAN, there is immune mediated axonal degeneration with poor recovery. In AIDP, there is immune mediated segmental demyelination that results in decreased conduction velocity and increased distal latency with or without conduction block and temporal dispersion.*

Table IX[31]: Antibodies in GBS and their clinical significance.

Antibody	Target site	Variant of GBS	Notable phenotypic features
Anti-ganglioside antibodies			
Anti-ganglioside GM1a/b	Node	AMAN	Anti-GM1 Abs are linked with reversible conduction failure
Anti-ganglioside GD1a	Node	AMAN, AMSAN	More specific and sensitive than GM1 antibodies
Anti-ganglioside GalNac-GD1a	Node	AMAN	Distal dominant weakness
Anti-ganglioside GD1b	Node	Acute ataxic neuropathy	Acute onset ataxia with or without Romberg sign
Anti-ganglioside GQ1b	Paranode	MFS and subtypes	Anti-GQ1b Abs suggest good treatment response prognosis
Anti – ganglioside GT1a	Paranode	PCB variant	
Non-Ganglioside antibodies			
Neurofascin (NF186)	Node	AMAN, AIDP	
Neurofascin (NF155)	Paranode	AIDP	More likely in CIDP than in AIDP
Contactin 1(CNTN1)	Paranode	AIDP	More likely in CIDP than in AIDP

AIDP: Acute inflammatory demyelinating polyradiculoneuropathy; AMAN: Acute motor axonal neuropathy; AMSAN: Acute motor sensory axonal neuropathy.

Table X[33- 41]: Electrophysiological criteria for GBS.

Diagnostic Criteria for AIDP														
Criteria	**Conduction velocity slowing**			**Distal latency prolongation**			**F wave latency prolongation**			**Conduction block amplitude reduction**		**Abnormal Temporal Dispersion**		**Abnormal parameters required**
	↓in CMAP ≥ 80% LLN	**↓in CMAP ≤ 80% LLN**	**Number of nerves**	**↓in CMAP ≥ 80% LLN**	**↓in CMAP ≤ 80% LLN**	**Number of nerves**	**CMAP ≥ 80% LLN**	**in CMAP ≤ 80% LLN**	**Number of nerves**	**% decrease in CMAP amplitude**	**Number of nerves**	**% increase in duration camp**	**Number of nerves**	
Albers 1985	>5	>15	2	>10	>20	2	>20	>20	2	>30	2	>30	1	1
Albers 1989	>10	>20	2	>15	>25	2	>25	>25	1	>30	1	>30	1	3
Asbury 1990	>20	>30	2	>25	>50	2	>20	>50	2	>20*	1 (PT excluded)	>15	1	3
Ho 1995	> 10	> 15	2	> 10	> 20	2	> 20	> 20	2	-	-	> 30	2	1
Dutch GBS 1995	> 30	> 30	2/1	> 50	> 50	2/1	> 50	> 50	2/1	16 (ulnar) 11 (median) 41 (peroneal)	2/1	>50	2/1	1/2 PT excluded
Italian GBS 1996	> 20	> 30	2	> 25	> 50	2	> 20	> 50	2	> 30*	1	> 30	1	2
Hadden 1998	> 10	> 15	2	> 10	> 20	2	> 20	> 20	2	> 50ï	2	-	-	1
Van den Berg 2004†	> 30	> 30	2	> 50	> 50	2	> 25	> 50	2	> 50ï‡ (definite) > 30 (probable)	2 (PT excluded from Probable)	> 30	2	1
Rajabally 2015†	> 30	> 30	2	> 50	> 50	2	> 20	> 50	2	> 30‡	2 (PT excluded)	-	-	1

**: Area of CMAP; ï: Distal CMAP > 20% LLN required for CB; †: Absence of F wave in 2 nerves in two nerves with distal CMAP ≥ 20% LLN, with an additional parameter, in one other nerve also one of the parameter, ‡: CB requires an additional demyelinating criterion in 1 other nerve;*

Diagnostic criteria for AMAN and AMSAN								
Criteria	**Demyelinating criteria allowed**	**Distal CMAP**		**Absent F wave**		**Reversible conduction failure**		**Number of parameters abnormal**
		% LLN	**Number**	**Criteria**	**Number**	**Criteria**	**Number**	

			of nerves		of nerves			
Ho 1995	0 nerves	< 20	1		-	1		
Hadden 1998	1 feature in 1 nerve if distal CMAP < 10% LLN	< 20	2	-	-	1		
Rajabally 2015	1 feature in 1 nerve if distal CMAP <10% LLN	< 20	2	Absent with distal CMAP ≥ 20% LLN	2*	Proximal/Distal CMAP < 0.7	2 (PT excluded) *	1
				Absent with distal CMAP ≥ 20% LLN	1†	Proximal/Distal CMAP < 0.7	1 (PT excluded) †	2

**: If criteria are met in 2 nerves then only 1 abnormality is required; †: if criteria are met in only 1 nerve, then 2 abnormalities are required; CMAP: Compound muscle action potential; LLN = Lower limit of normal; PT: Posterior tibial.*

Investigations

Routine laboratory testing is unrevealing in GBS as such and main purpose is to rule-out the mimics and differential diagnosis. The main role of CSF examination is to rule-out infectious causes of weakness such as HIV, Lyme disease and tubercular polyradiculopathy, conditions in which a CSF pleocytosis is present. Albuminocytological dissociation is defined as CSF with raised protein (> 45 mg/dl; lab reference at our centre) and total cell count of ≥ 10/mm^3 though 10% - 15% of patients have cell counts of 10 - 50 cells/mm3 particularly in the first few days can be used to support a diagnosis of GBS[5,29]. Cell counts > 50 cells/mm3 should stimulate a search for an alternative diagnosis such as polio-like illness, CMV radiculitis, Lyme disease, HIV, leptomeningeal metastasis and lymphoma. Albuminocytological dissociation is present in no more than 50% of patients with the Guillain-Barré syndrome during the first week of illness, although this percentage increases to 75% in the third week, but CSF protein may remain normal throughout the illness in 10% of patients[5,30]. CSF protein is more likely to remain normal in regional variants of GBS. Antiganglioside antibodies are found in axonal variants of GBS and MFS and are considered the gold standard for subtype classification. They can be used to support a diagnosis of GBS in difficult cases but are at best positive in about 40% cases (Table IX)[31]. Electrophysiology is the cornerstone for confirming a clinical diagnosis of GBS. In spite of this, NCS may not be helpful particularly early in the disease because common sites of demyelination are at the level of the nerve roots, most distal nerve segments, and at entrapment sites which are often inaccessible to routine NCS or excluded from diagnostic criterion. Prolonged distal motor latencies and prolonged or absent F-waves are often the earliest abnormalities. To increase the diagnostic yield of NCS, at least four motor nerves, three sensory nerves and F-waves should be investigated. The maximum degree of motor conduction abnormality occurs within 3 - 8 weeks, with 80 - 90% of patients with GBS[32]. Case vignette 1 describes the typical history and electrophysiology in a patient with classical GBS. Table X enlists the electrophysiological criteria for demyelinating and axonal GBS[33-41]. In general, cut-off values for acute demyelination differ notably from those for chronic demyelination as less strict cut-off values are used for AIDP as compared to CIDP. MRI of the spine is useful not only to exclude spinal causes of weakness but also to indicate nerve (root) enlargement and enhancement that may add to the diagnosis of GBS.

Table XI[42]: Differential Diagnosis of GBS and Variants

	Condition	Distinction
Classical GBS: Acute Flaccid Quadriparesis		
1.	Acute-onset chronic inflammatory demyelinating polyradiculoneuropathy	More prominent sensory signs and sensory ataxia Less likely to have autonomic involvementless likely to require mechanical ventilation Progression > 8 weeks antecedent infection less common Facial weakness less common
2.	Periodic paralysis	Nadir to weakness ~12 hours Serum Potassium low/high No antecedent infection Past history/family history of similar attacks No sensory symptoms and SNAPs normal No autonomic symptoms and signs Facial and bulbar involvement less common (except in 2° cases)
3.	Acute intermittent porphyria	Onset often in Upper limbs (may be confused with PCB variant) severe abdominal pain and show psychiatric symptoms or have seizures before developing porphyric neuropathyAnkle jerk preserved till latesensory loss in bathing trunk distribution past history of similar attacks
4.	Critical illness polyneuropathy	Intensive care unit onset in setting of sepsis, multi-organ failureabsence of a preceding event such as a diarrheal illnessnormal CSF proteinabsence of demyelination on NCS

5 Poliomyelitis	Fever, pure motor without any sensory symptoms Rapid evolution in < 24 hours Asymetrical CSF pleocytosis
6. Non-polio enterovirus	Fever, meningismus and encephalomyelitis followed by paralysis pure motor without any sensory symptoms CSF pleocytosis
7. Rabies	Dog bite 1 - 2 months prior to neurological illness behavioural changes and autonomic instability followed by ascending paralysis with sphincter involvement CSF pleocytosis
8. Diphtheritic neuropathy	Biphasic course with bulbar onset followed by sensory – motor weakness 3 - 6 weeks later History of pharyngitis with pseudomembrane formation Features of myocarditis may be present
9. Arsenic	Presence of gastrointestinal symptoms, anaemia/leukopenia, and subsequent skin rash and Mees lines
10. Thallium tick paralysis	Flu-like prodrome lasting 5 - 10 days may be followed by rapidly progressive symmetric ascending flaccid paralysis over 2 - 6 days
11. Vasculitic neuropathy	Onset suggestive of involvement of multiple non-contagious nerves Painful rapidly progressive asymmetric onset Systemic signs and symptoms: fever, weight loss, multiorgan involvement (e.g., joints, skin, kidney, respiratory tract) serological markers (e.g., elevated sedimentation rate, rheumatoid factor) normal CSF
12. Acute myositis	Fever, myalgia, tender muscles Pure motor Raised CPK, myoglobinuria
13. Inflammatory myositis	Proximal limb girdle type of weakness CPK raised NCS normal with EMG suggestive of myopathy
PCB variant	
1. Botulism	Symmetrical onset with internal and external opthalmoplegia No sensory symptoms and normal DTR Autonomic symptoms: Dry mouth, dizziness, and gastrointestinal symptoms Normal sensory NCS with post-exercise increment of 50 - 100% CSF is normal
2. Myasthenia gravis	Asymmetric fluctuating weakness with prominent extra-ocular involvement No sensory symptoms and normal DTR Normal NCS with decremental response on RNS AchR/MusK positive
3. Brainstem stroke	Hyperacute onset within seconds to minutes and step-wise progression Risk factors for cerebrovascular disease
BFP variant	
1. Bell's palsy	Acute onset with nadir within 48 - 72 hours Mastoid pain Hyperacusis and impaired tear production favour Bell's palsy No paresthesias and DTR – normal
2. Sarcoidosis	Systemic signs and symptoms CSF may show hypoglycorrhachia MRI may be abnormal – leptomenigeal, pachymeningeal enhancement, parenchymal masses Serum ACE elevated
Paraparetic GBS	
1. Transverse myelitis	Weakness in Lower limbs > upper limbs Sensory level usually identified Early loss of bowel and bladder control NCS – normal though F wave abnormalities may be present CSF pleocytosis and/or increased immunoglobulin G index MRI: focal area of increased T2, signal with or without gadoliniumenhancement
2. Viral Polyradiculoneuropathy	Ascending leg weakness, perineal paraesthesia, leg pain and variable bladder involvementIncreased polymorphs and protein with reduced glucose in CSF Usually seen in immunocompromised state (HIV)
3. Anterior spinal artery occlusion	Apoplectic onset with deficits reaching the nadir in less than 4 hours
Miller Fisher Syndrome and Bickerstaff brainstem encephalitis	
1. Wernicke encephalopathy	Profoundly disorientated and inattentive rather than hypersomnolenceopthal-moplegia is usually incomplete and gaze evoked nystagmus is more prominent predisposing condition is usually present MRI shows: Symmetric T2-signal change around the third and fourth ventricles and the aqueduct and, in most cases, also the mamillary bodies CSF is normal Pupillary involvement is common
2. Multiple sclerosis	Relapsing remitting course with involvement of multiple sites

		MRI abnormal with typical lesion NCS normal
3.	Acute disseminated encephalomyelitis	Acute onset multi – focal neurological deficits with encephelopathy Optic neuritis is common and bilateral CSF shows pleocytosis with raised protein MRI - Multifocal areas of increased T2-weighted signal abnormalities usually > 1 cms
4.	Lambert–Eaton myasthenic syndrome	Fluctuating proximal muscle weakness with minimal ocular involvement Autonomic dysfunction including pupillary abnormalities Incremental response on high frequency RNS P/Q-type VGCC antibodies are present along with underlying malignancy
5.	Brain stem tumours	Gradually progressive symptoms Signs of raised ICP with focality MRI is abnormal

SNAP: Sensory nerve action potential; PCB: Pharyngeal cervical brachial variant; NCS: Nerve conduction studies; CSF : Cerebrospinal fluid; CPK: Creatine phosphokinase; DTR : Deep tendon reflex; RNS: Repetitive nerve stimulation; AchR: Acetylcholine receptor, MuSK: Muscle-Specific Kinase; ACE: Angiotensin converting enzyme; MRI: Magnetic resonance imaging; VGCC: Voltage gated calcium channel; ICP: Intracranial pressure.

Differential diagnosis of GBS and variants

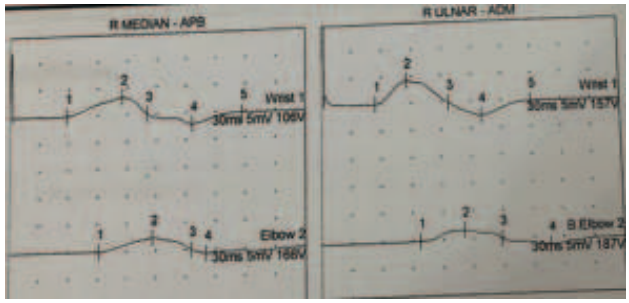
Differential diagnosis of GBS is broad, involving all parts of the neuraxis and depends on its regional variants (Table XI)[42]. Of importance, is hypokalaemic paralysis (Box 2), which can be a very close mimic of GBS and inadvertent treatment of a hypokalaemic patient with plasmapheresis can be catastrophic.

Box 1

Case vignette 1

Mr. SS, 35 years young man comes walking to the hospital with distal paraesthesias and mild weakness. Within the next 5 days. he developed areflexic flaccid becomes bed bound. On each visit he pleaded for some treatment and expresses concern about his life if not given some lifesaving treatment. After one week of illness he develops multiple cranial nerve palsies including bulbar and facial paralysis and shows signs of impending doom by gestural language. His nerve conduction studies showed increased distal latencies in median and ulnar nerves, with reduced conduction velocity in posterior tibial nerve and conduction blocks in median and ulnar nerves suggestive of AIDP.

Nerve/Sites	Latency	Amplitude	Distance	Velocity
Median – APB	5.85	5.4		
Wrist	9.15	3.1	20	60.6
Elbow				
Ulnar – ADM				
Wrist	5.40	6.9		
Elbow	9.75	3.1	22	51
Common peroneal (R)				
Ankle	5.05	8.2		
Fibular Head	11.65	6.5	30	46.2
Posterior Tibial (R)				
Ankle	6.65	2.4		
Knee	17	1.6	35	33.8



Box 2

Case vignette 2

A young man from Kashmir was wheeled into the ICU of our institute with an acute onset weakness of all 4 limbs that reached its nadir (0/5 MRC) in < 12 hours. On examination he had areflexic quadriparesis with neck weakness and a single breath count of 14. The referring physician had made a diagnosis of GBS as nerve conduction showed reduced amplitudes in all motor nerves tested. Serum Potassium report was 2.8 meq/l. He was sitting in the bed after 24 hours with correction of potassium. Differential diagnosis of weakness that reaches its nadir in < 12 hours includes: Periodic paralysis, Intoxications, Tick paralysis, Poliomyelitis and vascular myelopathy but GBS usually progresses over a period of 12 hours – 28 days. This case highlights the importance of determining serum potassium in patients with areflexic quadriparesis. The patient made a complete recovery within 1 day of potassium replacement.

Treatment

Good supportive care is the most important element of management since upto 30% of patients may progress to respiratory failure. Patients with rapidly worsening acute GBS should be observed in a critical care unit with monitoring of single breath count, FVC and negative inspiratory pressure every 4 to 6 hours while the patient is awake. A rapid decline of the expiratory forced vital capacities to less than 15 cc/kg of ideal body weight (adjusted for age) or of the negative inspiratory force to below 60 cm H2O, PaCO2 > 48 mmHg, PaO2 < 56 mm Hg or severe bulbar dysfunction (inefficient cough, impaired swallowing, and atelectasis) is an indication for elective intubation[43]. Immunotherapy with PE or IVIG is considered as the mainstay of treatment and should be started as soon as possible. The north American Trial and French Plasmapheresis Group trial have demonstrated that PE halves the need for ventilation, hastens recovery and improves outcome at 1 year if administered within 4 weeks of onset[44,45]. A Cochrane review confirmed the value of plasma exchange over supportive therapy in hastening the recovery from GBS when started within 30 days after disease onset[46]. It is indicated in moderate-severe cases who are unable to walk without support > 10 M, with a significant decrease in VC or oropharyngeal paralysis (Table XII)[46,47]. IVIG is more beneficial when started within 2 weeks of onset and the strength of recommendation is weaker for use of IVIG beyond 4 weeks[47]. In ambulatory patients, benefit of IVIG is not clear, but because there is no way to distinguish mild cases from progressive cases, ambulatory patients are also treated with IVIG, particularly if neurological deficits are progressing. The mean time to improvement of one clinical grade in the various controlled, randomised PE and IVIG studies ranged from 6 days to 27 days. With both PE and IVIG, one or more episodes of deterioration following the initial improvement or stabilisation after treatment, described as "treatment-related fluctuations (TRIF)" may be encountered in as many as 6 - 16% of patients. In patients who suffer such relapses or TRIFs, additional courses of PE or IVIG are definitely indicated. There is, however, no evidence that PE beyond 250 mL/kg or IVIG greater than 2 g/kg are of any added benefit in patients with AIDP, who have stable deficits that are not improving as quickly as the patient and their physician would like. The role of steroids is unclear as the four trials of oral corticosteroids oral corticosteroids may slow recovery, while IV steroids showed a non-significant trend towards more benefit as compared to placebo. The combination of IVIG with methylprednisolone failed to find significant long-term advantage over IVIG alone in one trial[48]. Prognosis is best for MFS and BFP variants with good recovery even without specific treatment. In classical GBS, AIDP has a good prognosis for recovery and some patients with AMAN may also have a good recovery because of rapid reversal of conduction failure, while others may have a poor recovery.

Table XII: Immunomodulation in GBS and variants.

Indication	Plasma Exchange	IVIG
Indications and level of evidence	Non-ambulatory patients: 4-5 PE (2 - 2.5 L each time) within 4 weeks of onset (Level A Class II Evidence)	Non-ambulatory patients: 2g/Kg over 5 days within 2 weeks of onset (level A, class II evidence) Non-ambulatory patients: 2g Kg over 5 days within 2 - 4 weeks of onset (level B, class II evidence)
	Ambulatory patients: 2 PE within 2 weeks of onset (level B, limited class II)	Ambulatory patients: No indication but may be used in patients who are progressing and present within 2 weeks of onset of illness.
Dose	200 - 250 ml/Kg (alternate day PE is better than daily PE)	2g/Kg over 5 days
Complications	Haemodynamic and cardiovascular Hypotension Acute respiratory distress syndrome Myocardial infarction Arrhythmias Complications due to vascular access Septicaemia Thrombosis Complications associated with replacement fluids Allergic reactions HIV, Hepatitis Bleeding Depletion of plasma components Loss of clotting factors, globulins Loss of protein-bound drugs	Headache including Aseptic Meningitis Deep venous thrombosis Myocardial Infarction Oligaemic renal failure Anaphylaxis – especially in IgA deficiency

Novel therapies

Advances in understanding of pathophysiology of GBS has led to development of targeted therapies that prevent the complement-dependent neuronal damage. Eculizumab a complement factor 5 inhibitor has been studied in two randomised, double blind, placebo-controlled phase 2 trials as an add on therapy to IVIG[49]. Although the predefined response rate threshold for the eculizumab group could

not be reached, it was well tolerated and a larger proportion of patients in the eculizumab group were able to run at 24 weeks (74%), than in the placebo group (18%)[49]. Other novel therapies that are being evaluated in GBS are anti-C1q antibody (ANX005) and an IgG-degrading enzyme secreted by Streptococcus pyogenes (IdeS)[50,51].

Conclusion

It has been over a century since GBS was first described. Since then there have been a number of advances in our understanding of the pathophysiology of GBS and several variations in clinical presentation have been recognised. It is essential to recognise that GBS may not always present classically as rapidly ascending quadriparesis and can present with several regional or localised variants and may even involve the CNS in form of BBE.This will help in recognising various variants and instituting early treatment to prevent complications.

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