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GUILLAIN-BARRÉ SYNDROME: RECENT APPROACHES IN PATHOPHYSIOLOGY, DIAGNOSIS AND MANAGEMENT

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ABSTRACT

Guillain-Barré syndrome (GBS) was named after the French neurologists Georges Guillain and Jean Alexandre Barré who together with a French physician André Strohl in 1916 described this condition. In view of the controversies in understanding the GBS and its subtypes, we have attempted in the present review to present the general background literature related to GBS, its causes, pathophysiology, diagnosis, treatment and other management measures, prognosis and future directions for better health care of the patients with various forms of GBS. Treatment of GBS is a challenge for the patients and physicians, since it has various levels of severity in different areas of the body and in different cases. There is an urgent need of establishing the molecular understanding of the potential biological treatments. Besides immunotherapy, there seems strong evidence of biological substances that can help modulating the pathogenesis processes of GBS. We suggest that the promising studies for biological targets and biological and clinicobiological basis of innovative immunotherapeutic approaches for investigating/ inventing the biological drugs are essentially required for the treatment and better outcome of GBS complications.

Key words: Guillain-Barré syndrome (GBS), GBS variants, causes and pathophysiology, diagnosis, management and prognosis, future recommendations

INTRODUCTION

Guillain-Barré syndrome (GBS) was named after the French neurologists Georges Guillain and Jean Alexandre Barré who together with a French physician André Strohl in 1916 (Guillan *et al.*, 1916) described this condition (van Doorn *et al*., 2008; Eldar *et al*., 2014; Guillan *et al.*, 1916). It is a rare acute usually monophasic immune mediated autoimmune neuromuscular disorder in the peripheral nervous system expressing as a polyneuropathy and showing a rapid onset muscle weakness in which peripheral nervous system is misguidedly attacked by the immune system and the myelin sheath is damaged in the specific variants. It occurs more commonly in adult men. It is the most common cause of a neuromuscular disorder-flaccid paralysis (Shahrizaila *et al*., 2021). The immune dysfunction in GBS may appear in response to infection, surgery, vaccination and such other procedures. Both infectious and noninfectious involvements occur in GBS, for triggering/ causing autoimmune system for neuronal damage (Liu *et al*., 2024).

The GBS that is found to be triggered by a prior bacterial or viral infection shows the epidemiology of estimated as 0.89-1.89 GBS cases in each 100, 000 individuals, though the adult men and especially elders are affected more than the children and young people (Yuki and Hartung, 2012). Various infections besides the genetic factors are related to the appearance of GBS (Shahrizaila *et al*., 2012; Yuki and Hartung, 2012; van den Berg *et al*., 2014).

The GBS was initially investigated as related to albuminocytological dissociation as a major abnormality in acute phase with normal cell count (without elevation of WBCs) but increased CSF protein concentration showing wide nerve root inflammation (Eldar *et al*., 2014). Its variant was described in 1956 by C. Miller Fisher (Miller Fisher syndrome, MFS) and as an encephalitis by Edwin Bickerstaff (Bickerstaff brainstem encephalitis, BBE), whereas Guillain described some of these features in 1938 that provided the basis to term this condition as 'anti-GQ1b antibody syndrome' (a variant of GBS including MFS, BBE and acute ophthalmoplegia) (Shahrizaila and Yuki, 2012).

The Fisher syndrome (a unique inflammatory neuropathy showing ataxia, ophthalmoplegia and areflexia) and Bickerstaff brainstem encephalitis (a type of pure CNS disease manifested by ataxia, ophthalmoplegia and consciousness disorders) appeared from the descriptions more than half a century earlier. Later studies describe diagnostic criteria, plasma exchange (PE) and its therapeutic advantages, use of intravenous immunoglobulins (IVIG) as easier to use and having better effects compared to PE (Walgaard *et al*., 2011; van den Berg *et al*., 2014), though both therapeutic procedures did not influence the curative efficacy.

Most significant weakness in GBS patients occurs within two weeks after the start of symptoms. The symptoms appear in hours to few weeks. Initial symptoms are numbness, tingling, and the pain, alone or in combination in fingers, ankles, toes, wrists, difficulty for facial movements, including speaking, chewing/swallowing, change in sensation or pain appearing often in the back, feet and hands spreading to arms and upper areas of the body with the weakness of muscles, unsteady walk or unable to walk or climb stairs. It is characterized clinically by acute onset, decreased muscle tone, symmetric limb weakness, constipation, abdominal distension and urinary retention after autonomic nerve damage (Liu *et al*., 2023)

Decreased or absent tendon reflexes occurs and some cases show hyperreflexia (van Doorn *et al*., 2008). With the change in functions of autonomic nervous system (ANS), cardiac arrhythmias and blood pressure (BP) fluctuations occur. Certain patients develop weakness of breathing muscles that requires the mechanical ventilation. Later, severe conditions manifest as life threating condition.

At least two features of the eye muscle weakness (related to ophthalmoplegia), abnormality in coordination (ataxia) and absent reflexes (areflexia) are noticed in the Miller Fisher syndrome (MFS)-a variant of GBS (Yuki and Hartung, 2012). Whereas, Bickerstaff brainstem encephalitis (BBE) is a rare type of GBS autoimmune disorder of peripheral and central nervous system (brainstem) that manifests with drowsiness, sleepiness, or coma (Shahrizaila and Yuki, 2012). The respiratory failure (Yuki and Hartung, 2012; van den Berg *et al*., 2014) and autonomic dysfunctions (Yuki and Hartung, 2012; van den Berg *et al*., 2014) occur in patients with GBS. There are three phases in GBS, a): progressive phase that is for days to four weeks; b): a plateau phase, that lasts for days to months; and c): recovery phase (Korinthenberg *et al*., 2020).

As a polyneuropathy, the GBS is diagnosed with nerve conduction studies, cerebrospinal fluid (CSF) examination, and assessing specifically the presence of certain antibodies (van den Berg *et al*., 2014) in association with the subtypes considering the areas of muscle weakness. GBS initially was considered a demyelinating disease until 1980s, when the acute axonal type of GBS was first reported/investigated. The most widely type of the GBS is acute inflammatory demyelinating polyradiculoneuropathy (AIDP). However, axonal variants (acute motor axonal neuropathy or AMAN) of GBS are also commonly seen in Asian region, and it was noted that incidence of both AMAN and AIDP in Asia was almost equal.

There is no known cure established yet for GBS, though treatment can provide improvement in the severity of symptoms. Immunotherapy is the best choice e.g., plasma therapy for removing the blood antibodies or providing intravenous immunoglobulin. The intravenous immunoglobulins (IVIG) and plasmapheresis or both combined together for better efficacy, along with other measures including supportive care provide significant recovery in most of the cases, though it may take weeks to years while some cases present permanent weakness.

In view of the controversies in understanding the GBS and its subtypes, we have attempted in the present review to present the general background literature related to GBS, its causes, pathophysiology, diagnosis, treatment and other management measures, prognosis and future directions for better health care of the patients with various forms of GBS.

CAUSES AND PATHOPHYSIOLOGY

Association of GBS with COVID-19 was documented (Ellul *et al*., 2020; Toscano *et al*., 2020; Abu-Rumeileh *et al*., 2021). Association between COVID-19 and GBS is still not clear due to geographical variations that are not easy to interpret (Liu *et al*., 2024). Some of the COVID-19 vaccines showed quite a rare side effect (Patone *et al*., 2021), though no measurable link could be reported between COVID-19 infection and GBS. The GBS symptoms appeared 19 days after having the COVID-19 with reflex reduction, facial paresis/paralysis, generalized weakness and hypoesthesia (Pimentel *et al*., 2022). Another report provides evidence of COVID-19 causing peripheral neuropathy, GBS and other autoimmune diseases (Finsterer *et al*., 2021).

Most of patients with GBS get an infection e.g., respiratory infection, gastroenteritis caused by Campylobacter jejuni showing nausea, vomiting and diarrhea and such other symptoms prior to the appearance of GBS, and in many cases the type of infection can be determined (van den Berg *et al*., 2014). The condition could be provoked and developed in some cases by bacteria, e.g., Campylobacter jejuni (the most common cause of the food poisoning), and Mycoplasma pneumoniae (no clear evidence of the role of M. pneumoniae known in the pathogenesis of GBS) and viruses, e.g., cytomegalovirus, Epstein–Barr virus/HHV-4 and varicella zoster virus/HHV-3 (Yuki and Hartung, 2012).

Herpes zoster, viral hepatitis and glandular fever may trigger to affliction of GBS. People with GBS get triggered by having flu. It was found that the surface lipopolysaccharides in Campylobacter may or may not induce GBS (van den Berg *et al*., 2014). If it is involved, the possible mechanism is termed as molecular mimicry for the Campylobacter for having ganglioside-like epitopes in eliciting autoantibodies to react with peripheral neural

targets. Occurrence of GBS is associated with influenza, dengue fever, Zika virus infection, previous hepatitis E virus infections and other infections (Eldar *et al*., 2014; Vellozzi *et al*., 2014; Gatherer and Kohl, 2016).

The incidence of GBS in past for swine flu outbreak was found increased after influenza immunization (Nelson, 2012). Association of GBS and seasonal flu vaccination varies considerably since data were obtained in different flu seasons. However, the occurrence of natural influenza is a higher risk factor than the influenza vaccination (DeStefano *et al*., 2019). On the other hand, heightened risk of GBS was noticed following 42 days of vaccines for Zoster vaccine Shingrix, and hence the manufacturer added the precautions for the risk of GBS. In general, all vaccines may show some side effects. Same is for the COVID-19 vaccines that may present side effects including the development of GBS, though the frequency of these side effects has not been well studied (Matarneh *et al*., 2021). Favorable effects of an antidepressant Zimelidine were seen but in view of rare case reports, it was not used any more. The risk of developing GBS increased about 25-fold after using Zimelidine while comparing against natural incidence of GBS. Corticosteroids, however should be avoided for GBS, though they are highly effective for chronic inflammatory demyelinating polyneuropathy (CIDP) (Harms, 2011).

The GBS has various variants damaging the peripheral nerves. However, the role of T-cells, B cells and macrophages, and complement for triggering the attacks on gangliosides present in axons and Schwann cells (Hagen KM, Ousman, 2021). Acute inflammatory demyelinating polyradiculoneuropathy (AIDP), a demyelinating variant of GBS manifests the damage to myelin sheath by white blood cells (WBCs: T-lymphocytes and macrophages) that occurs after the activation of various blood proteins called as complement (Yuki and Hartung, 2012). GBS especially causes damage to the proximal peripheral neuronal structures and nerve roots in AIDP by the infiltration of lymphocytic mononuclear cells and intense segmental demyelination associated to macrophages (Dimachkie and Barohn, 2013). All axonal variant types of GBS do not appear due to the direct effect of lymphocytes. They rather occur via IgG antibodies and complement against the axonal membrane (Yuki and Hartung, 2012).

The anti-ganglioside antibodies in certain patients with GBS become positive early in the disease process (Saeed *et al*., 2019). Various antibodies bind to gangliosides in axonal type of GBS, e.g., GQ1b antibodies associate with Miller Fisher variant GBS and other related forms including Bickerstaff encephalitis (Yuki and Hartung, 2012). When antibodies develop, they bind with gangliosides in axons (Saeed *et al*., 2019). Anti-GQ1b antibody syndrome is a typical triad variant of GBS that comprises MFS, BBE and AO (ophthalmoplegia). The antibodies are formed against infection as well where immune system reacts with the microbial contents, but they also react with the natural body substances (Yuki and Hartung, 2012; Kuwabara and Yuki, 2013).

The pathogenic antibodies are formed in body in response to the presence of other bacterial strains. Gangliosides GM1 are more commonly associated with severe axonal degeneration in any subtype. After suffering from a Campylobacter infection, the body produces IgA (IgG is also produced in a small proportion of people) against lipooligosaccharides and other bacterial substances that cross react with the human gangliosides, but it is not known how this immune dysregulation occurs that suppresses the antibody formation for body's own substances (Willison and Goodyear, 2013).

The C. jejuni is considered as the most common identifiable pathogen causing Guillain–Barré syndrome (GBS). Its mechanism has been suggested that the immune response to ganglioside-like structures in lipooligosaccharides of certain C. jejuni strains cross-react with human neuronal gangliosides and cause GBS (Viraj *et al*., 2007). Furthermore, it is important to realize that if the injection technique is not correct, it may cause an injury to the axillary nerves that may lead to peripheral neuropathy, and the vaccine transfection and translation may cause immune effect against the nerve cells causing GBS or other autoimmune conditions (Merchant, 2022).

DIAGNOSIS

Laboratory assessment of serum electrolytes, creatine phosphokinase (CPK), erythrocyte sedimentation rate (ESR) and liver function tests (LFTs) are helpful in diagnosis. Due to less secretion of antidiuretic hormone, retention of water and abnormally low levels of blood sodium is obtained in GBS (Spasovski *et al*., 2014). Blood potassium levels are also measured (Yuki and Hartung, 2012). The CSF of patients with GBS reveals elevated levels of protein and normal WBC called as cytoalbuminologic dissociation (Hegen *et al*., 2020). Elevated levels of proteins and normal WBC count are the important CSF findings in GBS that characteristically distinguishes from other conditions e.g., poliomyelitis and lymphoma (Ropper, 1992). Diagnosis depends upon findings related to absence of fever, absent reflexes, and development of muscle paralysis rapidly. The antiganglioside antibody tests are often performed, though these is not much helpful for diagnosing GBS (van den Berg *et al*., 2014).

Pulmonary function tests are helpful for diagnostic purpose. Bedside single breath count helps monitoring GBS. A variety of electrophysiological indicators (e.g., axonopathic GBS, abnormal diaphragmatic EMG, abnormal phrenic nerve conduction could be checked for their correlation with respiratory failure in patients with GBS (Garg, 2017).

There are several subtypes of GBS (Uncini and Kuwabara, 2012; van den Berg *et al*., 2014). It is difficult sometimes to classify some individuals with GBS. Subtypes of Miller Fisher syndrome have quite similar patterns of antiganglioside antibodies (AGA) (Shahrizaila and Yuki, 2012; Wakerley *et al*., 2014). The AGA is quite important in the development of MFS, and other ganglioside antibodies that might be present in MFS (Zhang *et al*., 2023). Bickerstaff's brainstem encephalitis (BBE) is now considered as forms of GBS and MFS (anti-GQ1b antibody syndrome) (Shahrizaila and Yuki, 2012).

The BBE and its variant MFS both show ataxia and external ophthalmoplegia (Yoshikawa *et al*., 2020). If coordination problems and drowsiness are found but muscle weakness is not present, the condition is termed as acute ataxic hypersomnolence (Wakerley *et al*., 2014). The sensory ataxic GBS variant has low-rate occurrence and appears in result of autoimmune damage to afferent nerves with molecular mimicry mechanism (Packiyarajah *et al*., 2023).

Characteristic features in BBE are: rapid onset of ataxia, ophthalmoplegia, Babinski's sign, absent or decreased tendon reflexes, and absence of consciousness (Wakerley *et al*., 2014). It is still not clear whether the isolated acute sensory loss can be considered as a type of GBS, as it rarely occurs comprising GBS with muscle weakness without sensory symptoms (Rinaldi, 2013). The MRI helps much in identifying brainstem abnormalities (Shahrizaila and Yuki, 2012).

Nerve conduction studies (NCS) and needle electromyography (EMG) are helpful for distinguishing various types of GBS. The NCS abnormal records consistent with demyelination are quite sensitive and help excluding other causes of acute muscle weakness (van Yuki and Hartung, 2012; Uncini and Kuwabara, 2012; Rinaldi, 2013; den Berg *et al*., 2014). Nerve conduction studies and the use of lumbar spinal puncture for the analysis of cerebrospinal fluid (CSF) are incorporated for diagnosing GBS (Yuki and Hartung, 2012; Eldar *et al*., 2014; van den Berg *et al*., 2014). Needle EMG along with nerve conduction studies show demyelination comprising nerve conduction showing conduction block or dispersion of responses generally where natural nerve compression occurs, prolongation of the distal latencies, weak muscles showing reduced recruitment evident by needle EMG examination and prolongation of the F-waves (Ye *et al*., 2010).

The spinal cord compression can be differentiated from GBS and any other conditions causing weakness of limbs by performing magnetic resonance imaging (MRI) (Yuki and Hartung, 2012; van den Berg *et al*., 2014). However, the severity of MRI does not essentially relate with severity of symptoms though it can be used as an aid for laboratory and other diagnostic tests for GBS (Yikilmaz *et al*., 2010). The GBS can be diagnosed if the enhancement of nerve roots is evident in MRI scan (van den Berg *et al*., 2014)., though other tests are required while consulting GBS in children (Ryan, 2013).

MANAGEMENT AND PROGNOSIS

The GBS is managed by two major immunotherapeutic ways: a) plasmapheresis better to use it in four weeks after the onset of GBS symptoms for speedy recovery (Hughes *et al*., 2003) by filtering antibodies out from blood for taking care of nervous system from body attacks (Liu *et al*., 2018), since the antibodies against infection also target/damage the neuronal structures leading to GBS. i.e. person's own plasma is replaced by plasma exchange having artificial plasma components containing albumin (Chevret *et al*., 2017); b): administering the intravenous immunoglobulins (IVIG) (IVIG is a treatment constituted from the donated blood containing healthy antibodies) that neutralize the unhealthy antibodies and inflammation. However, for having more efficacy, both of these treatments are combined (Hughes *et al*., 2014).

Administration of IVIG is done usually earlier owing to its better safety and ease in administering, though there are few risks of having kidney failure and liver inflammation in certain patients (Dantal, 2013). Recovery was found slow and less speedy while using glucocorticoids alone (Hughes *et al*., 2016). Corticosteroids are not preferred as they inhibit the recruitment of scavengers necessary for neuro-regeneration, and clinical improvement in GBS is delayed (Wang *et al*., 2015). The IVIG and plasmapheresis show good efficacy with fewer side effects even administering after two weeks of the appearance of GBS symptoms (Hughes *et al*., 2003). Corticosteroids were found highly effective for chronic inflammatory demyelinating polyneuropathy (CIDP), but are generally not prescribed in GBS (Doets *et al*., 2020). Despite all recent advances, there is a lack of proper evidence to make decision for implementing the use of immunomodulatory therapies in GBS patients with mild condition and those with various subtypes (Liu *et al*., 2024).

The physiotherapy has a potential for strengthening the week muscles for substituting and customizing the exercises. It is utmost important for certain patients to have intensive rehabilitation by experts of various disciplines for daily activities that helps improving the symptoms existing for long time (Khan and Amatya, 2012). Substituting the stronger to weaker muscles causes delay in uniform strength and required function. The other interventions include occupational therapy, home modifications, gait aids, orthotics, splint, speech-language therapy, nutritional

therapy, and behavioral/ psychological interventions (Khan and Amatya, 2012). It is hard to decide which pain medication be prescribed to the patients with GBS (Liu *et al*., 2015). Corticosteroids do not provide efficacy for pain. However, Epidural opioids and capsaicin were found effective in GBS patients suffering from pain (Liu *et al*., 2015).

Monitoring nutritional components, infectious complications and cardiac and respiratory functions are essentially required for proper management. Breathing support via mechanical ventilation (MV) by measuring the spirometry-based breathing (force vital capacity (FVC) and negative inspiratory force (NIF) is required in respiratory failure. Being a quite common cause of acute neuromuscular paralysis, about 20 to 30 % of the GBS patients are often accompanied by respiratory failure and essentially require MV (Islam *et al*., 2019). The FVC <15 mL/kilogram body weight and NIF <60 cmH2O are suggested as the markers for respiratory failure (Dimachkie and Barohn, 2013).

In general, the health-related quality of life after afflicting with GBS is substantially impaired, and fatigue, chronic pain, and difficult to carry out work and other life activities occur (Darweesh *et al*., 2014). The GBS patients after acute phase do well, mortality is less than 5% and independent ambulation after 6 months is seen in more than 80% patients. The outcome of GBS is measured considering the scale: 0-6 scale, where 0 indicates complete health; 1: minor symptoms and the subject can run; 2: walking is possible, but not running; 3: stick or other support required; 4: confined to chair or bed; 5: requires long-term respiratory support; 6: death (Hughes *et al*., 2007).

The rate and extent of recovery in GBS cases vary. Recovery in about 5-10% of GBS patients gets prolonged for several months of ventilator dependency, and even a very delayed, and incomplete recovery may prevail. In about 5% of the patients with GBS, blood clots, severe infections, cardiac arrest associated with autonomic neuropathy can cause death despite taking good care (Yuki and Hartung, 2012). If the best setting and proper care is observed, number of GBS patients is little that die due to lung clots, cardiac arrest, blood infections, and paralysis of breath related muscles. Those of age over 40 years may have poorer outcome. Prognosis of GBS is also determined by the severity of symptoms after about two weeks. Those cases who had diarrhea before the onset of the symptoms of GBS present worse prognosis. Those of 60 years or above age have greatest risk of long-term complications and death, especially those having diarrhea have poor diagnosis.

The presence of conduction block in nerve conduction study shows poorer outcome at 6 months. The conduction block is the major cause of the acute paralysis and sensory loss occurring in patients with GBS. Axonal degeneration the main cause of lasting condition contributes variably to the acute complication (Brown and Feasby, 1984). If blood presents little increase in IgG two weeks after the administration of IVIG, the patients are at poorer outcome at 6 months as compared to those whose IgG increased to a significant extent. The condition may be the chronic inflammatory demyelinating polyneuropathy, and hence, the treatment will be different in case the disease continues exceeding four weeks or variations in severity are more than two in eight weeks (van den Berg *et al*., 2014). If the standard dose of IVIG administered in the first two weeks, it decreases the time of recovery in GBS patients.

CONCLUSION

The patients with GBS have a serious condition that needs immediate hospitalization because it can worsen quite rapidly. It is necessary to start the treatment and care in the early stage to have a better chance of outcome. The GBS is a rare but quite serious disease that shows a high rate of morbidity and mortality.

No proper treatment could be investigated in view of the complexity of the disorder. Antibiotics are used mainly for the treatment of GBS. Intravenous immunoglobulin (IVIG) is the preferred treatment. However, some people having soft tissue and bone infections may require surgery and other treatment measures. In such cases, the treatment is started earlier and sorted out on the basis of the kind of infection caused by the GBS bacteria. The immunotherapeutic approaches have already evolved (Walgaard *et al*., 2011; Rinaldi *et al*., 2013). Since the immunosuppressive drugs including interferon beta (IFN-β), brain-derived neurotrophic factor (BDNF), mycophenolate mofetil (MM) etc have not been observed having benefit (Walgaard *et al*., 2011), it seems necessary to check whether a second course of IVIG can be considered for those GBS cases who obtained IVIG but their posttreatment blood antibody level showed a little increase (Walgaard *et al*., 2011). It was investigated that the BDNF theoretically pertains the potential for protecting the neurons from having axonal degeneration, but it was not found beneficial in GBS (Walgaard *et al*., 2011). The combination of methylprednisolone (MP) and IVIG did not provide significantly better effects after 4 weeks if not adjusted for the necessary prognostic factors. MM a relatively new immune suppressive agent, for B and T lymphocytes, was not found beneficial (Walgaard *et al*., 2011).

Eculizumab is a promising drug of choice for GBS, though larger trials are needed to confirm its beneficial effects for severe GBS. It may be beneficial considering the involvement of complement system (Walgaard *et al*., 2011). Later study found the inhibition of complement in GBS patients (Davidson *et al*., 2017).

Some compounds including fasudil (an inhibitor of the Rho-kinase enzyme; isoquinoline substituted by(1,4-diazepan-1-yl)sulfonyl group at the position 5), quinupramine (a tricyclic antidepressant compound (TCA), glatiramer acetate (immunomodulating drug) , and an antibody targeted against the anti-GD3 antiganglioside (Rinaldi *et al*., 2013) and flecainide (Walgaard *et al*., 2011) in experimental animal models (mainly autoimmune neuritis rat models) have shown encouraging results for future implications. Future investigations will hopefully provide more effective drug products for GBS.

Treatment of GBS is a challenge for the patients and physician, since it has various levels of severity in different areas of the body and in different cases. It is hard to predict about the outcome of a number of GBS patients with various variants, though many of the patients reach to the complete recovery. In certain patients, immunotherapy with traditional treatment is not successful. Hence, there is an urgent need for further insight about the mechanism of the occurrence of GBS variants.

There is an urgent need of establishing molecular understanding of the potential biological treatments. Besides immunotherapy, there seems strong evidence of the biological substances that can help modulating the pathogenesis processes of GBS. We suggest that the promising results for biological targets and biological and clinico-biological basis of innovative immunotherapeutic approaches for investigating/ inventing the biological drugs are essentially required for the treatment and better outcome of GBS complications.

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