A Review on Guillian Barre Syndrome

Gitendra Sahu[1], Tilotma Sahu[2]

[1]*Student, Rungta Institute of Pharmaceutical Sciences, kohka (C.G), Rungta Institute of Pharmaceutical Sciences and Research (C G), India.*

[2]*Associate Professor, Rungta Institute of Pharmaceutical Sciences, kohka (C.G), Rungta Institute of Pharmaceutical Sciences and Research (C G), India.*

Corresponding Author: tilu06sahu@gmail.com

Abstract— Guillain-Barré syndrome and its clinical variants are a group of rapidly progressing, potentially debilitating neurologic disorders that may have significant morbidity/mortality if left unrecognized or untreated. The most common symptoms include ascending limb weakness and paralysis, which may progress to respiratory failure. Diagnosis is made clinically with laboratory testing. Several treatment options exist, including plasma exchange and intravenous immunoglobulin administration. Most cases may resolve without sequelae, but those that do not may leave behind significant persistent debility.

***Index Terms*— Guillain-Barré syndrome, ascending limb weakness, paralysis.**

1. Introduction

Definition: "It is a rare disease in which the peripheral nerves are attacked and damaged by the immune system. It occurs at all ages but more commonly in adults with varying degrees of weakness. Although rare, it can lead to complete paralysis of the body."

"GBS is a progressive autoimmune disease or disorder which is commonly caused by campylobacter jejuni."

The clinical journey through Guillain-Barre syndrome follows a typical pattern which will be readily divided into its constituent phases and components (figure1).[1] Demyelinating and axonal sorts of the syndrome occur in varying proportions across different countries, and clinical variants, like Miller Fisher syndrome, are readily definable.[2] Within the quality disease course are many less well understood biological variations. First, Guillain-Barre syndrome is typically preceded by infection or other immune stimulation that induces an aberrant autoimmune response targeting peripheral nerves and their spinal roots. [3,4] Molecular mimicry between microbial and nerve antigens is clearly a serious drive behind the event of the disorder, a minimum of within the case of Campylobacter jejuni infection. However, the interplay between microbial and host factors that dictates if and the way the immune reaction is shifted towards unwanted autoreactivity remains not well understood.[5]Furthermore, genetic and environmental factors that affect an individual's susceptibility to develop the disease are unknown.[6]Unwanted autoimmunity doesn't arise in most people (>99%) exposed to an immune stimulus as a results of Guillain-Barre syndrome associated infections like C. jejuni.[7] The acute progression of limb weakness, often with sensory and nerve involvement 1–2 weeks after immune stimulation, proceeds to its peak clinical deficit in 2–4 weeks.[8]

When patients present with rapidly progressive paralysis, the diagnosis of GuillainBarre syndrome must be made as soon as possible. Although establishment of the diagnosis in typical cases is typically straightforward, there are many clinical and investigative components to think about, especially in atypical cases. The diagnosis is essentially supported clinical patterns, because diagnostic biomarkers aren't available for many variants of the syndrome. Identification of biomarkers and establishment of their pathophysiological roles, if any, in experimental models has been a major research challenge.[9,10] All patients with Guillain-Barré syndrome need meticulous monitoring and supportive care.[11] Early initiation of intravenous Immunoglobulins (IVIg) or plasma exchange is of proven benefit and crucial, especially in patients with rapidly progressive weakness.[12] Because 1/4 of patients need artificial ventilation and lots of develop autonomic disturbances, many patients need admission within the high or medical care setting. Symptoms peak within 4 weeks, followed by a recovery period which will last months or years, because the immune reaction decays and therefore the peripheral nerve undergoes an endogenous repair process. Efforts specialise in the measurement and prediction of clinical course and outcome to enhance the care and treatment of individual patients.[13] Good prognostic models are developed, but additional studies are needed to research whether these prognostic factors differ between different disease subgroups and areas within the world. In parallel, prognostic biomarkers now got to be developed to raised predict outcomes and guide action, like personalized treatment refinements in acute management.[14]

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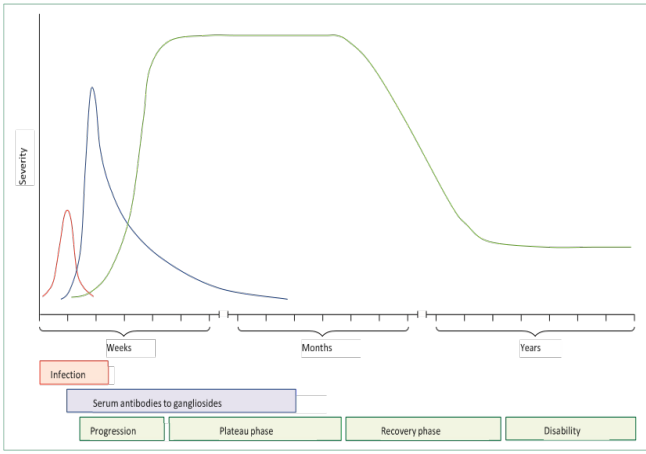

Figure 1: Guillain-Barré syndrome time course

2. History

The clinical features of GBS were described by Landry in 1859.[3] Eichorst in 1877 and Leyden in 1880 described the lymphocytic inflammation of nerve in some cases of peripheral neuropathy. In 1916, Guillain Barre' and Strohl described the characteristic cerebrospinal fluid (CSF) findings of increased protein concentration and normal cell count in two French soldiers (Guillain 1916). In 1949, Haymaker and Kernohan described the clinical and histopathological features, including inflammatory changes of the peripheral nerve in 50 fatal cases of GBS.[4] In the mid-1950s, Waksman and Adams produced experimental allergic neuritis in animals by injection of homologous or heterologous peripheral nerve tissue combined with Freund adjuvant. In the 1980s, plasma exchange was found to be an effective treatment, [5,6] and in the 1990s, efficacy was also demonstrated for intravenous immunoglobulin (IVIg). [7,8]

A. Epidemiology and preceding infections

Most studies that estimate incidence rates of Guillain Barré syndrome were wiped out Europe and North America, and showed an identical range of 0·8–1·9 (median 1·1) cases per 100000 people per year.[15]

The annual incidence rate of Countries. [23,24] Other infections associated with Guillain Barré syndrome are cytomegalovirus (CMV), Epstein-Barr Virus, influenza A virus, Mycoplasma pneumoniae, and Haemophilus influenzae. [22,25] An association of Guillain-Barré Syndrome with hepatitis E has been identified in patients from both Netherlands and Bangladesh. [26,27]

An Emerging relation between Guillain-Barre syndrome and Acute arbovirus infection including Zika and chikungunya Is being closely monitored and is that the subject of major Interest because the global epidemic spreads. As further Information emerges from epidemiological monitoring in Case-control studies, the precise incidence data for Arbovirus associated Guillain-Barre syndrome will become Clear.[28] the character of the preceding infection affects the Clinical phenotype and prognosis—for example, C.jejuni Infections are usually related to a pure motor axonal sort of Guillain-Barre syndrome , more severe limb Weakness, and a serological antibody response directed Against GM1 and GD1a gangliosides.[29,30]

These patients Generally have a poorer outcome. Whether the preceding Infections of childhood Guillain-Barré syndrome are Different has not been established. Guillain-Barré syndrome increases with age (0·6 per 100000 per year in children and 2·7 per 100000 per year in elderly people aged 80 years and over) and therefore the disease is slightly more frequent in males than in females. Seasonal fluctuations, presumably associated with variations in infectious antecedents, are reported, but these observations are rarely statistically significant.[16] Reports from several geographical areas are published within the past 5 years suggesting that the local incidence rate of the disorder might be higher in some areas, which is possibly associated with higher rates of exposure to infectious organisms.[17]

Several outbreaks of Guillain-Barre syndrome are reported, last in reference to C jejuni infections.18 The disorder can affect several relations, but this is often very unusual, might represent a chance finding, or could be caused by a standard antecedent infectious history or unknown heritable factors. [19,20] Equally, few infected individuals (estimated at *<1%) will mount the specific humoral immune response that drives the development of Guillain-Barré syndrome in C jejuni outbreaks.[21]

Overall, based on the incidence rate and life expectancy, the estimated lifetime risk of developing Guillain-Barré syndrome for any individual is less than one in 1000.Guillain-Barré syndrome is a typical post-infectious disorder, as shown by the rapidly progressive, monophasic disease course (<1 month) shortly after infection, usually without relapse. Two thirds of adult patients report preceding symptoms of a respiratory or gastrointestinal tract infection within 4 weeks of onset of weakness.[22]

Many different preceding infections have been identified in patients with the disorder, but only for a few microorganisms has an association been shown in case-control studies. C jejuni is the predominant infection, found in 25–50% of the adult patients, with a higher frequency in Asian Cases of Guillain-Barré syndrome have also been Reported shortly after vaccination with Sample rabies Vaccine and various types of influenza A virus vaccine. During the 1976 vaccination campaign for H1N1 influenza A virus, roughly one in 100000 people who had been Vaccinated developed Guillain-Barré syndrome.[31]

Although A similar association was suggested for the H1N1 influenza, A vaccination in 2009, extensive studies showed only 1·6 excess cases of Guillain-Barré syndrome per 1000000 people vaccinated, a frequency similar to all Seasonal flu vaccinations. [32,33] Vaccination might, in fact, Reduce the chance of an individual developing Guillain Barré syndrome after natural infection with influenza A, which is itself a possible candidate to precipitate the Disorder. A commonly asked clinical question is whether Vaccination increases the risk of Guillain-Barré syndrome Recurrence in previously affected individuals; this Hypothesis seems not to be the

case.[34] In a survey, none of the 106 patients with Guillain-Barré syndrome who had Been vaccinated against influenza (range of vaccinations Per person 1– 37 times, total 775 vaccinations) reported a Recurrence of Guillain-Barré syndrome after the Vaccination.[35]

B. Clinical features (guillain berre syndrome GBS)

The disease is characterized by weakness that affects the lower limbs first and rapidly progresses in an ascending fashion. Patients generally notice weakness in their legs, manifesting as "rubbery legs" or legs that tend to buckle, with or without numbness or tingling. As the weakness progresses upward, usually over a period of hours to days, the arms and facial muscles also become affected. Frequently, the lower cranial nerves may be affected, leading to bulbar weakness (oropharyngeal dysphagia, which includes difficult swallowing, drooling, and/or trouble maintaining an open airway) and respiratory difficulties. Most patients require hospitalization, and about 30% require ventilatory assistance. Sensory loss usually takes the form of loss of proprioception (position sense) and areflexia (complete loss of deep tendon reflexes), an important feature of GBS. Any loss of pain and temperature sensation is usually mild. In fact, pain is a common symptom in GBS, usually presenting as deep aching pain in the weakened muscles, which patients compare to the pain resulting from overexercising. These pains are self-limited and should be treated with standard analgesics. Bladder dysfunction may occur in severe cases. Acute paralysis in GBS is usually related to the presence of Na+ channel blocking factor in the cerebrospinal fluid. Morbid and iatrogenic events involving IV salt and water may occur unpredictably in this patient group, resulting in SIADH (syndrome of inappropriate anti diuretic hormone). This syndrome results from a deficit of sodium or a surplus of water due to iatrogenic fluid overload. It occurs in patients with GBS, meningitis, encephalitis, pneumonia, septicemia, severe malaria, bronchitis, or as a direct result of clinical insult. SIADH is often the first symptom of GBS. Na+ overload is almost always iatrogenic. Rapid correction of hyponatremia can cause osmotic brain demyelination [14, 16, 18, 21]. When infection precedes the onset of GBS, signs of infection subside before neurological features appear. Other possible precipitating factors include surgery, rabies or swine influenza vaccination, viral illness, Hodgkin's disease or some other malignant disease, and systemic lupus erythematosus [51]. Muscle weakness, the major neurological sign,usually appears in the legs first (ascending type) and then extends to the arms and facial nerves within 24 to72 h. Sometimes muscle weakness develops in the arms first (descending type) or in the arms and legs simultaneously. In milder forms of the disease, muscle weakness may affect only the cranial nerves or not occur [27].

The clinical course of GBS is divided into three phases;

- The initial phase begins when the first definitive symptom develops; it ends one to three weeks later, when no further deterioration is noted.
- The plateau phase lasts several days to two weeks.
- The recovery phase is believed to coincide with re-myelination and axonal process re-growth.

This phase extends over four to six months; patients with severe disease may take up to two years to recover, and recovery may not be complete.

Significant complications of GBS include mechanical entilatory failure, aspiration pneumonia, sepsis, joint contractures, and deep vein thrombosis. Unexplained autonomic nervous system involvement may cause sinus tachycardia or bradycardia, hypertension, orthostatic hypotension, and loss of bladder and bowel sphincter control. Up to two thirds of patients with GBS report an antecedent illness or event one to three weeks prior to the onset of weakness. Upper respiratory and gastrointestinal illnesses are the most commonly reported conditions. Symptoms of this initial illness have generally resolved by the time of medical presentation for the neurological condition [68, 69]. Autonomic changes can include tachycardia, bradycardia, facial flushing, paroxysmal hypertension, orthostatic hypotension, anhydrosis and/or diaphoresis. Urinary retention and paralytic ileus can also be observed. Bowel and bladder dysfunction is rarely present as an early symptom or persists for a significant period of time. Dysautonomia is more frequent in patients with severe weakness and respiratory failure. Upon presentation, 40% of patients have respiratory or oropharyngeal weakness. Typical complaints include dyspnea on exertion, shortness of breath, difficulty swallowing and slurred speech. Ventilatory failure with required respiratory support is observed in up to one third of patients at some time during the course of their disease. Facial weakness (cranial nerve VII) is observed most frequently, followed by symptoms associated with cranial nerves III, V, VI, IX, X, and XII. Limitation of eye movement most commonly results from a symmetric palsy associated with cranial nerve VI. Ptosis from cranial nerve III (oculomotor) palsy is also often associated with a limitation of eye movements. Pupillary abnormalities, especially those accompanying ophthalmoparesis, are relatively common as well.

C. Pathophysiology and immunopathology

Until 20 years ago Guillain-Barré syndrome was regarded as a homogeneous disorder, the outcome of which varied according to severity. This variation was believed to be largely caused by the extent of bystander axonal injury arising secondarily to adjacent demyelination, rather than Fundamental pathophysiological differences in the types of Guillain-Barré syndrome between individuals.[36]

Peripheral Nerve remyelination is a functionally effective, natural Repair process, whereas axonal regeneration is slow, and can be irreversible if widespread along the whole length of A nerve fibre. The advance in understanding that changed This viewpoint was the appreciation that distinct, clinical pathological phenotypes could be delineated within the Guillain-Barré syndrome spectrum, the main phenotypes Of which are termed acute inflammatory demyelinating Polyneuropathy and acute motor axonal neuropathy (figure 2).

Although this distinction of Guillain-Barré Syndrome phenotypes does not negate the idea of bystander Axonal injury, it does clarify the point that axons themselves Can be the primary target for autoimmune injury, rather Than being injured as a secondary phenomenon.[37]

Clinical variants such as Miller Fisher syndrome are now classified within the Guillain-Barré syndrome family of disorders. As shown by the descriptive terms, immune injury specifically takes place at the myelin sheath and related Schwann-cell components in acute inflammatory demyelinating polyneuropathy, whereas in acute motor axonal neuropathy, membranes on the nerve axon (the axolemma) itself are the primary target for immune-related injury. Classification into acute motor axonal neuropathy or acute inflammatory demyelinating polyneuropathy was first based on electrophysiological and pathological studies, and was subsequently supported by the identification of specific antibody biomarkers for acute motor axonal neuropathy, directed against neuronal membrane gangliosides (notably GM1 and GD1a).[38] This polarization has been the cornerstone on which many detailed clinical and basic studies were based, many of which were done on cohorts from Asia, where acute motor axonal neuropathy seems to be more prevalent than in western Europe, owing in part to different geographical patterns of C jejuni infection. However, this cannot be the whole explanation as in the UK and the Netherlands at least 25% of Guillain-Barré syndrome cases are preceded by C jejuni infection, yet axonal cases are proportionally fewer than demyelinating ones, a finding that cannot be explained by differences in serological assays as comparative studies have shown.[39]

In parallel with, and in part due to the dichotomisation Of Guillain-Barré syndrome into acute motor axonal Neuropathy and acute inflammatory demyelinating Polyneuropathy, the existing body of evidence has emerged That the disorder is mainly a humorally-mediated, rather Than T-cell-mediated disorder, at least in the progressive Phase of nerve injury. The extent to which T cells might be Involved in the induction phase of the disease, during Which the immune response is generated, remains Uncertain, and continues to be explored in new models.[40]

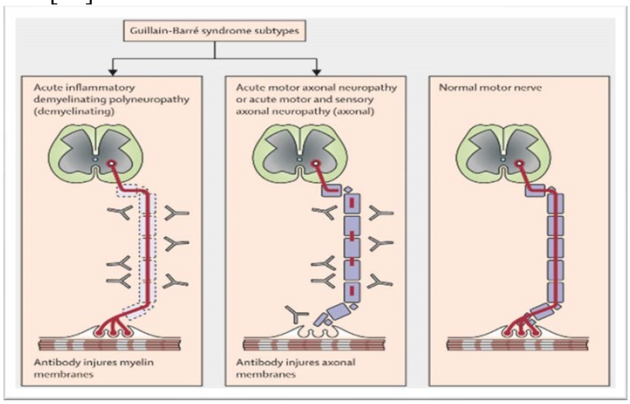

Fig.2. Guillain Barré syndrome subtypes in which antibody mediated effector pathways, including Complement activation, cause glial or axonal membrane injury with consequent conduction failure.

Few studies now use the myelin protein-specific T-cell mediated experimental allergic neuritis model of Guillain-Barre syndrome that dominated the preclinical field for 20 years, compared with newer antibody-mediated models in rabbit and mouse. Because of these data from the new Models, acute motor axonal neuropathy is thought of as an antibody mediated attack on the nerve axolemma Driven by molecular mimicry between microbial and Axolemmal surface molecules. [41,42]

The molecular mimics Are glycans (i.e. sugars) expressed on lipooligosaccharides (LOS) of preceding infectious organisms, notably C. jejuni,That are capable of inducing antibody responses to these Carbohydrate antigens.[5] Anti-carbohydrate antibody Responses are believed to be largely independent of T cells. Anti-LOS antibodies can then bind to structurally identical Glycans present on nerve gangliosides. Anti-ganglioside Antibodies in acute motor axonal neuropathy are Complement-fixing, of IgG1 and IgG3 subclass, and mainly bind to GM1 and GD1a gangliosides.[43]

In animal Models, they induce axonal injury by fixing complement, recruiting macrophages, and depositing membrane Attack complex in the axolemmal membrane.[44] This Immunological cascade disrupts the anatomical and Physiological integrity of exposed nerve membranes in Nerve terminals and nodes of Ranvier, causing a nerve Conduction blockade that is either reversible or, in severe Cases, results in severe, widespread axonal degeneration with poor recovery. A similar model is proposed for Miller Fisher syndrome associated with anti-GQ1b antibodies,[45] In which GQ1b ganglioside is the antigenic target, and is Disproportionately enriched in the motor nerves that Innervate extraocular muscles.[46]

In view of the high incidence of C jejuni infections in the general population, one might ask why so few people Develop acute motor axonal neuropathy after C jejuni infection. Two possible reasons could account for the low Number of people who develop acute motor axonal Neuropathy. First, only a small proportion of C jejuni Strains have ganglioside mimics on their LOS—most Strains bear other glycans.[47] Second, most individuals who Have been exposed to C jejuni maintain immunological Tolerance to the self-glycans on LOS, and instead mount a Projective immune response against other components of the bacterial surface. Why certain individuals break Tolerance and enter an autoreactive state is not known at Present. Unlike T-cell tolerance, the mechanisms Underlying B-cell tolerance to T-cell-independent Antigens, including gangliosides, are not well studied.[5]

By contrast with acute motor axonal neuropathy, the Immunological cascade involved in acute inflammatory Demyelinating polyneuropathy is less well understood For various reasons. First, a wider range of immune Stimulants cause acute inflammatory demyelinating Polyneuropathy compared with acute motor axonal Neuropathy, which includes bacterial and viral infections, And vaccines. Second, specific antibody biomarkers have Yet to be characterised, despite widespread screening Efforts to identify the putative nerve antigens. At present, A wider range of anti-nerve autoantibodies

directed at Both proteins and glycolipids could be responsible for Acute inflammatory demyelinating polyneuropathy Immunopathology than is the case for acute motor Axonal neuropathy or Miller Fisher syndrome. Alternatively, nerve specific T cells, directed against as Yet unknown antigens might play a greater part in acute Inflammatory demyelinating polyneuropathy than is Known at present. Historically, few studies have shown T-cell and B-cell responses to compact myelin proteins, Including P0, P2, and PMP22, although these responses Have been found in small numbers of cases.[48]

Antibodies Against proteins in the specialised domains at the node of Ranvier, including gliomedin, contactin, TAG-1, moesin, And neurofascin have been identified.[49]For example, a High proportion of antibodies against moesin, a Component of the ezrin–radixin–moesin cytoplasmic Complex in Schwann-cell microvilli that surround the Nodal axolemma, have been reported in cases of acute Inflammatory demyelinating poly neuropathy triggered By CMV infection,[50] although this result has not been Replicated.[51]

Nerve glycolipids expressed in glial Membranes, including myelin, are prime candidates as Important antigens in acute inflammatory demyelinating Polyneuropathy.[52] Anti bodies against the glycolipid LM1,Sulphoglucuronosyl paragloboside, galactocerebroside, And sulfatide are found in a small proportion of patients With acute inflammatory demyelinating polyneuropathy.[53]In addition to being present in axonal membranes, some Gangliosides (including GM1 and GQ1b) are expressed in Glial membranes at the node of Ranvier, where they Might mediate para nodal demyelination that causes the Pathophysiological features of acute inflammatory Demyelinating polyneuropathy.[54]

These so-called anti-complex Antibodies only bind heteromeric or multimeric lipid Complexes and are difficult to detect. In addition to being Found in some cases of acute motor axonal neuropathy, they might be widely present, but as yet, undiscovered in Acute inflammatory demyelinating polyneuropathy. Studies investigating these antibodies are continuing and involve the development of both technical platforms and study design. [56,57]

Although the distinction between acute motor axonal Neuropathy and acute inflammatory demyelinating Polyneuropathy is conceptually clear, the margins might Be more blurred than originally thought.[58] Electrophysiological methods are the mainstay of clinical Investigation. A substantial proportion of acutely Diagnosed patients with Guillain-Barré syndrome cannot Be classified into a category, either because the tractable Nerves (i.e. the upper and lower limb nerves that can be Readily accessed by surface electrodes used in clinical (Electrophysiology) are so severely affected that they are Inexcitable, or are physiologically normal; both states are Uninformative for classification as acute motor axonal Neuropathy or acute inflammatory demyelinating Polyneuropathy. Furthermore, electrophysiological recordings are ambiguous, change during the clinical Course in any one individual, and yield an acute Inflammatory demyelinating polyneuropathy pattern Early on and an acute motor axonal neuropathy pattern Later (reversible conduction block).[59,60] Thus, inflammatory Injury of either glial or axonal membranes (or both Simultaneously) in the nodal complex might result in Very similar electrophysiological features of reversible Conduction failure. The molecular architecture of the nodal complex, which Consists of specialised nodal, paranodal, and juxtaparanodal domains that mediate glial–axonal interactions, Has been well characterised and provides a foundation for The study of the fi ne details of Guillain-Barré syndrome Pathogenesis from a nodal perspective.[61] Although yet to Be established, immune responses focused on the nodal Complex probably underlie much of the pathogenic Cascade that takes place in Guillain-Barré syndrome, and The term nodo-paranodopathy has been coined to Emphasise the focus on this site.[62]

As noted previously, the Nodal area is richly decorated with potential antigens, including proteins and glycolipids, and is functionally Very sensitive to pathological perturbations induced by antibody deposits, complement activation, and Macrophage recruitment. Nodal conduction block, of glial or axonal origin, can arise quickly, but functionality can be Restored in equally short time periods through local repair of injured membranes.

Conversely, complete axonal transaction (which is always followed by Wallerian

Degeneration of the distal stump),[63] especially if proximally Located in the nerve roots at a long distance from the Innervation target, will be a permanent irreparable injury Because regeneration cannot effectively occur over long Distances. Although these considerations have clinical Relevance, prediction of how they might affect outcome in Individual cases is difficult, and there are no specific Therapeutic implications at present. [From GBS.pdf on my storage folder]

D. Pathogens and autoimmunity in GBS subtypes (from Guillain berre syndrome (GBS)

Several variants of GBS are recognized. These disorders share similar patterns of evolution, recovery, symptom overlap, and probable immune mediated pathogenesis. Types and variants of GBS are listed in Table 1 [38].

Table.1.
Types/variants of GBS

S.No.	Types	Symptoms
1	Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP)	Most common variant, 85% of cases. Primarily motor inflammatory demyelination ± secondary axonal damage (‘bystander effect’). Maximum of 4 weeks of progression
2	Acute Motor-Sensory Axonal Neuropathy	Motor and sensory involvement with (AMSAN) severe course respiratory and bulbar involvement.

		Primary axonal degeneration with poorer prognosis.
3	Acute Motor Axonal Neuropathy (AMAN)	Motor only with early and severe respiratory involvement. Primary axonal degeneration. Often affects children, young adults. Up to 75% positive C. jejuni serology, often also anti-GM1, anti-GD1a positive
4	Miller-Fisher Variant	Ophthalmoplegia, sensory ataxia, areflexia. 5% of all cases. 96% positive for anti-GQ1b antibodies
5	Pharyngeal-Cervical-Brachial Variant	Often associated with IgG anti-GT1a. Presents with proximal descending weakness. Must distinguish from botulism and diphtheria
6	Acute Pandysautonomia	Widespread sympathetic and parasympathetic failure

1) AIDP-associated infection

Cytomegalovirus (CMV), a cause of respiratory tract infections, is the second most common pathogen linked to cases of GBS in Europe and Japan. Autoantibodies against the human ganglioside GM2 have been isolated in patients with a CMV infection and GBS symptoms. Development of AIDP is seen predominantly in the cranial and sensory nerves as opposed to motor nerves. The immune response elicited in AIDP is focused on the Schwann cell or myelin sheath. Damage to the myelin or Schwann cells results in demyelination, which is characteristic of AIDP [90].

2) AMAN-associated infection

Infection by C. jejuni, a cause of bacterial gastroenteritis, is the leading cause of AMAN worldwide. Studies show that the production of autoantibodies by C. jejuni infection occurs in only 1 out of 3285 patients with C. jejuni enteritis. It has been found that only certain strains of C. jejuni are associated with GBS/AMAN cases [54]. The strains are divided by serotype based on their low molecular weight type lipopolysaccharide (LPS), called a lipooligosaccharides (LOS) [67]. Serotypes most commonly associated with AMAN are HS:19 and HS:41. A polymorphism in the gene cstII (Thr51) has been found to be closely associated with development of anti-GM1 and anti-GD1a autoantibodies [53]. The hypothesis of molecular mimicry is based on the fact that the bacterial LOS induces IgG, IgA, and IgM autoantibody against human gangliosides due to LOS ganglioside-mimicking epitopes [67]. Autoantibody have been isolated in GBS patients' serum and found to recognize C. jejuni LOS and human gangliosides GM1, GM1b, GD1a, and GalNAc-GD1a epitopes, providing evidence for molecular mimicry. Furthermore, Moran et al. concluded that the IgG LOSinduced anti-GM1 antibodies bound to sites at the nodes of Ranvier in humans. This is important because other studies have concluded that antibodies bound to nodes of Ranvier disrupt Na+ and K+ channels, interfering with nerve conduction.

3) MFS (Miller-Fisher syndrome)-associated

Infection MFS is a common variant of GBS, and is observed in about 5% of all GBS cases. The syndrome consists of ataxia, ophthalmoplegia (problems controlling eye movements), and areflexia (loss of neurological re-flexes). Ataxia is primarily noted during gait and in the trunk, with lesser involvement of the limbs. Motor strength is characteristically spared. The usual course is one of gradual and complete recovery over weeks or months. A close association exists between antiganglioside antibodies and the Fisher variant. Anti-GQ1b antibodies triggered by certain C. jejuni strains have a relatively high specificity and sensitivity for the disease. Dense concentrations of GQ1b gangliosides are found in the oculomotor, trochlear, and abducens nerves, which may explain the relationship between anti-GQ1b antibodies and the ophthalmoplegia presented by MFS patients in addition to symptoms similar to those seen in other forms of GBS. Autoantibodies have been isolated from these patients that bind to human ganglioside GQ1b as well as the GQ1b epitope present within the LOS of C. jejuni isolated from MFS patients. The dominant C. jejuni serotypes associated with MFS are HS:2 and HS:4. The gene polymorphism associated with the development of anti-GD1b autoantibodies was found to be cstII (Asn51). This provides a clear link to the clinical presentation of MFS because the GQ1b ganglioside is found predominantly in human oculomotor nerves. The axonal form of GBS, also referred to as acute motor-sensory axonal neuropathy (AMSAN), often presents with rapid and severe paralysis, with delayed and poorer recovery. Like AMAN, axonal GBS is associated with preceding C. jejuni diarrhea. Pathological findings show severe axonal degeneration of motor and sensory nerve fibers, with little demyelination [11, 17]. A pure sensory variant of GBS has been described in the medical literature, typified by a rapid onset of sensory loss and areflexia in a symmetric and widespread pattern [72]. Lumbar puncture studies show albuminocytologic dissociation in the cerebrospinal fluid (CSF), and electromyography (EMG) shows characteristic signs of a demyelinating process in the peripheral nerves [93]. Dysfunction of the sympathetic and parasympathetic systems results in severe postural hypotension, bowel and bladder retention, an hydrosis, decreased salivation and lacrimation, and pupillary abnormalities. The pharyngeal-cervical-brachial variant is distinguished by isolated facial, oropharyngeal, cervical and upper limb weakness without lower limb involvement. Other unusual clinical variants with restricted patterns of weakness are observed only in rare cases.

4) Role of anti-ganglioside antibodies

Anti-ganglioside antibodies that react to self-gangliosides are found in autoimmune neuropathies [56, 82]. These antibodies were first found to react with cerebellar cells. These antibodies

show the strongest association with certain forms of GBS [12,47]. Auto antigenic gangliosides that are currently Known are GD3, GM1, GQ3 and GT1 [24].

5) Anti-GD3

Anti-GD3 antibodies have been found in association with specific forms of GBS. In vivo studies of isolated Anti-GM1 and GD3 antibodies indicate that these antibodies can interfere with motor neuron function. Anti-GD1a antibodies were highly associated acute Motor axonal neuropathy, while high titers of anti-GM1 were more frequent, indicating that GD1a possibly targets the axolemma and nodes of Ranvier [34].

6) Anti-GM1

Levels of anti-GM1 are elevated in patients with various forms of dementia. Antibody levels correlate with increased severity of GBS [92]. In Japan, levels of GM1 were elevated in patients with prodromal diarrhea. Titers of GM1 are also elevated in other diseases (rheumatoid arthritis and systemic lupus erythematosus). Additionally, a highly significant association was found between rheumatoid arthritis and peripheral neuropathies [37]. The autoimmune role of anti-GM1 is still unclear. [13]

7) Anti-GQ1b

Anti-GQ1b antibodies are found in Miller-Fisher syndrome. Studies of these antibodies reveal large disruptions of the Schwann cells. Anti-GQ1b IgG levels were elevated in GBS patients with ophthalmoplegia [15].

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