Guillain–Barré syndrome: pathophysiology, etiology, causes, and treatment


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ABSTRACT

Guillain–Barré syndrome (GBS) is a polyradiculoneuropathy autoimmune disease that is characterized by significant inflammation that affects the peripheral nervous system in a rapidly progressive pattern that is mainly clinically presented by muscle weakness. The present literature review aims to broadly discuss GBS: etiology, pathophysiology and management in order to gain an understanding of the existing studies that are relevant to this literature review. Among the reported antibodies, anti-GM1 and anti-GQ1B have been reported to be responsible for attacking and damaging either the neuromuscular junctions or peripheral nerves. Moreover, it has been found that the anti-GD1a antibodies in patients bind to the neuromuscular junction and also bind to the nodes of Ranvier of the peripheral nerves and the paranodal myelin of the affected nerves. Reports have shown that this disease is identified as special forms of neuropathies that develop in immune-mediated, post-infection sequelae. Furthermore, in another study it was reported that Molecular mimicry has been previously reported to significantly correlate with the development of the disease as it was investigated in animal models. In addition, Campylobacter jejuni, a pathogen that causes gastrointestinal infections has been previously reported to predispose to the development of GBS in humans. However, scientists have found that plasma exchange and intravenous immunoglobulins (IVIG) remain the most significant and efficacious factors in managing the disease. Nevertheless, recent trials have investigated other approaches that are less efficacious and can lead to serious adverse events and complications.

Keywords: Guillain–Barré syndrome, Neurology, Management, Epidemiology, Etiology

INTRODUCTION

Guillain–Barré syndrome (GBS) is a polyradiculo-neuropathy autoimmune disease that is characterized by significant inflammation that affects the peripheral nervous system in a rapidly progressive pattern that is mainly clinically presented by muscle weakness in addition to adjacent sensory pictures. The symptoms can
develop acutely or sub acutely within few days to few weeks. The severity of the disease is hugely variable and can be mild or very severe that may cause serious morbidities and even mortality, such as autonomic dysfunction, respiratory failure and tetraplegia. Estimates show that the death from GBS occurs 2-3% of the cases among patients within the developed countries. However, previous studies have demonstrated that intravenous immunoglobulins (IVIG) administration and performing plasma exchange can significantly enhance the prognosis of the disease and lead to recovery. Although the prognosis of the disease tends to be good in many cases, it has been estimated that around 15% of the cases with GBS have poor outcomes, despite the adequate management with the currently-validated modalities owing to the development of severe complications especially respiratory muscle weakness, requiring patients to be mechanically-ventilated. Recent reports from Western countries have furtherly showed that the national campaigns aim to eliminate poliomyelitis as the GBS is now the leading cause of flaccid paralysis both the acute and subacute types. According to the various global reports, previous studies have revealed that the incidence of GBS rate between 0.16 and 0.4 /100,000 year in individual of all ages.

The diagnosis of GBS is mainly based on the clinical sequelae that patients usually have. This includes the development of lower limbs muscle weakness, reduced or absent deep reflexes and the monophasic pattern of the disease. Also, the nerve conductions studies and cerebrospinal fluid analysis are also important diagnostic tests that can help to confirm the diagnosis. Moreover, the disease includes a number of variants that differ from each other in the pattern of the clinical presentations related to the severity and prognosis of the condition. Moreover, previous reports indicated that these variants also differ from each other in the laboratory findings and the pathophysiology of the disease. The present literature review aims to broadly discuss the GBS: etiology, pathophysiology and management in order to gain an understading of the existing studies that are relevant to this literature review.

**METHODOLOGY**

A systematic search was conducted to identify relevant studies in the following databases: PubMed, Medline, Web of Science, Embase, Google Scholar, and Scopus. The following search terms were used: “Guillain–Barré syndrome” or “Guillain–Barré”, “pathophysiology” and “management” or “outcome” and “etiopathology” or “etiopathology” or “etiopathology”. The reference lists were manually searched to identify additional relevant studies meeting inclusion criteria. We included any study that reports GBS and its pathophysiology, causes and outcomes. No restrictions were applied.

**DISCUSSION**

**Etiology**

Specific factors have been previously reported to correlate with the development of GBS and its variants. Reports have shown that the disease is identified as special forms of neuropathies that develop in immune-mediated, post-infection sequelae. Molecular mimicry has been previously reported to significantly correlate with the development of the disease as it was investigated in animal models. *Campylobacter jejuni*, a pathogen that causes gastrointestinal infections has been previously reported to predispose to the development of GBS in humans. This is probably due to the similar antigenicity between the gangliosides that are involved in the structure of the peripheral nerve cells and the lipooligosaccharide component of the outer membranous layer of the bacterium, leading to a similar antibody-mediated attack against these nerve cells. Accordingly, whenever the infection occurs, it is anticipated that the neuropathic sequelae of GBS will secondarily develop as an immune-mediated reaction.

In addition to *Campylobacter jejuni*, other infections causing gastrointestinal and respiratory illnesses have also been correlated with the development of GBS. Within the first 1-6 weeks of eliciting GBS-related symptoms, it has been reported that more than two-thirds of the affected patients have been diagnosed with a previous infection. For instance, Dirlikov et al previously reported that many cases of GBS have been reported and diagnosed by following the infection of the Zika virus during its relevant previous pandemic.

Moreover, previous cases have reported that some other etiologies other than the viral infections as some medications and surgical manipulations might also predispose to the development of GBS. In the early vaccination campaigns against influenza A/H1N1 by the flu vaccines in 1976, it was noticeable that many cases of GBS and neuropathies have developed in relation to the vaccination administration, although it was reported that within the following years, the numbers of cases of GBS following the vaccination has significantly reduced to only one case per one million vaccines administered. In the same context, previous studies have demonstrated that GBS is seven times more likely to develop following influenza infection than being vaccinated against the disease.

**Epidemiology**

The burden of GBS on the global healthcare facilities cannot be ignored. Despite that this disease is marked as a rare disorder that affects some minor populations, the estimated incidence for GBS varies from 0.4 and 0.2 per 100,000 population. A total of $318,966 cost burden has been estimated for the provided medical care for patients with GBS. Moreover, previous reports also has shown that
the annual costs for taking care of GBS patients might reach a total of $1.7 billion per year. Regarding gender, the estimation has shown that male patients are more frequently diagnosed with GBS than females. Besides, evidence from the current literature shows that GBS can affect up to 100,000 patients per year globally.\(^{19,21}\)

**Pathophysiology**

This section is extensively discussed studies related to this literature. Estimates show that infections contribute to the development of GBS as previous investigations have shown that in 70% of cases with GBS, patients had a history of infections.\(^{22}\) Accordingly, efforts were directed to understand more about the potential role and molecular similarity that the infecting organisms might have with the cells and tissues of the infected patients that developed GBS especially the axonal type. Yuki et al previously indicated this by showing that the molecular structures of the gangliosides that are found within the peripheral nerves are similar to the lipooligosaccharide that is extensively found in the structure of Campylobacter jejuni.\(^{23}\) Previous studies have indicated this theory by laboratory experiments in rabbits that were subjected to the lipooligosaccharide that mimics the human gangliosides of peripheral nerves and found that these rabbits significantly developed GBS-like symptoms (acute motor axonal neuropathy) more specifically developing flaccid tetraplegia.\(^{24,25}\)

Antibodies that concomitantly develop against the host gangliosides attack different parts of the peripheral nervous system. Among the reported antibodies, GM1 and GQ1B antibodies have been reported to be responsible for attacking and damaging either neuromuscular junctions or peripheral nerves.\(^{25,26}\) Moreover, it has been found that the anti-GD1a antibodies in patients bind to the neuromuscular junction and also bind to the nodes of Ranvier of the peripheral nerves and the paranodal myelin of the affected nerves.\(^{27,28}\) According to the different parts that have been affected by the different antibodies and antigenic stimulation, it has been suggested that such differences are the major causes of the variation of the course of the disease.

Besides, a previous investigation by Susuki et al showed that after being infected with the pathogenic organism that presented with a similar antigenicity, complement activation was observed among the infected patients which was an indicator of its major role in the pathogenesis and development of the disease.\(^{29}\) As previously mentioned, it has been found that certain antibodies might predispose to certain variants and clinical symptoms of GBS. For instance, anti-GQ1B antibodies have been previously reported to correlate with Miller-Fisher syndrome while it has been reported that anti-GM1 antibodies predispose to the development of the variant of axonal motor neuropathy.\(^{30,31}\) Moreover, anti-GT1A antibodies have also been reported to have a direct correlation with the development of the GBS variant pharyngeal-cervical-brachial syndrome.\(^{32}\) However, the validity of these antibodies including both the specificity and sensitivity in detection and diagnosis of the different variants remains low and should be only considered for confirmation of the evaluation and diagnosis. Therefore, further investigations might be needed for further elucidation of the potential primary roles that these antibodies might play in the pathogenesis and differentiation of GBS and its variants, which will be reflected in inaugurating better diagnostic and management modalities of the disease. Additionally, although acute inflammatory demyelinating polyneuropathy has been marked as the most prevalent variant of GBS within the United States, the pathophysiology of this disorder remains vague and further investigations are needed.

**Management**

Previous randomized controlled trials have demonstrated the efficacy of previous modalities in the management of GBS. Plasma exchange and intravenous immunoglobulins (IVIG) remain the most efficacious and currently validated modalities that are recommended for administration in patients with GBS. Furthermore, the previous investigations have shown that plasma exchange is being useful by enhancing the removal of antibodies complement proteins and humoral mediators that are usually observed to mainly contribute to the development and pathophysiology of GBS. It has been recommended that plasma exchange should be administered on five different sessions as a volume exchange. However, the exact mechanism of action of plasma exchange has not been fully understood yet and still needs further investigations. On the other hand, it has been observed that IVIG might have potent immune-modulating activities, although it has been reported that the main mechanism behind the action and physiology of IVIG in playing this role remains controversial, and has not been proven, yet. IVIG should be administered over five days and a total dose of 2 grams per kilogram should be considered.\(^{33}\) However, previous investigations that compared the efficacy and safety of both modalities have demonstrated that both of them equally contribute to the successful management of the disease.\(^{34}\)

Previous studies have demonstrated that for both modalities to be efficacious in the management of the disease. Any of them should be administered for consecutive four weeks with no advantage of any of them over the other. Besides, for a more efficacious and successful management plan, treatment with any of these modalities should be initiated within the first two weeks.\(^{35-37}\) Although corticosteroids have been used in the management of immune-mediated reactions within the past decades, recent investigations have demonstrated that the efficacy of using corticosteroids (whether the intravenous or the oral combinations) was observed to be less than that of using placebo or when compared to the efficacy of using IVIG and plasma exchange whether alone or when used in combination. In general, it has been
reported that the applications of these management modalities can significantly decrease the recovery period from GBS. In previous investigations, independent ambulations were observed among patients that were treated with the previous management modalities within 32 days from the start of the disease course.5,34,36,38-40

Reports have shown that the prognosis of GBS is generally good and estimates show that around 80% of patients and more have a significant chance of recovery and reduced morbidities; however, the other percentage of patients usually develop complications and significant morbidities. Moreover, the concurrent administration of plasma exchange and IVIG at time intervals or the administration of steroids following IVIG administration were not associated with significant favorable events.41,42 This was indicated by a recent 2021 randomized controlled trial, which reported a second IVIG dose was not significantly associated with any significant improvements in patients with severe GBS and it can negatively impact the prognosis by inducing some adverse events.43 The same results were also previously reported by an observational study by Verboon et al which showed that second IVIG doses could not significantly enhance the prognosis of poor GBS.44 Although previous investigations have approached the efficacy of some other management modalities, none of these approaches have been proven to be significantly efficacious as compared to plasma exchange and IVIG.45

CONCLUSION

In the present study, we have reviewed the findings from previous studies about the GBS: etiology, pathophysiology and management. Viral infections are the most frequent cause that predispose to the development of GBS. Therefore, proper interventions should be offered for the patients at risk. Plasma exchange and IVIG remain the most significant and efficacious factors in managing the disease. However, recent trials have investigated other approaches that have been found to be less efficacious and can lead to serious adverse events and complications.

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