

## Review Article

# Guillain Barre Syndrome

+Gaur Arun\*, Gaur Rajni \*\*

\*Senior Specialist & Head, Department Of Medicine,\*\*Senior Specialist & Head, Department of Ophthalmology, Mahatma Gandhi Hospital, Bhilwara. Rajasthan 311001

Corresponding author\*

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### Abstract:

Guillain–Barré syndrome (GBS) is a rapidonset muscle weakness caused by the immune system damaging the peripheral nervous system.<sup>[2]</sup> The initial symptoms are typically changes in sensation or pain along with muscle weakness, beginning in the feet and hands. This often spreads to the arms and upper body with both sides being involved. The symptoms develop over hours to a few weeks.<sup>[2]</sup> During the acute phase, the disorder can be lifethreatening with about 15% developing weakness of the breathing muscles requiring mechanical ventilation.<sup>[1]</sup> Some are affected by changes in the function of the autonomic nervous system, which can lead to dangerous abnormalities in heart rate and blood pressure.

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### OVERVIEW

Guillain–Barré syndrome (GBS) is a rapidonset muscle weakness caused by the immune system damaging the peripheral nervous system.<sup>[2]</sup> The initial symptoms are typically changes in sensation or pain along with muscle weakness, beginning in the feet and hands. This often spreads to the arms and upper body with both sides being involved. The symptoms develop over hours to a few weeks.<sup>[2]</sup> During the acute phase, the disorder can be lifethreatening with about 15% developing weakness of the breathing muscles requiring mechanical ventilation.<sup>[1]</sup> Some are affected by changes in the function of the autonomic nervous system, which can lead to dangerous abnormalities in heart rate and blood pressure.<sup>[2]</sup>

The cause is unknown. The underlying mechanism involves an autoimmune disorder in which the body's immune system mistakenly attacks the peripheral nerves and damages their myelin insulation.<sup>[2]</sup> Sometimes this immune dysfunction is triggered by an infection or, less commonly, surgery or vaccination.<sup>[2][1]</sup> The diagnosis is usually made based on the signs and

symptoms, through the exclusion of alternative causes, and supported by tests such as nerve conduction studies and examination of the cerebrospinal fluid.<sup>[2]</sup> There are a number of subtypes based on the areas of weakness, results of nerve conduction studies, and the presence of certain antibodies.<sup>[3]</sup> It is classified as an acute polyneuropathy.<sup>[1]</sup>

In those with severe weakness, prompt treatment with intravenous immunoglobulins or plasmapheresis, together with supportive care, will lead to good recovery in the majority. Recovery may take weeks to years. About a third have some permanent weakness.<sup>[2]</sup>

Globally death occurs in about 7.5% of those affected.<sup>[1]</sup> Guillain–Barré syndrome is rare, at one or two cases per 100,000 people every year.<sup>[2][4]</sup> Both sexes and all parts of the world have similar rates of disease.<sup>[2][1]</sup> The syndrome is named after the French neurologists Georges Guillain and Jean Alexandre Barré, who described it with André Strohl in 1916.<sup>[5][6]</sup>

### HISTORICAL BACKGROUND

French physician Jean-Baptiste Octave Landry first described the disorder in 1859.<sup>[34]</sup> In 1916,

Georges Guillain, Jean Alexandre Barré, and André Strohl diagnosed two soldiers with the illness and described the key diagnostic abnormality—albumin cytological dissociation—of increased spinal fluid protein concentration but a normal cell count.<sup>[5][6] [35]</sup>C. Miller Fisher described the variant that bears his name in 1956.<sup>[10][36]</sup> Edwin Bickerstaff, described the brainstem encephalitis type in 1951 with Philip Cloake, and made further contributions with another paper in 1957.<sup>[10][37][38]</sup> Further subtypes have been described since then, such as the form featuring pure ataxia and the type causing pharyngeal-cervical-brachial weakness.<sup>[10]</sup>The axonal subtype was first described in the 1990s.<sup>[16]</sup> Diagnostic criteria were developed in the late 1970s after the series of cases associated with swine flu vaccination. These were refined in 1990.<sup>[3][39]</sup> Plasma exchange was first used in 1978 and its benefit confirmed in 1985.<sup>[41]</sup> Intravenous immunoglobulins were introduced in 1988, and its efficacy compared to plasma exchange was shown in early 1990s.<sup>[41]</sup> Development of new treatments has been limited since immunotherapy was introduced in the 1980s and 1990s.<sup>[41]</sup>

### **Epidemiology**

Worldwide incidence is between 0.89 and 1.89 cases per 100,000 people. Children and young adults are less likely to be affected than the elderly: the risk increases by 20% for every decade of life.<sup>[4]</sup> Men are more likely to develop GBS than women; The relative risk for men is 1.78 compared to women.<sup>[8][4]</sup>

The distribution of subtypes varies between countries. In Europe and the United States, 60–80% of people with GBS have the demyelinating subtype (AIDP), and AMAN affects only a small number (6–7%). In Asia and Central and South America, that proportion is significantly higher (30–65%). This may be related to the exposure to different kinds of infection, but also the genetic

characteristics of that population.<sup>[3]</sup> Miller Fisher variant is thought to be more common in Southeast Asia.<sup>[8][10]</sup>

### **Causes**

Two thirds of people with GBS have experienced an infection before the onset of the condition. Most commonly these are episodes of gastroenteritis or a respiratory tract infection. In many cases, the exact nature of the infection can be confirmed.<sup>[3]</sup>

Approximately 30% of cases are provoked by *Campylobacter jejuni*. A further 10% are attributable to cytomegalovirus (CMV, HHV-5).

Despite this, only very few people with *Campylobacter* or CMV infections develop GBS (0.25–0.65 per 1000 and 0.6–2.2 per 1000 episodes, respectively).<sup>[8]</sup>

Two other herpesviruses (Epstein–Barr virus/HHV4 and varicella zoster virus/HHV3) and the bacterium *Mycoplasma pneumoniae* have been associated with GBS.<sup>[8]</sup>

Dengue fever and Zika virus have also been associated with episodes of GBS.<sup>[12][13]</sup> Previous hepatitis virus infection has been found to be more common in Guillain–Barré syndrome.<sup>[3][6]</sup>

Epidemiologic studies looking at H1N1 vaccination demonstrated a slight increased risk of GBS. Older type rabies vaccine, prepared in nervous system tissue, is implicated as trigger of GBS in developing countries where it is still used. GBS also occurs frequently than can be attributed to chance alone in patients with lymphoma (including Hodgkin's disease), In HIV-seropositive individuals and in patients with systemic lupus erythematosus (SLE).

### **Genetic Influence of Disease**

HLA-incidence of HLA DR3 is 3 times in patients with GBS as compared to Controls<sup>[55]</sup>. Chronic relapsing form of diseases<sup>2</sup> is associated with HLA A1, B-8 and RW 3.

### **Mechanism**

Different types of Guillain–Barrésyndrome feature different types of immune attack. The demyelinating variant (AIDP) features damage to the myelin sheath by white blood cells (T lymphocytes and macrophages);this process is preceded by activation of a group of blood proteins known ascomplement. In contrast, the axonal variant is mediated by IgGantibodies and complement against the cell membrane covering the axon without direct lymphocyte involvement. Various antibodies directed at nerve cells have been reported in Guillain–Barré syndrome. In the axonal subtype, these antibodies have been shown to bind to gangliosides, a group of substances found in peripheral nerves. A ganglioside is a molecule consisting of ceramide bound to a small group of hexose-type sugars and containing various numbers of *N*-acetylneuraminic acid groups. The key four gangliosides against which antibodies have been described are GM1, GD1a, GT1a, and GQ1b, with different antiganglioside antibodies being associated with particular features;for instance, GQ1b antibodies have been linked with Miller Fisher variant GBS and related forms including Bickerstaff encephalitis.<sup>[8]</sup> The production of these antibodies after an infection is probably the result of molecular mimicry, where the immune system is reacting to microbial substances but the resultant antibodies also react with substances occurring naturally in the body.<sup>[8][16]</sup>After a *Campylobacter* infection, the body produces antibodies of the IgA class; only a small proportion of people also produce IgG antibodies against bacterial substance cell wall substances (e.g. lipooligosaccharides) that crossreact with human nerve cell gangliosides. It is not currently known how this process escapes central tolerance to gangliosides, which is meant to suppress the production of antibodies against the body's own substances.<sup>[17]</sup> Not all antiganglioside antibodies cause disease, and it

has recently been suggested that some antibodies bind to more than one type of epitope simultaneously (heterodimeric binding) and that this determines the response. Furthermore, the development of pathogenic antibodies may depend on the presence of other strains of bacteria in the bowel.<sup>[17]</sup>

### Signs and Symptoms

The first symptoms of Guillain–Barré syndrome are numbness, tingling, and pain, alone or in combination.This is followed by weakness of the legs and arms that affects both sides equally and worsens over time.<sup>[7][8]</sup> The weakness can take half a day to over two weeks to reach maximum severity, and then becomes steady.<sup>[8]</sup> In one in five people, the weakness continues to progress for as long as four weeks.<sup>[3]</sup> The muscles of the neck may also be affected, and about half experience involvement of the cranial nerves which supply the head andface; this may lead to weakness of the muscles of the face, swallowing difficulties and sometimes weakness of the eye muscles.<sup>[3]</sup> In 8%, the weakness affects only the legs (paraplegia or paraparesis).<sup>[3]</sup> Involvement of the muscles that control the bladder and anus is unusual.<sup>[8]</sup> In total, about a third of people with Guillain–Barré syndrome continue to be able to walk.<sup>[3]</sup> Once the weakness has stopped progressing, it persists at a stable level ("plateau phase") before improvement occurs. The plateau phase can take between two days and six months, but the most common duration is a week.<sup>[3]</sup> Pain related symptoms affect more than half, and include back pain, painful tingling, muscle pain and pain in the head and neck relating to irritation of the lining of the brain.<sup>[3]</sup>

Many people with Guillain–Barré syndrome have experienced the signs and symptoms of an infection in the 3–6 weeks prior to the onset of the neurological symptoms. This may consist of upper

respiratory tract infection (rhinitis, sore throat) or diarrhea.<sup>[8]</sup>

In children, particularly those younger than six years old, the diagnosis can be difficult and the condition is often initially mistaken (sometimes for up to two weeks) for other causes of pains and difficulty walking, such as viral infections,<sup>[3]</sup> or bone and joint problems.<sup>[9]</sup>

On neurological examination, characteristic features are the reduced power and reduced or absent tendon reflexes (hypor areflexia, respectively). However, a small proportion has normal reflexes in affected limbs before developing areflexia, and some may have exaggerated reflexes.<sup>[3]</sup> In the "Miller Fisher variant" subtype of Guillain-Barré syndrome (see below), weakness of the eye muscles (ophthalmoplegia) is more pronounced and may occur together with abnormalities in coordination (ataxia).<sup>[8]</sup> The level of consciousness is normally unaffected in Guillain-Barré syndrome, but the Bickerstaff brainstem encephalitis subtype may feature drowsiness, sleepiness, or coma.<sup>[5][10]</sup>

#### **Involvement of Cranial Nerves**

In children frequency of Cranial Nerve paresis is 28-41 %(45%). All Cranial Nerves except I, VIII have been reported to have been involved. In adults cranial nerve involvement may be 38-94%<sup>[42,43]</sup>. VIIth Cranial is most frequently involved 50%<sup>[45]</sup>. Other cranial nerves to be involved are Vth<sup>[43,44]</sup>, III, IV, VI<sup>[45]</sup>, 11%, IX, X 25-94%, XI 22%<sup>[46]</sup>, XII 7-20%.

#### **Respiratory failure**

A quarter of all people with Guillain-Barré syndrome develop weakness of the breathing muscles leading to respiratory failure, the inability to breathe adequately to maintain healthy levels of oxygen and/or carbon dioxide in the blood.<sup>[8][3][11]</sup> This life threatening scenario is complicated by other medical problems such as pneumonia, severe infections, blood clots in the lungs and

bleeding in the digestive tract in 60% of those who require artificial ventilation.<sup>[8]</sup>

#### **Headache**

Headache occurs in 8-23% cases<sup>[46]</sup>.

#### **Fever**

By and large the diseases pursue an afebrile course. When fever occurs it is due to overlapping of preceding illness with the course of diseases or sometimes secondary infection and rarely fever occurs without these few cases usually viruses have been seen CSF<sup>[47]</sup>, which has cast doubt about diagnosis.

#### **Automatic Neuropathy**

It is quite a common accompaniment it manifests as variations in Blood Pressure, Hypertension<sup>[48]</sup>, postural hypotension sinus tachycardia, abnormal setting<sup>[49]</sup> and flashing episodes. Its incidence 40-60%. SIADH also occurs with serum sodium as low as 105 mEq/L.

#### **Papilloedema**

It occurs rarely in Guillain Barre Syndrome. Although believed to be due to increased proteins in CSF<sup>[50,51]</sup> which hinders absorption through villi, the relation of level of protein with papilloedema is lacking and even in Papilloedema, radio iodine is absorbed normally<sup>[52]</sup>.

#### **Diagnosis**

The diagnosis of GBS depends on findings such as rapid development of muscle paralysis, absent reflexes, absence of fever, and a likely cause. Cerebrospinal fluid analysis and nerve conduction studies are supportive investigations commonly performed in the diagnosis of GBS.<sup>[8][3][6]</sup> Testing for antiganglioside antibody is often performed.<sup>[3]</sup> Blood tests are generally performed to exclude the possibility of another cause for weakness, such as a low level of potassium in the blood.<sup>[8]</sup> An abnormally low level of sodium in the blood is often encountered in GBS. This has been attributed to the inappropriate secretion of

antidiuretic hormone, leading to relative retention of water.<sup>[18]</sup> Magnetic resonance imaging (MRI) of the spinal cord is performed to distinguish between GBS and other conditions causing limb weakness, such as spinal cord compression.<sup>[8][3]</sup> If an MRI scan shows enhancement of the nerve roots, this may be indicative of GBS.<sup>[3]</sup> In children, this feature is present in 95% of scans, but it is not specific to GBS, so other confirmation is also needed.<sup>[9]</sup>

### Spinal Fluid

Characteristic findings in GBS are an elevated protein level, usually greater than 0.55 g/L, and fewer than 10 white blood cells per cubic millimetre of fluid ("albumin cytochemical dissociation").<sup>[19]</sup> This combination distinguishes GBS from other conditions (such as lymphoma and poliomyelitis) in which both the protein and the cell count are elevated. Elevated CSF protein levels are found in approximately 50% of patients in the first 3 days after onset of weakness, which increases to 80% after the first week.<sup>[3]</sup>

### EMG and Nerve Conduction Velocity

Needle electromyography (EMG) and nerve conduction studies are performed to exclude other causes of acute muscle weakness, as well as distinguish the different types of GBS. In the first two weeks, these investigations may not show any abnormality.<sup>[3][15]</sup>

Formal criteria exist for each of the main subtypes of GBS (AIDP and AMAN/AMSAN, see below), but these may misclassify some cases (particularly where there is reversible conduction failure) and therefore changes to these criteria have been proposed.<sup>[20]</sup> Sometimes, repeated testing may be helpful.<sup>[20]</sup>

### Clinical Subtypes

- **Type 1-** Acute Inflammatory Demyelinating polyneuropathy (AIDP) is most common in North America and Europe and characterized by Sensory

symptoms and muscle weakness, often with cranial nerve weakness and autonomic involvement.

- **Type 2-** Acute motor axonal neuropathy (AMAN) is Axonal polyneuropathy also sometimes called as 'Chinese Paralytic Syndrome' has its roots in Asia and Central and South America characterized by isolated muscle weakness without sensory symptoms. It is associated with GM1a/b, GD1a & GalNacGD1a (Antiganglioside antibodies)
- **Type 3-** Acute motor and sensory axonal neuropathy (AMSAN) is Axonal polyneuropathy with reduced or absent sensory action potential characterized by severe muscle weakness similar to AMAN but with sensory loss. It is Associated with GM1, GD1a (Antiganglioside antibodies).
- **Type 4-** Pharyngeal-cervical-brachial variant is characterized by weakness of throat, face, neck and shoulder muscles. It is associated with Mostly GT1a, occasionally GQ1b, rarely and GD1a (Antiganglioside antibodies).
- **Type 5-** Miller Fisher Syndrome occurs more commonly in men than in women (2:1). Cases normally occur in the spring and the average age of occurrence is 43.<sup>[22]</sup> Characterized by ataxia, eye muscle weakness, areflexia with rare limb weakness. Generally associated with GQ1b, GT1a antibodies.
- **Bickerstaff's brainstem encephalitis (BBE)** is characterized by the rapid onset of ophthalmoplegia, ataxia, and disturbance of consciousness, and may be associated

with absent or decreased tendon reflexes and as well as Babinski's sign.<sup>[21]</sup> The course of the disease is usually monophasic, but recurrent episodes have been reported. MRI abnormalities in the brainstem have been reported in 11%.<sup>[10]</sup>

### **Treatment**

#### **Immunotherapy**

Plasmapheresis and intravenous immunoglobulins (IVIg) are the two main immunotherapy treatments for GBS. Plasmapheresis attempts to reduce the body's attack on the nervous system by filtering antibodies out of the bloodstream. Similarly, administration of IVIg neutralizes harmful antibodies and inflammation. These two treatments are equally effective and a combination of the two is not significantly better than either alone.<sup>[23]</sup> Plasmapheresis speeds recovery when used within four weeks of the onset of symptoms.<sup>[24]</sup> IVIg works as well as plasmapheresis when started within two weeks of the onset of symptoms, and has fewer complications.<sup>[24]</sup> IVIg is usually used first because of its ease of administration and safety. Its use is not without risk; Occasionally it causes liver inflammation, or in rare cases, kidney failure.<sup>[25]</sup> Glucocorticoids alone have not been found to be effective in speeding recovery and could potentially delay recovery.<sup>[26]</sup>

#### **Respiratory failure**

Respiratory failure may require intubation of the trachea and breathing support through mechanical ventilation, generally on an intensive care unit. The need for ventilatory support can be anticipated by measurement of two spirometry-based breathing tests: the forced vital capacity (FVC) and the negative inspiratory force (NIF). An FVC of less than 15 ml per kilogram body weight or an NIF of less than 60 cmH<sub>2</sub>O are considered markers of severe respiratory failure.<sup>[27]</sup>

#### **Pain**

While pain is common in people with Guillain-Barré syndrome, studies comparing different types of pain medication are insufficient to make a recommendation as to which should be used.<sup>[28]</sup>

#### **Rehabilitation**

Following the acute phase, around 40% of people require intensive rehabilitation with the help of a multidisciplinary team to focus on improving activities of daily living (ADLs).<sup>[29]</sup> Studies into the subject have been limited, but it is likely that intensive rehabilitation improves longterm symptoms.<sup>[30]</sup> Teams may include physical therapists, occupational therapists, speech language pathologists, social workers, psychologists, other allied health professionals and nurses. The team usually works under the supervision of a neurologist or rehabilitation physician directing treatment goals.<sup>[29]</sup>

Physiotherapy interventions include strength, endurance and gait training with graduated increases in mobility, maintenance of posture and alignment as well as joint function. Occupational therapy aims to improve everyday function with domestic and community tasks as well as driving and work. Home modifications, gait aids, orthotics and splints may be provided.<sup>[29]</sup> Speechlanguage pathology input may be required in those with speech and swallowing problems, as well as to support communication in those who require ongoing breathing support (often through a tracheostomy). Nutritional support may be provided by the team and by dietitians. Psychologists may provide counselling and support. Psychological interventions may also be required for anxiety, fear and depression.<sup>[29]</sup>

#### **Prognosis**

Guillain-Barré syndrome can lead to death as a result of a number of complications: severe infections, blood clots, and cardiac arrest likely due to autonomic neuropathy. Despite optimum care this occurs in about 5% of cases.<sup>[8]</sup>

There is a variation in the rate and extent of recovery.<sup>[8]</sup> The prognosis of Guillain–Barré syndrome is determined mainly by age (those over 40 may have a poorer outcome), and by the severity of symptoms after two weeks. Furthermore, those who experienced diarrhea before the onset of disease have a worse prognosis.<sup>[11]</sup> On the nerve conduction study, the presence of conduction block predicts poorer outcome at 6 months.<sup>[11]</sup> In those who have received intravenous immunoglobulins, a smaller increase in IgG in the blood two weeks after administration is associated with poorer mobility outcomes at six months than those whose IgG level increased substantially.<sup>[11]</sup> If the disease continues to progress beyond four weeks, or there are multiple fluctuations in the severity (more than two in eight weeks), the diagnosis may be chronic inflammatory demyelinating polyneuropathy, which is treated differently.<sup>[3]</sup>

In research studies, the outcome from an episode of Guillain–Barré syndrome is recorded on a scale from 0 to 6, where 0 denotes completely healthy, 1 very minor symptoms but able to run, 2 able to walk but not to run, 3 requiring a stick or other support, 4 confined to bed or chair, 5 requiring long-term respiratory support, 6 death.<sup>[31]</sup>

The health-related quality of life (HRQL) after an attack of Guillain–Barré syndrome can be significantly impaired. About a fifth are unable to

walk unaided after six months, and many experience chronic pain, fatigue and difficulty with work, education, hobbies and social activities.<sup>[32]</sup> HRQL improves significantly in the first year.<sup>[32]</sup>

#### Research directions

The understanding of the disease mechanism of GBS has evolved in recent years.<sup>[15]</sup> Development of new treatments has been limited since immunotherapy was introduced in the 1980s and 1990s.<sup>[15][41]</sup> Current research is aimed at demonstrating whether some people who have received IVIg might benefit from a second course if the antibody levels measured in blood after treatment have only shown a small increase.<sup>[11][41]</sup> Studies of the immunosuppressive drug mycophenolate mofetil, brain-derived neurotrophic factor and interferon beta (IFN $\beta$ ) have not demonstrated benefit to support their widespread use.<sup>[41]</sup>

An animal model (experimental autoimmune neuritis in rats) is often used for studies, and some agents have shown promise: glatiramer acetate, quinpramine, fasudil (an inhibitor of the Rhokinase enzyme),<sup>[15]</sup> and the heart drug flecainide.<sup>[41]</sup> An antibody targeted against the antiGD3 antiganglioside antibody has shown benefit in laboratory research.<sup>[15]</sup> Given the role of the complement system in GBS, it has been suggested that complement inhibitors (such as the drug eculizumab) may be effective.<sup>[41]</sup>

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