Guillain – Barré Syndrome: What we know, and Where we can improve

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Abstract
Guillain-Barre Syndrome (GBS) is a neurological syndrome in which the axon and myelin sheaths of the peripheral nervous system are attacked by the immune system. GBS is characterised by its rapid onset and ascending paralysis. It is classified as post-infectious, as its onset is often preceded by an infection, most commonly Campylobacter jejuni. The mechanism of GBS is not fully understood although it is believed that antigens such as GM1 on the virus capsule mimic those in gangliosides on C. jejuni. Thus leading to T-cell cross-reactivity, and ultimately host nerve cell damage. Currently, plasmapheresis and intravenous immunoglobin (IVIG) administration are the most effective treatments. Advances in this field are needed to better understand the mechanisms behind this condition at the molecular and cellular level, and ultimately improve mortality in the post-treatment period.

Introduction
Guillain–Barré Syndrome (GBS), is an immune-mediated neurological syndrome. A predisposition to GBS remains unclear, as the exact cause has not been defined. Currently, the main factor related to GBS onset, is a pulmonary or alimentary bacterial infection. GBS is an umbrella term which covers a large number of subtypes. These subtypes can be grouped under the following terms: “purely demyelinating, purely axonal, and demyelinating with axonal involvement” (1). The current understanding of the mechanism behind GBS is that certain antibodies formed during the immune response to an infection, cross-react and attack host cells, specifically neurons as they present the same gangliosides.

GBS was first officially described as an “ascending paralysis” in 1859 by Jean Baptiste Landry, a French physician (2,3). In 1916, George Guillain and Jean-Alexandre Barré, published a case study of two soldiers with “acute and progressive limb weakness” and elevated albumin protein levels in the cerebrospinal fluid (CSF) (1–3). This was not in line with an increase in lymphocyte count commonly observed in cases of syphilis a common disease at the time, indicating a different disorder (1,2). In 1949 the general term Landry-Guillain-Barré syndrome was given.

The incidence of GBS increases by 20 percent for every decade of a person’s life. Therefore, the age group with the highest incidence is those aged between 70 and 79 years for whom the incidence is 8.6 cases per 100,000 per annum (1). Although it has a low incidence in young children, it is the “most common cause of acute flaccid paralysis in healthy infants and children in the post-polio era” (1,4,5). Another influential variable is sex, as males are 1.5 times more likely to have an onset of GBS than their female counterparts. It remains unclear whether this is throughout their entire lifetimes or after 40, the mean age of GBS onset (3–5).

A review by McGrogan et al., found that Western countries had the lowest recorded incidence of GBS (approximately 0.38/100,000/year), with the highest in developing countries (approximately 2.53/100,00/year). While the general incidence of GBS is fairly consistent throughout the world, the same cannot be said of individual subtypes of GBS where there is an observable geographic predominance. In the West, 90 percent of cases of GBS are Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP) (1,5). In contrast to this, China, Japan, and Mexico had highest incidences of the AMAN and AMSAN subtypes (1,5,6). However, as most of the data comes from Western countries with similar incidence rates, this creates a biased global epidemiological view. The GBS subtypes, pathophysiology, diagnosis, etiology, prognosis, and treatment will discussed to provide a coherent review
of the current understanding of GBS.

GBS Subtypes

Acute Inflammatory Demyelinating Polyneuropathy (AIDP)
This subtype is most prevalent in North America and Europe, as it constitutes 90 percent of GBS cases. AIDP is most commonly preceded by a *C. jejuni* enteritis (3,4). The effects of AIDP is demyelination of the PNS by macrophages due to cross-reactivity of antibodies(3).

Acute Motor Axonal Neuropathy (AMAN)
This is a “purely motor” subtype with its highest incidence seen in paediatric groups. The highest incidence has been observed in Central and South America, and East Asia (3,4). AMAN is “characterized by rapidly progressive symmetrical weakness and ensuing respiratory failure”. The majority of patients have an antecedent *C. jejuni* infection, meaning large quantities of anti-ganglioside bodies are also present (3).

Acute Motor-Sensory Axonal Neuropathy (AMSAN)
AMSAN is similar to AMAN but also includes damage to sensory nerves. Unlike AMAN, AMSAN has its highest incidence in adults. AMSAN is characterised by lesions in motor and sensory neuron axons, however Schwann cells are left untouched, which leads to severe dysfunction in these areas (3,4). As this is a more severe subtype, recovery is inferior to AMAN (3).

Miller-Fisher Syndrome (MFS)
The main features include a lack of muscle coordination, reflexes, and eye muscle paralysis (3). Patients may experience slight muscle weakness, ptosis, facial palsy, or bulbar palsy (3). This type of GBS leads to a reduced or complete lack of action potentials in sensory neurons (3). Antibodies against the ganglioside GM1 are the most specific to MFS as sensory nerves tend to have high concentrations of this ganglioside e.g. oculomotor, trochlear, and abduces nerves (3).

Other Variants
Less common variants include: Bickerstaff encephalitis, polynuertis cranialis, and pharyngeal-cervical-brachial weakness. Some examples of even rarer subtypes of GBS are: acute pandysautonomia, facial diplegia and distal limb paresthesia, sixth nerve palsy and distal paresthesia, bilateral lumbar radiculopathy, and paraparesis (4).

Pathophysiology
GBS is primarily characterised by sudden ascending muscular weakness. GBS subtypes are often referred to on a spectrum due to the overlap in symptoms and characteristics (7). Since the first descriptions of what is now called “Classic GBS”, there have been descriptions of several other subtypes of GBS, in which attack of the neurons differ. Although the onset of GBS may appear spontaneously, it is most commonly preceded by a bacterial infection of the respiratory and digestive tract, e.g. by *Campylobacter jejuni* (3). There are several mechanisms and factors which contribute towards GBS symptoms including the presence of anti-ganglioside antibodies, molecular mimicry and cross-reactivity, complement activation, and host factors.

Anti-ganglioside antibodies
In one study, 50 percent of the patients had serum antibodies to several peripheral nervous system gangliosides (8). The most common including: GM1, GD1a, GalNa-GD1a, and GQ1b. These antibodies bind either individual gangliosides or complexes, inhibiting their function (9).

Molecular Mimicry and cross-reactivity
Cross reactivity occurs when host cells and a bacteria both present the same antigen. The synthesis of lipooligosaccharides (LOS) by *C. jejuni* mimics the carbohydrates of gangliosides found in the peripheral nervous system (3,7,8). When the immune system is in a heightened state following an infection, immune cells identify the neural gangliosides, which mimic the LOS antigens, as harmful. T and B cells with the complementary receptor attack the host neural cells in addition to *C. jejuni* (7,8). In case of the ganglioside GM1, lymphocytes target both the PNS and CNS. After infiltration, macrophages strip the axon of myelin. This leads to difficulties in salutatory conduction and the propagation of electrical nerve impulses (3). Although further elucidation is required, associations have already been made between the type of GBS, and “the specificity of the anti-ganglioside antibodies” (7).

Complement activation
When neural damage progresses, the complement system is activated, leading to the formation of the membrane attack complex (7,8). Post-mortem studies showed that complement activation at the nerve membrane is strongly associated with nerve damage in GBS, this is particularly prevalent in axons in AMAN and myelin sheaths in AIDP” (7).
Researchers using animal models, found that complement activation may play a role in the neurotoxic effects of anti-ganglioside antibodies (7). In addition, further destruction at the axon terminal and the teloglia (perisynaptic non-myelinating Schwann cells) took place (8).

**Host Factors**

The probability of developing GBS after an infection of *C. jejuni* is below 0.001. This indicates that the onset and or severity of GBS is most likely due to host factors. It is speculated, that single nucleotide polymorphisms (SNPs) may play a role in creating the environment which accommodates GBS (8). The SNPs promote the expression of genes (such as MBL2) which codes for mannose-binding lectin (MBL) (8), the product of which activates the MBL-pathway through the complement system. A study by Geleijns et.al showed that GBS patients with elevated MBL levels were linked to the severity of GBS damage, this was confirmed in a more recent study by Farrokhi et.al (10,11).

**Diagnosis**

It is often difficult to discern the GBS subtype as patients may have an onset of a combination of subtypes, hence why GBS may be referred to as a spectrum. The onset of symptoms can range from mild to very severe. Some cases are so mild that the patient recovers without diagnosis or hospitalisation (3). To diagnose GBS, tests include biochemical screening, nerve conduction studies, pulmonary function tests, spinal tap or a lumbar puncture, and potentially neuroimaging (magnetic resonance imaging (MRI)) (1,3).

**Etiology**

In the majority of cases the onset of GBS symptoms follows a viral or bacterial infection in the airways or in the gut; this is true for 2 out of 3 patients (3). Besides this, vaccines have been suggested to be related to GBS, but the causal link lacks substantial evidence.

Among the infections, *Campylobacter jejuni*, cytomegalovirus (CMV), Epstein-Barr virus (EBV), influenza A, *Mycoplasma pneumoniae*, *Haemophilus influenzae*, Hepatitis (A,B,E), and Zika virus have been proposed. *C. jejuni* appears to be the most common antecedent pathogen to GBS. In one Dutch trial, 32 percent of the patients had *C jejuni* prior to onset of GBS, and in a Northern Chinese trial this was true for 60 percent of the patients (3). Patients with a *C. jejuni* infection often exhibit symptoms in the respiratory system and gastrointestinal tract and have a more severe onset of pure motor and axonal forms of GBS (3). In the same Dutch trial, CMV was the antecedent infection for 13 percent of patients with GBS (3). Symptoms of CMV include infections of the respiratory tract, pneumonia, and non-specific flu-like illnesses (3). The Zika virus is another source of antecedent infection which is widespread in Latin-American countries such as Brazil, Colombia, and El Salvador (3,12,13). Despite these statistics the reliability of the diagnosis is poor to unknown.

In addition, there is some evidence that vaccines have a temporal association with GBS, however there is no definite causal relationship. Studies have compared GBS cases before and after the seasonal influenza vaccination programmes over several years, and each year no significant increase was observed (3).

**Treatment**

The efficacy of plasma exchange (plasmapheresis) and IVIG treatments have been demonstrated in randomized controlled trials (RCT). The first RCTs for plasmapheresis were in the USA and France in 1978 and 1985, respectively (1,14). The first RCTs for IVIG were in 1988, where it was shown to treat GBS (15). In 1992, RCTs were held to investigate whether a combination of IVIG and plasmapheresis would give a more promising outcome than each therapy alone. From this study it was concluded that a dual therapy treatment did not have a superior effect (1,14). Steroidal medication has no significant benefit to GBS recovery. Combination of IVIG and IV methylprednisolone combo may show some short-term improvement (8).

Plasma exchange or plasmapheresis (PE) is a process in which antibodies and inflammatory particles such as complement and MBL are removed from the blood. It is thought that this aids in improving the T-cell suppressor function. The blood serum is replaced with a fluid composed of 5 percent albumin or crystalloid-colloid combination (1,16). The standard procedure is to have 5 plasma volume exchanges over a fortnight. It requires specific equipment which not all hospitals have access to (7,17). This therapy is deemed superior to IVIG, as patients often have a faster recovery, and the need
of mechanical ventilation is decreased. Although the mechanism is not fully understood researchers believe that the PE functions by modulation of the humoral immune response and may involve the elimination of pathogenic autoantibodies, complement, cytokines and other mediators of inflammation (7).

The intravenous administration of immunoglobulins is the preferred method of treatment, despite being more expensive than plasmapheresis, it is more readily available (1,7). This method uses IgG from healthy donors, the procedure is to give 0.4 g/kg of body weight per day at an infusion rate of 1-3 mL/min for 5 days. Although the mechanism is not fully understood researchers believe that IVIG works as a form of immunoregulation of B and T cells and works to neutralize the antibodies which presumably cause the root of the issue (1).

Despite their efficacy, PE and IVIG exhibit low specificity because the pathophysiological cause of GBS is not fully known. Further research will elucidate information pertaining to certain pathways such as the complement system which can be targeted by specific immunotherapies. Nevertheless, plasmapheresis and IVIG are the best therapies currently available, as corticosteroids have been shown to be ineffective in the treatment of GBS. It is thought that they may interfere with the activities of macrophages in the muscle and nerve tissue (7). With the current treatments available, recovery can take around 3 weeks, however patients often require up to a year to recuperate (1,3).

Prognosis

In order to determine the most accurate prognosis for a patient, several scales have been developed. The most widely used scale is the Erasmus GBS Outcome Scale which is based on physical disability e.g. will the patient be able to walk independently after 6 months (8). One indicator is the level of immunoglobin G (IgG) two weeks following IVIG treatment. If the patient has high titer of IgG then they will have a lower disability score and therefore a higher chance of independent walking after the six-month period (8).

A patient is at risk of a worse prognosis, if any of the following are true to the patient’s condition: an antecedent infection that was gastrointestinal or diarrhoea-related, older than middle-aged, muscle weakness in the arms, had or required an ICU or hospital stay >11 days, had or required the use of mechanical ventilation, or had elevated levels of neurofilament, enolase and S-110b proteins in CSF which indicate increased recovery time due to increased immunoglobin M anti-GM1 levels. The current treatment is insufficient due to a high mortality rate with 1-5 percent of patients dying, 25 percent requiring artificial respiration, 20 percent still unable to walk unaided after 6 months, and 85 percent of patients with residual symptoms e.g. fatigue and pain (7).

Conclusion

GBS is an rare post-infectious disorder and the frequent cause of neuromuscular paralysis occurring at all ages with an incidence 1.75 per 100,00 per year (8). There are many subtypes of GBS which target both the peripheral and central nervous systems. Elucidation of the mechanisms behind GBS onset is required. Advances in treatment are also required as current treatments are not effective enough, and personalised therapy can be very expensive. In addition to treatment expenses, residual effects are very common with studies citing 31 percent of patients left permanently disabled (1,8). Continued research is required in the inhibition of the complement cascade and blocking molecular mimicry from occuring (1). Improvement of the diagnostics in order to identify the severity of the prognosis is needed, as it is important to start treatment as early as possible (7). Furthermore, there are currently several differing sets of criteria which describe GBS. A universal set of criteria should be created to increase the ability to compare studies and data reliability. General standardization is not only required in determining a patient’s prognosis but also the measurement of the treatment outcome.

References


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