



## Updates in the management of Guillain Barre Syndrome

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### ABSTRACT

Guillain-Barre syndrome (GBS) was originally described by Landry in 1859 and Guillain, Barré and Strohl in 1916. Although GBS has a good prognosis (5% mortality rate), about 10% of patients experience serious disability one year after the start of neurological onset. Recent research of GBS shows that the process involves a number of subtypes with different immunological mechanism and a spectrum of clinical syndrome of acute inflammatory neuropathy. Antibodies against peripheral nerve gangliosides and their own complements are recognized as an important mechanism of nerve damage in GBS. Pharmacokinetics of intravenous immunoglobulin (IVIg) therapy and other related factors that influence prognosis has been researched. In order to investigate the possible role of complement inhibition in GBS management, new studies will be conducted. The management of GBS should be provided in appropriate hospital units, with specialist teams, intensive care and rehabilitation facilities as essential parts. This article aims to provide updated management of GBS.

**Key words:** Guillain-Barre syndrome; GBS; Management; Immunotherapy

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### INTRODUCTION

Guillain-Barré syndrome (GBS) is a polyradiculoneuropathy that is acute, frequently severe and an uncommon autoimmune condition.<sup>1,2</sup> The incidence of GBS ranges from 1 to 2 cases per 100,000 adults and 0.4 to 1.4 cases per 100,000 children per year in North America and Europe, respectively.<sup>3</sup> The incidence in many countries is about 1/100,000 as shown by several studies. Incidence is increased with age and male gender.<sup>4</sup>

### CLINICAL FEATURES

Diagnosis of GBS are based on clinical judgement, analysis of cerebrospinal fluid and electrophysiological studies, e.g. electromyography (EMG). Several variants of GBS could be classified by their different clinical presentation, pathological features, and electrophysiological parameters which all give key clinical features of that subtype.<sup>3</sup> Common

GBS variants include the classic acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN), acute inflammatory demyelinating polyradiculoneuropathy (AIDP).<sup>2,3,5</sup> Miller Fisher syndrome (MFS), another famous variant of GBS, consists of classic triad of ataxia, areflexia and ophthalmoplegia, without any weakness.<sup>3,6</sup> Another GBS variant is bulbar and pharyngeal-brachial variant.<sup>7</sup>

### AIDP

Acute Inflammatory Demyelinating Polyneuropathy (AIDP) is the most common GBS variant. It involves demyelination of the peripheral nerves detected by EMG studies and histopathological evaluation. Myelin is constructed by concentric rings of Schwann cell cytoplasm which encircle a segment of peripheral axons.<sup>7</sup> Diagnosis of AIDP is made by the pattern of paralysis that is rapidly developing together with areflexia, lack of fever or other systemic symptoms.<sup>2</sup>

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Most severe form of demyelinating disease is termed as acute inflammatory “demyelinating” polyneuropathy (AIDP), which typically presents by hyporeflexia or areflexic paralysis, acute onset of flaccid, dysautonomy, and frequently sensory symptoms and cranial neuropathy. AIDP is the most common subtype of GBS in Europe and North America.<sup>8</sup>

### AMAN

The most common form of GBS in China and Bangladesh is acute motor axonal neuropathy (AMAN), and is the second most common in North America and Europe, approximately 6%-78% cases. The patients with AMAN have only motor axon involvement (while sensory symptoms are positive in only 10% of patients). It differs from AIDP in that autonomic nervous system disturbances and cranial nerve involvement are infrequent, and deep tendon reflexes are often normal or even brisk in AMAN,<sup>8</sup> After being diagnosed with AMAN subtype of GBS, which is related to production of anti-ganglioside antibodies, the patients will be given Rituximab and this medicine effectively reduces pathogenic B cells. Due to its effectiveness to ameliorate antibody-dependent subtypes of GBS (AMAN), it is important to conduct further research,<sup>9</sup> on it to find its effectiveness in other variants.

### AMSAN

In the beginning it was reported as Chinese paralytic illness in Northern China, affecting both peripheral motor and sensory axons.<sup>3</sup> In several patients with axonal GBS, sensory as well as motor fibers are affected. This subtype, called acute motor and sensory axonal neuropathy (AMSAN), by some authors is considered to be a severe variant of AMAN.<sup>10</sup>

### MILLER FISHER SYNDROME

One variant of GBS was Miller Fisher Syndrome (MFS), composed of ataxia, areflexia without any weakness and ophthalmoplegia. Patients with MFS, though rarely, present with at least two features and typical autoantibody characteristics and elevated CSF.<sup>6</sup> These patients, because their gangliosides have similar molecular configuration as bacterial lipo-oligosaccharides, will have antibodies against GD3, GT1a, GD1b, and GQ1b gangliosides as effect of molecular mimicry. GQ1b and GT1a gangliosides found in highest amount at bulbar nerves and oculomotor nerves, such as extraocular muscle motor end plate (terminal axon). Anti-GQ1b IgG antibodies (IgG/IgM/IgA anti-GQ1b antibodies) can be detected in more than 95% patients with MFS, which emphasizes a potential role in the pathogenesis

of the disease. Anti-GQ1b antibodies, as one type of biomarker, have been shown to activate complement at neuromuscular junctions *in vitro* and *in vivo* in mice, which serves as primary pathogenic mechanism in MFS<sup>11</sup> and is marked on the perisynaptic Schwann cells and presynaptic nerve terminal.

### PATHOLOGY

Pathological studies of AMAN shows minimal inflammatory infiltrate and little axonal damage although macrophages were localized between axons and the myelin sheath, mostly at the nodes of Ranvier area. The pathological studies propose that the macrophage is the effector of nerve breakdown, but it could also be due to targeting of either the myelin or axons by the antibodies. Pathological changes of AMSAN are equivalent but involve dorsal and ventral roots.<sup>4</sup> Pathological studies clarify that demyelinating type neuropathy is related to cellular infiltrates, while axonal type neuropathy is associated with nerve breakdown at the nodes of Ranvier because of complement induced damage to the nerves.<sup>12</sup>

### IMMUNOLOGY

In 1859 when pathogenesis of GBS was first suggested, immunology has attracted a lot of interest. It was first known that the process of GBS disease involves T-cell mediated immune system.<sup>9</sup> Two thirds of GBS cases usually begin after gastrointestinal or respiratory infection and just a few pathogens are found in about 50% of cases. The most common pathogen found is *Campylobacter jejuni* as agent of infection associated with GBS, ranging from 26-65% cases depending on the geographic region. *Hemophilus influenzae*, CMV, EBV, hepatitis E virus, Zika virus, *Mycoplasma pneumoniae* are other common pathogens.<sup>8</sup> One hypothesis states that the infection caused by above-mentioned agents enhances production of antibodies which cross-react with some components of nerve membrane, such as gangliosides and glycolipids breaking down myelin sheath. Another hypothesis states that antibody binds to macrophages and activates them or by complement activation, leading to nerve demyelination,<sup>4</sup> One molecule owned by *C. jejuni* which is similar to human gangliosides in the peripheral nerves is lipooligosaccharides. The synthesis of this similar molecule is expressed by polymorphic gene of *C. jejuni*, and it varies between *C. jejuni* strains. The common Thr51 variant is associated with GBS cases, while Am51 variant is related to MFS.<sup>10</sup> Antibodies produced by humans have different structures related to each GBS subtypes and also show different neurological manifestations and distribution according to different gangliosides.

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AMAN subtype primarily is caused by *C. jejuni*, and produces antibodies against GM1a, GalNAc-GD1a and GM1b gangliosides.<sup>10</sup>

### NEUROPHYSIOLOGY

Electrophysiological studies are important to make sure whether the diagnosis is really GBS or not and to exclude patients with similar symptoms and suspected with GBS. Differential diagnosis of paralytic syndromes includes other diseases with quadriplegia / paralysis, for example myasthenic crisis, idiopathic inflammatory myopathies and the uncommon motor neuron disease with acute respiratory failure. Associated symptoms are frequently useful in distinguishing these from GBS. EMG is considered as a nice modality because it can exhibit unique characters of GBS. At least two extremities are evaluated; 4 motor nerves and 3 sensory nerves showing F wave latencies. Diagnosis of AIDP or AMAN is made based upon EMG findings, which show typical characteristics of electrodiagnostic criteria. If there is a decrease in sensory nerve conduction and action potential amplitude by 50% of the normal lower limit in at least two nerves, then we can diagnose a person to be suffering from AMSAN type.<sup>13</sup> Severity of distal motor latencies and conduction velocities can determine whether demyelinating process does exist or not. Several studies indicate abnormal temporal dispersion of CMAPs in AIDP.<sup>14</sup>

### MANAGEMENT

GBS is an acute immune-mediated disorder which affects peripheral nerves, nerve roots, and it has been defined as polyradiculoneuropathy. It is characterized by rapidly progressive limb weakness and usually is worse in proximal extremities than distal extremities. In many cases, it results in respiratory failure, and or autonomic dysfunction. Several immune modulating therapies are administered to improve outcomes and prevent disability. Plasma exchange (PE) and IVIg have proven to be effective immunotherapies for GBS in regard to improved neurological outcomes.<sup>15,13</sup>

#### Plasma Exchange (PE):

The Quality Standards Subcommittee of the American Academy of Neurology (AAN) provided evidence-based guidelines for physician practice as follows:

- For non-ambulatory GBS patients, PE is recommended within 4 weeks of symptoms onset (Level A, Class II evidence)
- For ambulatory patients, PE is recommended within 2 weeks of onset (Level B, limited Class

II evidence)<sup>3</sup>.

For mild GBS, usually two plasma exchanges result in more fast recovery compare with untreated patients. For severe GBS, at least four plasma exchange are necessary to improve neurological deficit. PE lessens the extent of demyelination or peripheral axonal injury, causing shorter clinical recovery period compared with just supportive and symptomatic care alone.<sup>3</sup> The therapeutic results may be seen within 2 weeks of disease onset, especially for non- ambulatory patients. Usually, the treatment consists of five plasma exchanges, one plasma exchange volume each time (dose 50 ml/kg body weight) and the duration of administration is 1-2 weeks.<sup>3</sup> However, PE is associated with significant side effects such as hypocalcemia, risk of thrombosis, dilutional coagulopathy, septicemia, pneumonia and hemodynamic instability; which are complications of central venous access and allergic reactions. Metabolic acidosis or hypocalcemia are consequences from citrate infusion as part of the exchange fluid. Relative contraindication to PE, such as hemostatic disorders, unstable cardiovascular status, active infection, and pregnancy.<sup>3</sup> Limitations for PE are lack of access to plasma exchange (until now, typically restricted to tertiary care hospitals due to need for specialized and sub-specialized equipment and clinical expertise), need for close monitoring and potentially serious adverse events, all restricting the general use of PE for GBS. Prolonged hospitalization and medical costs, also contributed as restrictive factors to undergo PE immunotherapy for GBS.<sup>3</sup>

#### IVIg:

IVIg originates from pooled immunoglobulins from many donors and undergoes a purifying process. It proves effective immunotherapy for GBS. The Quality Standards Subcommittee of the AAN recommended IVIg to shortened recovery period for GBS patients who require other device or support by other people to walk within 2 weeks of symptom onset.<sup>3</sup> The IVIg dosage administered for GBS is about 0,4 g/kg body weight daily for 5 days, consecutively, so the total is 2g/ kg body weight.<sup>3</sup> One study, who compare efficacy between 2 days and 5 days total dose administration of IVIg showing that the first method have superior efficacy than the last. The efficacy shows the best result on 2 weeks after treatment. Although the mechanism of IVIg is not clear, it has been shown empirically limit the production of antibody, especially autoantibody as a group inside it via anti-idiotypic antibodies.<sup>3</sup> It also inhibit the formation of complement and its effector (Membrane attack complex) and modulating expression and function of Fc receptor on macrophages and other effector cells,

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suppression of chemokine, cytokine, T-cell functions, and adhesion molecule. The most important, It also blind self antigen-antibody recognition which lead to be mechanism in GBS pathogenesis. The final product is clinical recovery and better outcomes because of reduction in demyelination process and axonal injury. It is important however, to remember in our mind that IVIg is not simply a single drug, and the immunoglobulin component vary depending of manufacturer and also donor. The most serious adverse event of IVIg reported from GBS clinical trials are renal failure, myocardial infarction, headache, vomiting (The last two condition come from meningeal irritation known as meningism). High triglycerides, elevated serum viscosity, hypergammaglobulinemia are the relative contraindication for IVIg

administration due to thromboembolic events risk<sup>3</sup>. IVIg should be used cautiously in congestive heart failure, DVT, coronary artery disease, history or preexisting kidney disease, and patients with IgA deficiency because of anaphylaxis risk. To reduce the risk, giving intravenous fluid simultaneously with transfusion, slowing the infusion's rate, to use low osmolality product, and screening for IgA deficiency are important. IVIg is not contraindicated for pregnancy<sup>15</sup>.

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as potential conflict of interest.

**Authors' contribution:** All of the authors took equal part in data search, manuscript writing, and manuscript editing.

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