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Guillain-Barre Syndrome: A Review of Current Diagnostic Tools, Treatments, and Research

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Abstract:

Guillain-Barre Syndrome is a rare post-infection inflammatory disorder. It is caused by the cross-reactivity of antibodies produced from a recent infection which then attack the gangliosides of the peripheral nervous system. Guillain-Barre syndrome includes multiple subtypes which are categorized based on both disease course and symptoms, which include length of progression phase, pain, and cranial nerve involvement. This paper will serve as a review of diagnostic tools and treatment options used for Guillain-Barre syndrome patients. It will also discuss recent research on these topics as well as studies on viral outbreaks which may be linked to Guillain-Barre syndrome. These will include Zika, a large viral outbreak from 2016, and COVID-19, a current pandemic at the time of completion of this paper. Lastly, an overview of potential future studies will be explored on these topics.

One sentence summary: This review explores the current diagnostic tools and treatments used for Guillain-Barre Syndrome as well as discusses ongoing research regarding the disorder.

Introduction:

Guillain-Barre Syndrome (GBS) is an inflammatory disorder in which the peripheral nervous system experiences damage by an inappropriate immune response. This disorder is associated with a recent viral or bacterial infection within six weeks of the onset of symptoms (See Figure 1). The most common infection that leads to GBS is by *Campylobacter jejuni*, which typically presents with diarrhea, fever, and occasionally vomiting. Other infections known to be associated with the disorder are Epstein-Barr virus and cytomegalovirus. Studies have determined that after the initial infection antibodies produced against the pathogen are able to cross react with gangliosides in the peripheral nervous system which may be molecularly similar. Once the immune system has begun to attack these nerves the onset of symptoms begins.(*1*) Symptoms of GBS include weakness in extremities, numbness, and ascending paralysis. Severe cases of GBS can be life-threatening as the antiganglioside antibodies can attack the respiratory system. This disorder most commonly affects males above the age of sixty, however cases in women and children have also been reported. What causes an individual to be more susceptible to developing GBS is still unknown.

Figure 1.

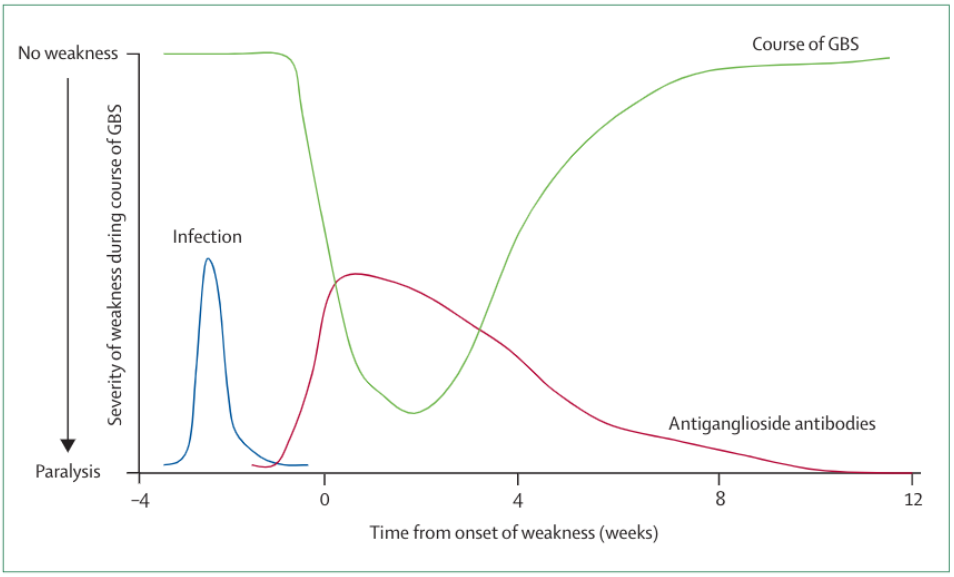


Figure 1: **Relation between infections, antiganglioside antibodies, and clinical course of GBS**

Adapted from van Doorn, et al. (6) Physical representation of the progression of GBS beginning with an initial infection. After infection the antiganglioside antibodies attack the peripheral nervous system which then starts the course of GBS. As antibody levels decrease the patient will experience an improvement in symptoms.

Diagnosis of GBS:

GBS is a rare disorder that can be difficult to accurately diagnose. Weakness of the limbs and areflexia, the most common symptoms experienced in GBS, are often attributed to other diseases due to the infrequent diagnosis of GBS. This along with a wide range of diversity in other symptoms can be problematic when identifying the cause of a patient's symptoms. In children, GBS is even more difficult to recognize, resulting in only one-third receiving a correct diagnosis at admission.(*1*) Currently, only two diagnostic tools are used to diagnose GBS: electromyography and cerebrospinal fluid analysis.

Electromyography is a diagnostic tool which uses probes, either attached to the skin or inserted into the muscle, that send out electrical impulses to detect nerve activity in potential

GBS cases. In GBS patients the electrical impulses being sent may show signs of slowed nerve conduction or conduction being blocked completely. These findings indicate that the patient's paralysis can be contributed to nerve damage in the limbs.

GBS has several subtypes based on how the peripheral nerves are being affected by the autoantibodies. Electromyography is a useful tool to assist in identifying which subtype a patient may be experiencing. These subtypes are acute inflammatory demyelinating neuropathy (AIDP), acute motor axonal neuropathy (AMAN), and acute motor and sensory axonal neuropathy (AMSAN).(*2*) AIDP is the most common subtype of GBS and is characterized by the demyelination of peripheral nerves. AMAN does not show signs of demyelination but has a clinical presentation of decreased compound muscle action potential, specifically affecting the motor neurons.(*3*) While AMAN only affects the motor neurons, AMSAN includes damage to both the motor and sensory neurons. Determining which subtype a patient has can help to obtain a more accurate prognosis. Even with electromyography there is a possibility that one subtype may mimic another. This can occur with reversible conduction failure (RCF), an electrophysiological characteristic that can be seen in patients with AMAN subtype. If the patient is not tested multiple times using electromyography they can be miscategorized under the AIDP subtype.(*2*) Under current diagnostic protocol, when determining if a patient is suffering from GBS, this test is typically only performed once.

Cerebrospinal fluid analysis is the second tool that medical professionals use to diagnose GBS. When a patient is suspected of developing GBS a cerebrospinal fluid sample is obtained through a lumbar puncture. This fluid is then analyzed for any abnormalities. Typically with GBS patients there will be a significant increase in protein levels in the cerebrospinal fluid while maintaining a normal white blood cell count. However, this factor does not lead to a definitive

diagnosis. Many other conditions that affect the peripheral nervous system, such as chronic inflammatory demyelinating polyneuropathy (CIDP), will have a similar result when using this analysis. CIDP also presents similarly to GBS in the early stages of the disorder and current diagnostic tools cannot differentiate between the two at disease onset.(*4*)

Currently, electromyography and cerebrospinal fluid analysis are the only diagnostic tools used for potential GBS cases. However, neither provides a definite diagnosis. Given this analysis of current diagnostic tools used for GBS, it is imperative that new tools for identifying GBS cases and determining the specific subtype are developed. This will ensure a quick and accurate diagnosis and prognosis for patients.

Treatment:

Treatment options for GBS are dependent on the severity of the disease. Currently, in mild cases there is typically no prescribed treatment. A mild case is defined as an individual who is still able to walk with or without assistance. In these cases, however, physical therapy may be beneficial. For more severe cases there are two treatment options, plasma exchange and intravenous immunoglobulin.

Plasma exchange is a procedure in which the patient's blood is removed from their body and filtered before being returned to the body system. The goal of this treatment is to remove the harmful, soluble antibodies that are causing damage to the nerves from the blood.(*5*) However, the timing of this treatment plays a key role in determining how effective it is. A study conducted in North America showed that plasma exchange had the greatest improvement when given within two weeks of the onset of symptoms. It was also found to be effective to a lesser degree at four weeks.(*6*) Only individuals who could not walk without assistance were given the treatment

in this study. Based on their findings it may be beneficial to repeat this experiment with individuals who have varying severity of the disease to determine if this timing applies to all cases of GBS.

Intravenous immunoglobulin is another treatment for GBS and is more commonly used than plasma exchange. For this treatment, donated blood is processed and separated such that the immunoglobulin is isolated. The antibodies, which are in the immunoglobulin, are then given to the patient through an IV to help stop the harmful, cross reacting antibodies from damaging the nerves. Several mechanisms have been suggested as to how this treatment is beneficial. These mechanisms include a blockage of receptors found on macrophages which prevents the harmful antibodies from attacking the myelin and that the donor antibodies help to regulate the antiganglioside antibodies or cytokines. Although this treatment is more common it has not been shown to be more effective than plasma exchange.(*7*) Previous studies have also shown that a combination of the two treatments does not have a significant effect on improving recovery time.(*8*)

While these treatments can be beneficial to a patient with GBS they have both been found to be time-sensitive. Given the difficulty in diagnosing GBS, it is likely that a significant portion of affected patients will miss the two-week window for either treatment to be the most effective. On top of this, 5-10% of individuals who initially improve from either treatment will begin to experience deterioration again.(*1*) It is still unclear as to why this may occur. However, it is clear that more studies should be done to determine other beneficial treatments for GBS that are not restricted by time.

Current Research:

Given the limitations on current diagnostic tools it is imperative that research be conducted on discovering more definitive ways of diagnosing GBS. Recent studies have focused on the presence of biomarkers in an attempt to differentiate between GBS and other similar autoimmune diseases. Some studies on the effectiveness of alternate treatment options have been conducted as well, the findings from these will be discussed in detail.

With the current rise in viral outbreaks, such as Zika and SARS-CoV-2, in recent years studies have been conducted that look at the percentage of these cases that contract GBS to determine a possible link between GBS and these viruses. This information can help to determine what types of viruses or infections are most likely to result in GBS and thus the hospitals can be better prepared to manage patients with this diagnosis.

IL-8 as a biomarker:

Chronic inflammatory demyelinating polyneuropathy (CIDP) is the most common chronic autoimmune neuropathy. Unlike GBS, there has not been any autoantibodies or antigen identified as a trigger for the disorder currently. However, the two disorders do share some similarities. CIDP also presents with weakness in the arms and legs which is caused by damage to the myelin sheath that surrounds the peripheral nerves.(*10*) It is also recommended that treatment should be started as soon as possible to prevent the loss of nerve axons. A significant difference between these two diseases is that CIDP is chronic whereas GBS is a monophasic disorder. Other differences are evident between GBS and CIDP when it comes to disease course, prognosis, and responsiveness to steroids. Similar to GBS, CIDP can be treated with intravenous immunoglobulin and plasma exchange, however steroids are also typically prescribed as well. In

contrast, research has shown that corticosteroids may worsen GBS in some cases.(*11*) This difference in treatment effectiveness makes a prompt and accurate diagnosis crucial.

A recent study has provided evidence of another possible diagnostic tool that could be used to differentiate between CIDP and GBS. The article published in November of 2019 found that IL-8 levels in the cerebrospinal fluid were significantly elevated in patients diagnosed with GBS. IL-8 is a cytokine which is responsible for activating neutrophils in inflammatory areas. (*12*) In this study the authors compared groups of individuals who had been diagnosed with GBS, CIDP, non-inflammatory polyneuropathies, migraines, and a group with functional neurological disorders. The authors included individuals with several different types of non-inflammatory polyneuropathy which included drug-related, cryptogenic, and hereditary origins. All patients were from the Neurology Clinic of the University Hospitals of Geneva between the years 2010 and 2018.(*4,13*)

For this study, cerebrospinal fluid was acquired from each individual and concentrations of IL-8, IL-6, and TNFα were analyzed. Specifically, the authors were most interested in IL-8 due to it being a pro-inflammatory chemokine. Its expression is stimulated by specific cytokines, such as IL-1, IL-6, and IL-12.(*4*) To determine the significance of differences in the compared groups the mean and standard deviation were calculated and ANOVA was performed. The level of significance was set to $p<0.05$. (*4,13)*

Figure 2.

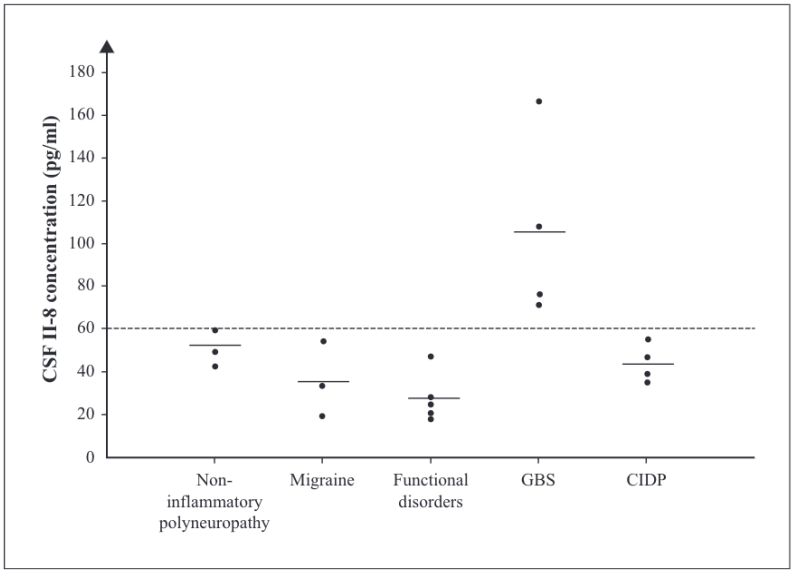


Figure 1
IL-8 concentration in the CSF. Individual CSF IL-8 levels are depicted per patient and distributed by group. The dotted black line indicates a virtual cutoff of 60 pg/ml. Horizontal black lines correspond to the mean of the dots per category. Patients diagnosed with GBS had higher concentrations of IL-8 compared to other inflammatory and noninflammatory causes.

Breville, G., Lascano, A.M., Roux-Lombard, P. *et al.Eur Cytokine Netw* 30, 130–134 (2019).

Second, the authors performed another experiment in which they analyzed levels of proteins, IgG index, albumin quotient, and IgG intrathecal synthesis if present in the cerebrospinal fluid.(*4*) They also observed the C-reactive protein levels in the serum, which can be used as an indicator for inflammation. Individuals who were diagnosed with CIDP had protein levels that ranged from 0.4-0.6mg/ml whereas GBS protein levels were found to range from 0.6-1.1mg/ml. For reference, normal protein levels of cerebrospinal fluid are typically 0.15-0.6mg/ml. All other measurements taken during this experiment were deemed not significant for this study. However, one individual diagnosed with GBS was found to have a white blood cell count of 29 per cubic millimeter. The normal range is 0-5 WBC per cubic millimeter.

The main findings from this paper is that there is potential for IL-8 to be a biomarker for diagnosing GBS as it appears that it can be used to differentiate between similar neurological

diseases, such as CIDP.(*13)* The authors hypothesize that if this diagnostic tool is used, IL-8 concentrations should be analyzed in the cerebrospinal fluid as it will be more reliable than if it is measured in blood. They suggest that there may be fluctuations in concentrations changing throughout the day due to the circadian rhythm.(*9*) While this study appears promising, future research involving larger groups of patients are required as this initial study was limited to only four patients with GBS.(*4*) Additionally, these future studies will help to establish a standardized cutoff for IL-8 concentrations in the cerebrospinal fluid. In doing so this will further assist in differentiating between GBS and other diseases.

This pilot study serves as a starting point for further research regarding the use of IL-8 as a biomarker for GBS. While this experiment is valuable to expanding the field of diagnostic tools currently involved in neurological diseases, the sample size of each group was small. Because of this there is a possibility of skewing the results in a way that may not accurately reflect the data. In future studies involving IL-8 a larger group should be used to confirm the results found in this study. The authors also state that when looking at IL-8 concentrations they arbitrarily chose 60 pg/ml as the cutoff for their experiments (See Figure 2). While the mean concentration of IL-8 for GBS patients was significantly higher than the other groups, this random selection of the cutoff does not have much significance. Their choice may skew the results in this study.(*13)*

Possible next steps for research on this topic could be to include a larger patient population, as stated previously. Doing so could either provide more evidence to back up the findings of this study or refute the collected data. Another possible avenue could be to implement other proinflammatory cytokine analysis into potential future studies, which could bring to light another possible biomarker for GBS. Lastly, future research should include testing the concentration of these cytokines in blood samples to determine if the authors were correct in

their suggestion that cerebrospinal fluid is more reliable. If incorrect this could suggest a less invasive diagnostic tool for medical professionals to implement into practice. (*13*)

Methylprednisolone:

Methylprednisolone is a corticosteroid that is known to have anti-inflammatory properties. It accomplishes this by binding to specific nuclear receptors which then affects gene expression and inhibits the production of proinflammatory cytokines. (14) Early studies regarding its use have suggested that corticosteroids may also be beneficial in treating pain. (15) It is because of these properties that the drug has been of interest in regards to its effects on recovery from GBS.

One study involving the drug was performed as a double-blind, placebo-controlled, randomized study, in which they had 233 participants who had been diagnosed with GBS. Each was assigned to receive either intravenous methylprednisolone or a placebo for five days with concurrent intravenous immunoglobulin treatment. (16) A disability score was taken at the beginning of treatment and analyzed for improvement in each participant four weeks after randomization. It was found that 68% of the methylprednisolone group and 56% of the placebo improved by one grade or more on the disability score. Given this information it was concluded that there was no significant difference in improvement between the two groups. However, the authors did note that further studies should be conducted on the drug in terms of treatment for GBS.

Another study that was published in 2016 compiled data from six previous trials regarding the use of methylprednisolone in cases of GBS. The studies were either randomized controlled trials (RCT) or quasi-RCT and included both adults and children. From the data

collected they compared disability grade changes after four weeks similar to the previous study discussed. (*11*) The scale was graded from zero to six with increasing disability; grade zero was individuals that were deemed healthy while grade six was deceased. From the six trials 297 participants in total received corticosteroids while 290 were placed in the placebo group. From this research the authors found that four trials using an oral form of corticosteroids saw less improvement in the steroid group versus the placebo group. The other two trials involving intravenous methylprednisolone showed no significant difference between the groups. (*11*)

Given the data collected from these two studies it does not seem beneficial to include methylprednisolone or other corticosteroids as a treatment plan option for GBS patients. In the case of oral steroids they seem to have a negative effect and could potentially delay recovery further. (*11*) While the data does not show significant improvement in either use, it is still not well understood why this is. Future research is required to fully understand how the corticosteroid is not able to assist in decreasing inflammation and improving symptoms in cases of GBS.

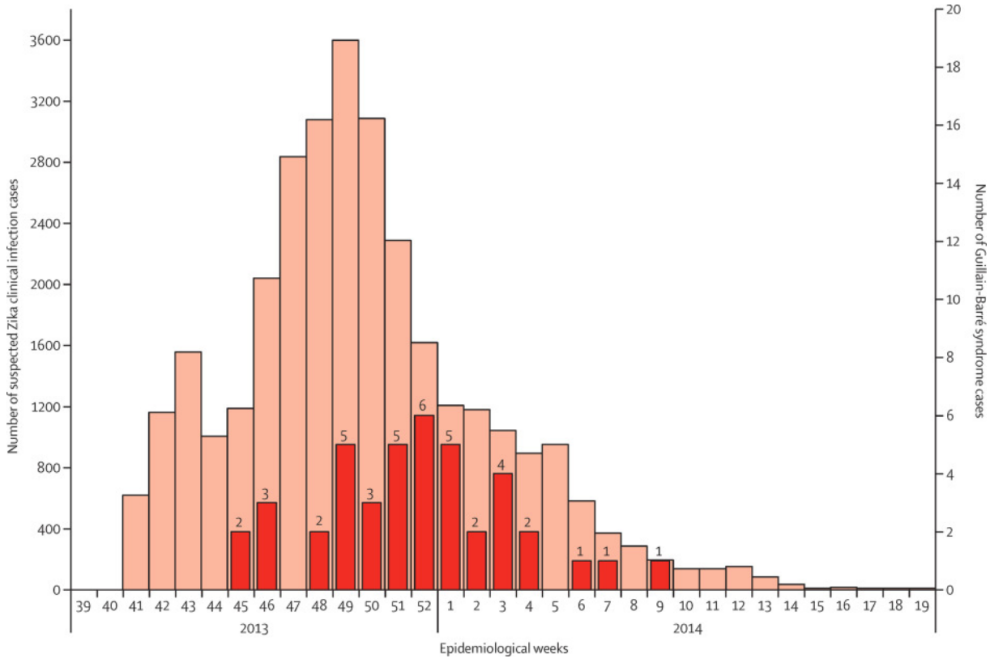
Zika Virus:

There are many infectious pathogens that have been linked to an increased risk of developing GBS. However, prior to a study published in 2016 Zika virus had not been associated with the disorder. From October 2013 to April 2014 a large Zika outbreak occurred in French Polynesia. During this outbreak over 32,000 individuals were suspected of having been infected with Zika virus. (*17*) Of this group 42 patients developed GBS after infection (See Figure 3). The goal of this study was to determine if there was an association between Zika and GBS. The

authors were also interested in examining if dengue virus co-infection or immunity played a role in susceptibility to GBS.

Dengue virus is a common arbovirus with forty percent of the world's population living in areas at risk of dengue. (*18*) Symptoms of dengue infection include body aches, nausea, and rash. (*19*) This virus had already been linked to causing GBS, however Zika had not. During the 2013 Zika outbreak there was a concurrent dengue outbreak that affected the region. (*17*) This occurrence allowed for the authors to study not only Zika but also how dengue could affect GBS case numbers.

Figure 3.



Graph comparing the number of cases of Zika virus versus the number of cases of GBS by week.
Cao-Lormeau, V.-M., Blake, A., et al. (2016). Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. *The Lancet*, *387*(10027), 1531–1539. https://doi.org/10.1016/s0140-6736(16)00562-6

For this study the authors formed three groups of patients from the Centre Hospitalier de Polynésie Française (CHPF) in Papeete, Tahiti, French Polynesia. The first group was made up of the 42 patients that had been diagnosed with GBS, while the other two groups were used as control groups: group two was patients with non-febrile illnesses and group three was patients who had been diagnosed with Zika but that had not developed any neurological disorders. Group two was used to estimate the proportion of Zika virus infections in the general population while group three was used to investigate the possible role of past dengue infection in developing GBS in a Zika virus infected patient.

To accomplish their goals the authors took blood samples from all patients. For the GBS group and group two IgM and IgG levels were determined for both Zika and dengue virus while group three was only tested for IgG to Zika and dengue virus. The third group was not tested for IgM antibodies. Given that IgM is produced as a first response to a new infection and this group was already diagnosed with Zika, it was not deemed necessary. (*17*)

From these experiments it was found that 93% of GBS patients had IgM antibodies against Zika, and of these 74% did not have IgM antibodies against dengue virus. It was also found that there was not a significant increase in dengue virus incidence between the GBS group and group two. Given this information it was concluded that dengue virus infection or immunity did not play a role in GBS susceptibility. Based on a 66% attack rate, the percentage of an at-risk population that contracts the disease during a specified time interval, GBS cases were estimated to be 0.24 per 1,000 Zika infections. (*17*) These findings also supported that Zika virus should be added to the list of infectious pathogens susceptible to causing GBS. Lastly, the authors suggest that at risk countries should be prepared to have an adequate capacity of intensive care beds to manage patients with Guillain-Barré syndrome.

COVID-19:

SARS-CoV-2 is the virus responsible for coronavirus disease 19. At the completion of this paper coronavirus disease 19 (COVID-19) is an ongoing global pandemic that is currently responsible for 2.7 million deaths. (*20*) Neurological symptoms of the disease include loss of taste and smell, tingling and numbness in the hands and feet, and muscle weakness. (*21*) In a recent study it was found that neurological symptoms were seen in 36.4% of individuals with COVID-19. (*22*) Currently, mRNA vaccines are being produced and almost 398 million have been administered worldwide. (*20*) While this is a relatively new and rapidly evolving situation, there are already published case studies regarding GBS and Covid-19.

An article published in September of 2020 outlined a case of GBS in a 36-year-old male who was immunocompromised and COVID-19 positive. (*23*) In this case the patient was admitted to the hospital 10 day after being diagnosed with COVID-19. During his six day stay he was given oxygen via nasal cannula as well as several drugs which improved his overall state. At discharge he did not have any neurological symptoms. (*23*) Four days after being discharged the patient presents again to the emergency room, however this time he is experiencing numbness and tingling in his extremities, as well as weakness in his legs that is causing difficulty walking.

Cerebrospinal fluid is taken for analysis. Clinical findings highly suggest that the patient is experiencing GBS and treatment using intravenous immunoglobulin is started. However even with treatment the patient's state continued to decline which then led to intubation for 13 days. Ultimately, the patient stayed in the hospital for 23 days and was then released to a physical therapy facility in a stable condition.

A second paper published around the same time served as a review for published cases of GBS following infection by SARS-CoV-2. At the time of publication approximately 31 cases of COVID-19 related GBS had been reported. Of these cases the youngest patient was age 5 while the oldest was 84. (*24*) Currently, there is only one case study that has been published of a child developing GBS after being infected with coronavirus. (*25*) In most of these cases GBS presented typically one to four weeks post infection, however in two cases symptoms began at the time of infection. (*26*) While it is too early to claim there is a definite link between GBS and COVID-19 the authors concluded that it is a possibility. To determine if this association is legitimate more data and further studies are necessary.

Suggestions for future studies regarding the association between GBS and COVID-19 include studying the relationship between COVID-19 and the nervous system as well as comparing COVID-19 related GBS to non-COVID-19 GBS cases. (*26,27*) Additionally, while there is currently no correlation between a specific variant of GBS and COVID-19 this may be useful data to collect if another coronavirus outbreak occurs in the future. (*28*) Lastly, current data shows that GBS symptoms begin approximately 10 days after infection by SARS-CoV-2 which is a similar interval seen with GBS in association to other infections. (*29,30*) As more data is acquired with the spread of COVID-19, a timeline should be made showing the average onset of GBS symptoms after infection.

Future research and conclusion:

GBS is a rare autoimmune disorder that is difficult to quickly diagnose and treat. Currently used diagnostic tools are not definitive and treatment options are time-sensitive. While recent studies have shown some promising insight on new ways to diagnose GBS there is still

much more research required in this field. Moving forward it is paramount that future studies focus on finding better ways to diagnose and treat this disorder.

On top of this, increases in viral outbreaks as seen in recent years may contribute to an increase in annual cases worldwide. Currently, COVID-19 has caused a global pandemic which may be associated with the development of GBS. As this global situation continues more studies should be conducted to determine if SARS-CoV-2 should be added to the list of pathogens known to cause GBS. Knowing which infections contribute to the development of GBS will assist in better planning for patient care. As these outbreaks occur affected countries will need to be prepared by increasing intensive care bed capacity as well as medical staff to care for these patients. While there are still many questions surrounding this rare autoimmune disorder it is imperative that further research be conducted in this field.

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Notes:

Author declares no competing interests.

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