Guillain Barré syndrome and Coronavirus infection

Síndrome de Guillain Barré e infecção por Coronavírus

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ABSTRACT
The coronavirus (COVID-19) pandemic is a major problem of public health worldwide since 2020. The virus that first started causing pneumonia in Wuhan, China, has spread throughout all six continents and is now also known for causing other health issues, including neurological infection. In the last months, there were many case reports of Guillain-Barré Syndrome (GBS) in patients with SARS-CoV-2 infection, raising concerns over a possible association. The coronavirus infiltrated in neuronal tissue is able to modify the pathophysiology of GBS, that is a polyneuropathy and also an autoimmune disease, commonly triggered by infections of the human body. Acute inflammatory demyelinating polyneuropathy (AIDP) is one of the most common types of demyelinating polyneuropathy, causing loss of the myelin sheath, what makes electrical messages cannot travel between the brain and the periphery of the body. This association must be early diagnosed so that the physician can manage it to avoid respiratory depression and other consequences of the condition.

Keywords: Guillain Barré Syndrome, COVID-19, neurologic infection COVID-19, SARS-CoV-2.
RESUMO
A pandemia de coronavírus (COVID-19) é um grande problema de saúde pública em todo o mundo desde 2020. O vírus que começou a causar pneumonia em Wuhan, China, espalhou-se pelos seis continentes e é agora também conhecido por causar outros problemas de saúde, incluindo a infecção neurológica. Nos últimos meses, houve muitos relatos de casos de síndrome de Guillain-Barré (GBS) em doentes com infecção por SARS-CoV-2, suscitando preocupações sobre uma possível associação. O coronavírus infiltrado no tecido neuronal é capaz de modificar a fisiopatologia da SRA, ou seja, uma polineuropatia e também uma doença auto-imune, normalmente desencadeada por infecções do corpo humano. A polineuropatia inflamatória aguda desmielinizante (AIDP) é um dos tipos mais comuns de polineuropatia desmielinizante, causando a perda da bainha de mielina, o que faz com que as mensagens eléctricas não possam viajar entre o cérebro e a periferia do corpo. Esta associação deve ser diagnosticada precocemente para que o médico a possa gerir de modo a evitar a depressão respiratória e outras consequências da doença.


1 INTRODUCTION

In December 2019, the world heard about the coronavirus disease caused by the SARS-COV-2 virus with high ability of contamination and transmissibility that started in Wuhan, capital of Hubei province, in China. The infection was defined as a pandemic in March 2020 by the World Health Organization, since it had spread throughout all six continents. It is known that this disease leads to neurological manifestations, even though the lungs are the main target; anosmia and dysgeusia are intriguing symptoms that are commonly seen in early phases of COVID-19 infection . [1]

SARS-CoV-2 has a higher affinity for angiotensin-converting enzyme receptor 2 (ACE-2) that is expressed on endothelial cells and neurons, which explains a higher neuro-invasive capacity of the SARS-CoV-2 virus when compared to previous coronaviruses. [2] However, the neurological symptoms associated with SARS-CoV-2 are attributable to secondary mechanisms (i.e., multiorgan dysfunction or systemic inflammation), an abnormal immune response or the direct injury of the virus still unknown. [3]

In the last months, progressively intensifying case reports of Guillain-Barré Syndrome (GBS) in SARS-CoV-2 infection raised the concern over a possible association. GBS is a type of peripheral neuropathy—a condition involving the degeneration of nerves extending head, body, and limbs, that is also an autoimmune disease. This association may not be a surprise, since many events can trigger the Guillain
Barre syndrome, including infectious diseases—approximately 70% of patients with GBS have a preceding sickness, and infectious agents such as Campylobacter jejuni, Influenza virus, Cytomegalovirus and, recently, Zika virus have been demonstrated to trigger GBS. [4]

Acute inflammatory demyelinating polyneuropathy (AIDP) is one of the most common types of demyelinating polyneuropathy, and it is considered another type of GBS. In this disease, the immune attack is directed against the myelin, causing loss of the myelin sheath and leading to a "short circuit," so that electrical messages cannot travel between the brain and the periphery of the body. [5]

The association between GBS and COVID-19 infection makes it critically important for physicians to diagnose and manage GBS as soon as possible in all COVID-19 patients, recognizing that respiratory compromise due to GBS may be rapidly onward but treatable with a high success rate in COVID-19 patient. [6]

2 OBJECTIVE

To present the Guillain-Barré Syndrome associated with the SARS-CoV-2 infection, describing the pathophysiology, epidemiology and discussing possible approaches to reduce mortality.

3 METHODS

We searched PubMed/MEDLINE for literature concerning COVID-19 disease associated with GBS. We selected scientific papers published since the coronavirus outbreak in December 2019, as well as Journal pre-proof articles. The search terms included “COVID-19,” “Guillain-barre, Syndrome”. For exclusion criteria, we used articles published before 2019, articles referring to pediatric patients and articles in non-English language. The search yielded a total of 250 articles. After reading the titles and abstracts, some of them didn't meet the criteria of this study. Then, 33 articles which met the proposed criteria were selected and used as the basis for this literature review. We also used the book “Guillain Barré Syndrome - an American Academy of Neurology press quality of life guide”

The results of the present study were divided in thematic categories.
4 DISCUSSION

4.1 PATHOPHYSIOLOGY OF GUILLAIN BARRE SYNDROME

The Guillain Barre Syndrome is a peripheral neuropathy, a condition that involves degeneration of the nerves from the head, trunk and limbs. It is an acute neuropathy since it evolves in days or weeks. The acute inflammatory demyelinating polyneuropathy is also known as AIDP. It is also defined as an autoimmune disease because in this case, the immune attack is directed against the myelin sheath. The myelin sheath usually isolates the axle so that the electrical message can run throughout all the nerve and get to the terminal part with the necessary speed, so in GBS we have loss of the myelin sheath. For that reason, the electrical message cannot travel between the brain and the periphery of the body. [5]

The immune system is responsible for recognizing and eliminating invaders from outside the body such as viruses and bacteria, and for eliminating damaged cells within the body, such as cancer cells. Whenever there is an autoimmune disease, the response from the immune system is misdirected and it attacks the body itself, and the reasons for that are still unknown. Therefore, this explains why there is loss of the myelin sheath in GBS. Other examples of autoimmune diseases are rheumatoid arthritis, juvenile (insulin-dependent) diabetes, systemic lupus erythematosus (lupus) and multiple sclerosis. [5]

Autoimmune diseases can be triggered by recognized antecedent events that stimulate the immune system. In Guillain Barre Syndrome, most people are able to identify the event that triggered the attack. SGB is mostly related to an infection, but it can also be related to vaccination, to postoperative or any other trauma. Regardless of the triggering event, the neurologic symptoms can appear as early as 1 week and as late as 4 weeks after the event, but they usually appear within 2 weeks. It is worth mentioning that, the shorter the interval between the event and the onset of neurologic symptoms, the more severe the GBS. [5]

4.2 GBS EPIDEMIOLOGY

GBS is considered a rare disease. A rare disease can be defined by a disease that affects up to 65 people every 100,000 people, according to the World's Health Organization (WHO). As for GBS, its incidence is unknown in many parts of the world, and studies prove that it can vary depending on each region within each country. In North America there are only 1.5 to 2.0 cases for every 100,000 people each year, meaning that there are 4,000 to 4,500 new cases every year in the United States. [5] In Brazil, a study
made in São Paulo state found that GBS incidence is 0.6 cases every 100,000 people, but a study made in Rio Grande do Norte state found its incidence of 0.3 cases every 100,000 people. [7] There are many reports of outbreaks of the syndrome. One of these outbreaks happened in the US, following the swine influenza vaccination program in 1976. [5] In 2015, in Brazil, The Nation Program of Dengue Control of the Ministério da Saúde also registered an increase in the number of hospitalizations due to GBS. [7] The study related this increase to the chikungunya epidemic in the country and the fast spread of zika virus. [7]

GBS incidence is higher in men and in Caucasian, but it can affect males and females of all ages and races. There is no explanation for this prevalence. It is specifically rare in children, particularly in the first 2 years of life. Its frequency increases throughout life. It is worth mentioning that there is no report of seasonality on the syndrome’s occurrence. [5]

Approximately 25% of the GBS cases end up with respiratory failure, 5% in death and 20% in definite significant disability. [7]

4.3 EPIDEMIOLOGY: COVID-19 AND GUILLAIN BARRÉ SYNDROME

The relationship between COVID-19 and the Guillain Barré Syndrome can already be established, even though more studies are important to define some questions about these two conditions combined. In November 2020, the first case of GBS caused by the COVID-19 infection was identified by Rutgers University, in the United States, and its study was published by the Pathogens periodical. A study published by the New England Journal found five cases of GBS in three hospitals in Italy. In this study, the admissions of COVID-19 patients were between 1000 and 1200, showing that the GBS incidence in patients with the coronavirus infection is pretty low. Even though it is rare, this is a pretty severe condition.

4.4 PATHOPHYSIOLOGY OF THE NEUROINFECTION CAUSED BY COVID-19

The upper respiratory tract of humans can be infected with opportunistic pathogens - respiratory viruses; some have neuroinvasive properties and activate one immune response in the brain. Responsible for the Coronavirus Acute Respiratory Syndrome (SARS-COV-2), the new coronavirus belongs to a group of positive sense RNA viruses in the Coronaviridae family. Highly contagious, it can progress with severe neurological problems, with symptoms that can persist for months after infection. [8]
The central nervous system (CNS) is an organ protected against most viral infections due to the external multilayer barrier, the blood-brain barrier and effective immune responses. However, the coronavirus gains entry by infecting blood brain barrier endothelial cells in the choroid plexus or by using inflammatory cells, such as leukocytes. In addition, the virus can enter the CNS via hematogenous or neuronal retrograde pathways, using smell, respiratory and enteric nervous system networks. [9,10]

The SARS-COV-2 receptor invading host cells is an angiotensin-converting enzyme (ACE2), which has an enzymatic modification function of the vasoconstrictor peptides angiotensin I and angiotensin II and, associated with transmembrane serine protease 2 (TMPRSS2), damages the blood-brain barrier and replicates in human cells. [8]

The neurovirulence of SARS-CoV-2 is related to the degree of expression of the ACE2 receptor in the CNS, which is very expressed in the substantia nigra, choroid plexus, olfactory bulb, among others. A variety of positive neurological disorders in COVID-19 can be attributed to different types of pathways in which it can travel. One is through the transcervical route, using the olfactory epithelium along the olfactory nerve until it reaches the olfactory bulb, inside the CNS. Another way to be used is during infection in the gastrointestinal tract, in which the sympathetic afferent neurons of the enteric nervous system are used to reach the CNS. In addition, it can move from the lungs to the spinal cord and travel between synapses for cardiorespiratory neurons in the brain. [10]

The bloodstream can be a means by which the virus can reach the cerebral circulation. The sluggish circulation of blood within microcirculation may facilitate the binding of spike protein with ACE2 receptors expressed on the capillary endothelium. [10]

When the virus reaches neuronal tissues, as proteins increase interaction with the ACE2 receptor for the start of viral replication, with neuronal destruction without substantial inflammation. [10] The manifestations of the disease in the CNS can occur directly after infection, at the end of the disease course or after recovery.

The coronavirus infiltrated in neuronal tissue is able to modify the pathophysiology of Guillain-Barré Syndrome, a type of peripheral neuropathy - a condition involving degeneration of the nerves extending into the head, body and limbs, through molecular mimicry generating a cytokine storm and, consequently, hyperinflammation - which leads to the appearance of the syndrome. Thus, cytokines with
Interleukin-6 and tumor necrosis factor alpha, present in the inflammation cascade, are responsible for the worsening of GBS. [8]

4.5 CLINICAL MANIFESTATIONS OF GBS AND COVID-19

Guillain Barré Syndrome is a post-infectious disorder and most patients present respiratory or gastrointestinal infection 2 to 3 weeks prior to the onset of neurological symptoms. Concerning the SARS-CoV-2 infection, patients can present GBS either having or not the symptoms of COVID-19. The post-infectious profile includes the onset of symptoms after recovery from COVID-19 and the infectious profile is marked by the onset of symptoms during active SARS-CoV-2 infection with an overlap of symptoms from both pathologies, the latter being more severe. [11] The gap between the onset of COVID symptoms and the first symptoms of GBS were between 8 and 24 days, being 9 the mean and 10 the median. [12]

The clinical manifestations mostly found in SARS-CoV-2 infection were cough, fever or both [13], dyspnea and/or pneumonia. [14] The diagnosis is set by nasopharyngeal, oropharyngeal or fecal PCT. Most patients had abnormalities on lung imaging consisting of ground-glass opacity, interstitial pneumonia, consolidation or bibasilar opacities. [13] Less frequent symptoms of the infection are hypo/ageusia, hypo/anosmia and diarrhea. [14] Some patients may present asymptomatic pictures for COVID-19 and still develop GBS.

According to Kajumba et al, in a systematic review with 51 case reports of COVID-19 patients, aged 23 to 84 years, diagnosed with GBS in 11 different countries, the predominant clinical manifestation in infectious patients was acute inflammatory demyelinating polyneuropathy (65.23%), followed by acute sensory motor axonal neuropathy (6.52%) and Miller-Fisher syndrome (6.52%).

The neuromuscular symptoms found in a patient with acute inflammatory demyelinating polyneuropathy (AIDP) include ascending quadriparesis, areflexia, impaired movement, facial paralysis/diplegia, oropharyngeal/hypoglossal paralysis, ophthalmoparesis, psychomotor agitation, fatigue, decreased muscle tone and ascending tetraplegia/paraplegia. Sensory symptoms are anosmia and ageusia, dysesthesia/paresthesia, vibratory and proprioceptive loss, loss of light touch and prick sensation, stocking and glove hyperesthesia, distal allodynia, lumbar and/or thoracic pain, headache, confusion and syncope. [11]
A systematic review by Caress et al of 37 published cases of GBS associated with COVID-19, with a mean age of 59 years, showed that one-third of the patients required mechanical ventilation due to the condition of neuromuscular respiratory failure. GBS caused by COVID-19 can worsen severe respiratory dysfunction and general symptoms, in addition to increasing the need to determine invasiveness.

4.6 GBS DIAGNOSIS

The diagnosis of GBS is primarily clinical. However, complementary tests are necessary to confirm the diagnostic hypothesis and exclude differential diagnoses. The most used diagnostic tests are electrophysiological studies and examination of the cerebrospinal fluid (CSF), which is obtained by lumbar puncture.

The electrophysiological examination is of paramount importance for a definitive diagnosis and consequently adequate treatment and prognosis. In addition, because of the risk of respiratory failure and the ability to accelerate recovery with appropriate immunomodulatory therapies, treatment can be instituted in a timely manner and in an appropriate setting. This test can be completed in any setting but is usually done in a specialized laboratory. Electrophysiological landmarks of demyelination include prolonged distal latencies, slowing of conduction velocity, temporal dispersion, conduction block, and prolonged F-wave latencies, all of which are usually symmetrical and multifocal. There is controversy regarding the early electrophysiological findings. [5]

On the CSF exam, on the other hand, the characteristic abnormality of GBS includes an increased protein concentration with normal cell numbers, which represents minocyte dissociation from albumin. Normally, the CFS contains 15 to 60 milligrams of protein per 100 milliliters of fluid. In GBS, this protein concentration is usually above 100mg/dL making the cerebrospinal fluid slightly yellowish. If the protein levels are normal at the first lumbar puncture, it may be necessary to repeat the test within 7 days because it can be normal in the early stages of the disease but it is usually elevated by the end of the first week. In addition to this change, there might be a slight increase in white blood cells (lymphocytes) particularly earlier in the disease. [5]
4.7 TREATMENT MODALITIES FOR GBS ASSOCIATED WITH COVID-19 INFECTION

A large number of studies were analyzed for this present article. The treatments used in cases of Guillain Barre Syndrome caused by the COVID-19 infection are represented in the table below.

Table 1 - Treatment modalities for Guillain Barre Syndrome in patients with COVID-19 infection

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Treatment used</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNCINI et al, 2020</td>
<td>Intravenous immunoglobulin and/or plasma exchange</td>
</tr>
<tr>
<td>ZITO et al, 2020</td>
<td>Intravenous immunoglobulin and/or plasma exchange, but only one case received symptomatic treatment3</td>
</tr>
<tr>
<td>MANGANOTTI, BELLAVITA et al, 2020</td>
<td>Intravenous immunoglobulin</td>
</tr>
<tr>
<td>SRIWASTAVA et al, 2021</td>
<td>Intravenous immunoglobulin and/or plasma exchange</td>
</tr>
<tr>
<td>SIMÕES e BAGATINI, 2021</td>
<td>Inhibition of P2X7R</td>
</tr>
<tr>
<td>MANGANOTTI, PESAVENTO et al, 2020</td>
<td>Intravenous immunoglobulin</td>
</tr>
<tr>
<td>CARESS et al, 2020</td>
<td>Intravenous immunoglobulin and/or plasma exchange</td>
</tr>
<tr>
<td>FRAGIEL et al, 2020</td>
<td>Intravenous Immunoglobulin</td>
</tr>
<tr>
<td>DUFOUR et al, 2021</td>
<td>Intravenous immunoglobulin</td>
</tr>
<tr>
<td>ALBOLMAALI et al, 2020</td>
<td>Plasma exchange; plasma exchange; intravenous immunoglobulin and plasma exchange.</td>
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</tbody>
</table>

Many other articles were analysed to write this article. In all of those, the treatment used was intravenous immunoglobulin or intravenous immunoglobulin associated with plasma exchange.

Intravenous immunoglobulin therapy was found to be effective and safe to treat the reported neurological symptoms, with no side effects reported. Moving forward, further studies are needed to clarify and test treatment options.

5 CONCLUSION

The neurological symptoms caused by the SARS-CoV-2 have already been explained by the invasion of the ACE2 cells in the brain. More than GBS, this invasion is also responsible for the anosmia reported by those who have been infected. Although
we know how the damage is made, we still don’t know how to prevent the neurological symptoms once infected.

The symptoms of Guillain-Barre Syndrome usually appear five to seven days after the first symptom of COVID-19. That being said, it is important to tell the patients to watch for symptoms such as difficulty to swallow, weakness or numbness on the legs or arms, loss of sensibility in certain parts of the body or any other symptom of GBS.

Considering that both conditions (GBS and COVID-19) may cause respiratory depression, power ventilation or orotracheal intubation may be necessary in severe cases. It is important to emphasize the importance of early diagnosis of SGB associated with coronavirus infection, because this is the main element in changing the patient’s prognosis.
REFERENCES


