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Analysis of the correlation between Guillain-Barré and post-COVID-19 syndromes

Matheus Lopes Martins, Sabrina Carvalho Melo, Amanda de Brito Silva, Luan Kelves Miranda de Souza

Abstract

OBJECTIVE: To correlate Guillain-Barré as a consequence of the Post-COVID-19 syndrome, evaluating the pathophysiological, immunogenic and epidemiological mechanisms. METHODOLOGY: A systematic review was carried out, with secondary data, using articles published in the following databases: Latin American Caribbean Literature on Science and Health (LILACS), Scientific Electronic Library (ScIELO) and Pubmed; using the descriptors: Guillain-Barré syndrome; Demyelinating Diseases and COVID-19, using the Boolean operator "AND", swapping between them. RESULTS AND DISCUSSION: According to Abu-Rumeileh et al. (2021), patients with COVID-19, even if asymptomatic, were more likely to develop GBS, with a predominance of the male population, in the classic sensorimotor form and in acute inflammatory demyelinating polyneuropathy, with an increase in pediatric cases also being observed, due to of the wide age range of Sars-Cov-2. The post-infection immune-mediated pathophysiological mechanism observed some predisposing factors, namely: neurological symptoms after Sars-Cov-2 infection, improvement of the clinical picture of GBS with immunomodulators and absence of viral RNA in the cerebrospinal fluid. CONCLUSION: Guillain-Barré Syndrome consists of an immune-mediated neuromuscular condition usually subsequent to an infectious process, which triggers an inflammatory response followed by a molecular mimicry that causes an autoimmune response in the individual's peripheral nervous system. Although there is no consensus in the scientific community regarding the causal relationship between COVID-19 and GBS, it is believed that infection with the new coronavirus precipitates an immune-mediated reaction that triggers this neuromuscular condition characterized by progressive, symmetrical and ascending weakness, in addition to areflexia.

Keywords: Guillain-Barré syndrome; Demyelinating Diseases; COVID-19.

1. Introduction

The Sars-Cov-2 virus, known to cause COVID-19, is characterized by an acute flu syndrome (SARS) that emerged in December 2019 in Wuhan, China, and triggered a global public health emergency. In March 2020, the World Health Organization (WHO) declared the state of a pandemic, characterizing the global spread of the disease (Peña et al., 2021).

The coronavirus is an enveloped and spherical virus, of the coronaviridae family, obligatorily intracellular, which requires active metabolic cells to replicate, which has single-stranded RNA. Its invasion process to the

organism occurs through some proteins characteristic of its structure, among them the Spike glycoprotein (S) and M-pro stand out, in addition to highlighting a host protein, the angiotensin converting enzyme (ACE), being the recipient of access to the organism. ACE is expressed in different parts of the body, influencing its numerous manifestations, affecting the respiratory system, circulatory system, gastrointestinal system and central and peripheral nervous system (Velavan & Meyer, 2020).

Neurological manifestations in COVID-19 patients include headache, dizziness, hyposmia or anosmia, and hypogeusia or ageusia. In addition to studies indicating the specific involvement of the peripheral nervous system, with an increase in the incidence of disorders of the same, an increase in cases of Guillain-Barré syndrome in patients with COVID-19 is reported, with the first case being located in January 2020 caused by by Sars-Cov-2 infection (Collantes et al., 2020).

Acute inflammatory demyelinating polyneuropathy, known as Guillain-Barré syndrome (GBS) consists of a disease that affects the peripheral nervous system through an autoimmune process, causing damage to the myelin sheath or neuronal axon, leading to derangement of nerve transmissions. The triggering of GBS is a previous infection, generally about three weeks before the onset of the first symptoms, which is characterized by weakness, paresis, pain/low back pain, with an ascending aspect, that is, from distal to proximal, bilateral, symmetrical and reduced or abolished tendon reflexes, with an evolution of 2 to 4 weeks (Sansone et al., 2021).

The main cause of GBS is a gram-negative spiral bacterium that causes diarrhea in individuals, called Campylobacter jejuni, which has its pathophysiology linked to the process of mimicry of the bacterial membrane with the nonosiatoride glanglioside (GMI), the main component of the axolemma, causing the axon to be compromised by the antibodies produced against the bacteria. Other agents such as arboviruses, cytomegalovirus, Epstein-Barr virus, viral hepatitis and other situations such as surgery, pregnancy and immunization (vaccination), can trigger the deposition of immune complexes on the membrane of the external surface of the myelinating fibers, with infiltration of lymphocytes and macrophages, causing Guillain-Barré syndrome. COVID-19, as a triggering factor of the syndrome, has shown clinical and pathophysiological similarity to the classic etiologies, but its mechanism has not yet been fully clarified (Aladawi et al., 2022).
Thus, the purpose of this work is to correlate the pathophysiology and incidence of GBS cases as a consequence of COVID-19, in addition to defining the main clinical manifestations, being of great value to establish preventive measures adopted after the acute period of the disease.

2. Methodology

This is a systematic literature review, in which studies researched in the Latin American Caribbean Literature on Science and Health (LILACS), Scientific Electronic Library (ScIELO) and Pubmed databases were used. The descriptors in Portuguese “Guillain-Barre Syndrome”, “demyelinating diseases” *and* “COVID-19” were used, in addition to the descriptors in English “Guillain-Barre Syndrome” *and* “COVID-19”. The Boolean operator AND was used, swapping the descriptors in the searches.

As inclusion criteria, articles written in English and Portuguese, published between 2017 and 2022, were selected and filters were used: analysis, meta-analysis and systematic review. For the exclusion of articles,

publications that escaped the main theme of this research were adopted as criteria, in addition to those with more than 5 years of publication or articles in languages other than those selected. The excluded articles underwent a manual selection process, excluding those that, after reading the title and abstract, were not related to the theme proposed by this study.

After the electronic search, 578 studies were pre-selected. After reading the articles and according to the proposed selection criteria, 18 articles were selected to form the sample.

3. Results and discussions

After the selection of the 578 articles, each one was read in full, 18 of them being chosen for writing this article, taking into account the main objective determined by the authors and the variables analyzed in the publications described, being exposed in the following table (Table 1):

Table 1. Analyzed articles, authors' data and their respective results

Article / Year	Objectives	Methods	Results
Peripheral neuropathy in COVID-19 is due to immunomechanisms, pre-existing risk factors, antiviral drugs, or bedding in the Intensive Care Unit (FINSTERER et al., 2021).	Review and discuss advances in the clinical, pathophysiological, diagnosis, treatment and evolution of peripheral neuropathies resulting from COVID-19 infection.	Literature review with 105 articles searched in the Pubmed database.	The review shows that the majority of cases (220) of neuropathy are on the GBS spectrum, age ranges over a broad spectrum from 8 to 94 years; the majority (179) of patients are male and more than half (119) of diagnosed GBS cases are of the acute inflammatory demyelinating neuropathy form.
Neuromuscular presentations in patients with COVID-19 (Paliwal et al., 2020).	To analyze the main neuromuscular manifestations of COVID-19 infection.	Review of articles on neuromuscular manifestations resulting from COVID-19 infection on PubMed, Google Scholar, Scopus and Preprint platforms.	Among the various studies analyzed, it was observed that there was an increase in cases of GBS subsequent to COVID-19, with a different presentation from the common GBS, marked by affecting older people,

			presenting concomitant pneumonia or acute respiratory distress syndrome, in addition to the majority of cases. with demyelinating neuropathy and with a poor prognosis outcome.
Review article on COVID-19 and Guillain-Barré Syndrome (Patnaik, 2021)	Conduct bibliographic research, classify and compile the relevant information on COVID-19 and Guillain-Barré syndrome.	Published reports on Guillain-Barré syndrome associated with COVID-19 were analyzed by searching PubMed and Google Scholar databases and individual case reports.	Due to the small number of reported cases of GBS and COVID-19, the pathophysiology of the relationship between GBS and COVID-19 remains unknown. There is an increase in the occurrence of Guillain-Barré syndrome after infection with COVID-19 (Sars-Cov-2). The average time taken by COVID-19 positive patients to develop Guillain-Barré syndrome is < 2 weeks according to case reports.
Association of Guillain-Barré syndrome with COVID-19 infection: an updated systematic review (Sheikh et al., 2021)	To determine demographic, clinical, laboratory evaluation, management and complications characteristics of studies focusing on Guillain-Barre syndrome (GBS) as a sequela of the novel coronavirus (COVID-19) infection.	This is a systematic review, searching PubMed and Web of Science and Cumulative Index to Nursing & Allied Health Literature (CINHAL) databases	Among the neurological findings, paresthesia was the most typical symptom (48.9%). Most patients were diagnosed by reverse transcriptase polymerase chain

		of all GBS case descriptions associated with COVID-19 articles, published from January 1, 2020 to September 15, 2020. Data regarding demographic and clinical characteristics, diagnosis and management were analyzed using International Business Machines (IBM) Statistics SPSS 21.	reaction (RT-PCR) (69.2%). Acute inflammatory demyelinating polyneuropathy (AIDP) was most likely associated with lower extremity paresis ($p < 0.05$) and higher glucose levels on cerebrospinal fluid (CSF) analysis ($p < 0.05$). GBS is being recognized as one of the many presentations of COVID-19 infection.
Spectrum of Guillain-Barré syndrome associated with COVID-19: an updated systematic review of 73 cases (Abu-Rumeileh et al., 2021)	Provide a comprehensive and up-to-date overview of all GBS case reports and series related to COVID-19 to identify predominant clinical, laboratory and neurophysiological patterns and discuss possible associated pathophysiology.	This is a systematic review, searching PubMed and Google Scholar databases, published until July 20, 2020. Analyzing 73 patients, who were reported in 52 publications.	In this study, patients who developed GBS had both symptomatic and asymptomatic cases of COVID-19. The most prevalent subtype was the classic sensorimotor form and acute inflammatory demyelinating polyneuropathy. In addition, it showed higher rates of involvement in the male population. The pathophysiological development predicts a post-infection immune-mediated mechanism, contributing to this idea

			the neurological symptoms after viral infection, improvement of symptoms with immunomodulators and the absence of indicators of COVID-19 in the cerebrospinal fluid.
Emerging Infection, Vaccination and Guillain-Barré Syndrome: A Review (Koike et al., 2021).	To describe an association between Guillain-Barré Syndrome and newly emerging infectious diseases, with a focus on Zika virus and COVID-19 infection.	Review based on previous studies.	The article brings studies that point to an increase in the incidence of GBS cases at pandemic peaks in countries such as Spain and Italy when compared to individuals who did not contract COVID-19 and when compared to the same period a year ago, respectively. In addition, studies speak in favor of the predominance of a demyelinating electrophysiological manifestation, compatible with acute inflammatory demyelinating neuropathy, in relation to axonal forms of the disease, as well as more severe muscle weakness in individuals who have previously had

			COVID-19.
Sars-Cov-2 infection and Guillain-Barré syndrome: a review of potential pathogenic mechanisms. (Shoraka et al., 2021)	Elucidate the likely pathogenic mechanisms based on current and past knowledge about the relationship between COVID-19 and Guillain-Barré Syndrome.	A meta-analysis was carried out, with articles that relate the corona virus and the pathophysiological mechanism of GBS, with 128 articles being analyzed	Guillain-Barré syndrome associated with Sars-Cov-2, in addition to the classic post-infectious profile, can follow the pattern of a para-infection, which is an important consideration for early diagnosis. Thus, its pathophysiological mechanism is still unknown, but it is believed that it may be related to the loss of self-tolerance and the release of cytokines caused by COVID-19.
Neurological Manifestations in Patients with COVID-19: A Meta-analysis (D et al., 2021).	To jointly analyze based on pooled data from individual studies that reported neurological manifestations in patients with COVID-19.	This is a meta-analysis, in which 240 articles published in PubMed, Google Scholar and Clinical trials.gov databases between December 1, 2019 and December 3, 2020 were selected.	The article brings a relationship between COVID-19 infection and neurological manifestations of the central and peripheral nervous systems. In that study, GBS had a greater association with demyelination in patients with COVID-19, in addition to being clinically more severe compared to patients who did not contract the infection, with a pooled proportion of 6.9% (2.3-13 ,7),

			suggesting significant involvement of GBS in patients with COVID-19.
Prevalence, clinical features and outcomes of COVID-19-associated Guillain-Barré syndrome spectrum: a systematic review and meta-analysis (Palaiodimou et al., 2021)	To evaluate GBS and COVID-19-related publications focusing on the prevalence, clinical features, and outcomes of GBS in COVID-19-positive patients compared to COVID-19-negative patients in contemporary or historical controls.	Systematic review and meta-analysis of observational cohort studies and case series reporting the occurrence of clinical characteristics and outcomes of patients with GBS associated with COVID-19.	A prevalence of 0.15% was found in patients positive for COVID-19, overlapping the general population, with about 0.02% acquiring GBS from other etiologies. In addition, a prevalence of demyelinating subtypes was observed, with a probable immune-mediated etiology.
Relationship between COVID-19 and Guillain-Barré syndrome in adults: a systematic review (Gittermann et al., 2020).	To analyze, in the adult population, the available evidence on the relationship between COVID-19 and Guillain-Barré Syndrome	This is a systematic review of 24 studies published in PubMed, Cochrane, Science Direct, MEDLINE and WHO COVID-19 databases.	Analysis of 30 patients in 24 articles reveals that GBS associated with COVID-19 is more prevalent among older patients and is more severe. Furthermore, there was an increase in cranial nerve involvement in cases of demyelinating peripheral neuropathy, which previously had 5% of reported cases, but in this study it was present in 47% of patients.
Guillain-Barré syndrome: the first	Expose GBS associated with COVID-19 as a counterpoint to	Analysis of eleven cases of GBS to	Patients who have acute paralytic disease

documented autoimmune neurological disease triggered by COVID-19 (Dalakas, 2020)	other forms of emerging autoimmune diseases developed after COVID-19 and address potential concerns with ongoing neuroimmunotherapies.	discuss the relationship between the clinical picture presented, clinical response to the therapy used and cross-reactivity between COVID spike proteins (Spike and M-pro) with nervous system glycolipids.	can raise the suspicion of COVID-19, which may be its first manifestation. Thus, some clinical characteristics may draw attention to this association, which are: anosmia or ageusia and lymphocytopenia or thrombocytopenia. Patients with GBS peak between the fifth and tenth day after the first symptoms of COVID-19. In addition, data indicate that the virus can cause other neurological diseases, requiring early diagnosis and initiation of treatment.
Guillain Barré syndrome associated with COVID-19 - lessons learned about its pathogenesis during the first year of the pandemic, a systematic review (Freire et al., 2021).	To review the evidence on the pathogenic mechanism of the association between GBS and COVID-19.	Literature review with clinical cases reported up to 1 February 2021 of GBS patients with a previous history of COVID-19 infection.	Analysis of 82 articles with 104 clinical cases showed that 73% of the cases present the AIDP form of the syndrome; the mean time between the onset of COVID-19 and the symptoms of GBS was 11 days, with a prevalence of the inflammatory process in relation to the immune-mediated ones. With respect to antibody-mediated injury, only 6 of 58

			cases in one study developed anti-gangliside antibodies.
Guillain-Barré syndrome associated with COVID-19: the initial experience of the pandemic (Caress et al., 2020).	Clarify knowledge about COVID-19 associated with GBS during the initial period of the pandemic based on a review of existing literature.	Retrospective literature review of English-language publications linking GBS to COVID-19 identified by a Medline search via PubMed through June 22, 2020.	In a sample of 37 patients, most of them (31 of 37.84%) had GBS while they had symptoms of COVID-19. The most prevalent symptoms were paresthesia in the limbs or pain and weakness, with varying degrees. One third of the patients required mechanical ventilation.
Guillain Barre syndrome as a complication of COVID-19: a systematic review (Mohammadian et al., 2021)	Examine COVID-19-associated GBS cases to assess their clinical presentations, latency period between symptoms of viral infection and onset of GBS, and the global distribution of these cases.	Systematic review using PubMed, EMBASE and academic Google search, selecting 109 cases of GBS with confirmed or suspected COVID-19 infection, excluding patients with a latency greater than 6 weeks between infection by the virus and the first manifestations of the syndrome.	There was a higher frequency of the demyelinating sensorimotor subtype, often associated with facial paralysis, more frequently in males. Observed the manifestations of GBS preceding the symptoms of COVID-19, in its minority of cases. In addition, HLA polymorphism was observed, being related to the development of GBS.
Guillain-Barré syndrome associated with Sars-Cov-2 infection: a systematic	Summarize and meta-analyze the main features and prognosis of GBS associated with Sars-Cov-2.	The survey was conducted in accordance with the Preferred Reporting	We studied 61 cases of laboratory-confirmed Sars-Cov-2 -associated GBS from 45 articles.

review and meta-analysis of data from individual participants. (Hasan et al., 2020)		Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. Studies from all geographic regions describing participants of all age groups, ethnicities and genders were included. Articles published in English between January 1 and August 5, 2020 were analyzed. Search made in MEDLINE through PubMed, Web of Science and Cochrane library databases.	Most patients had the classic sensorimotor presentation and the demyelinating subtype of GBS. Indicating that the GBS associated with Sars-Cov-2 infection resembles the classic presentation of GBS. Research carried out in Italy showed a 5.4-fold increase in the incidence of GBS in the peak period of the pandemic.
Guillain-Barré syndrome in Sars-Cov-2 infection: an instantaneous systematic review of the first six months of the pandemic (Uncini et al., 2020).	Conduct a systematic review of reported cases of GBS in Sars-Cov-2 infection, clarify the clinical and electrophysiological phenotype, discuss, based on available data, whether the disease mechanism may be para-infectious or post-infectious, and speculate on the possible pathogenesis.	Published articles on Guillain-Barré syndrome associated with COVID-19 were analyzed using PubMed data, full-text articles in English and those reporting sufficiently detailed information, according to a pre-screened list, were analyzed. defined. The systematic review was performed following, where applicable, the statement Preferred Reporting Items for	42 patients were included in the systematic review. The clinical features of GBS reported were: limb weakness (64.3% tetraparesis, 11.9% lower limb paraparesis), hyporeflexia (80.9%), sensory disturbances (66.7%) and facial paralysis (38, 1%, in 81.2% bilateral). Most patients had the classic presentation of GBS, but virtually all variants and subtypes have been reported.

		Systematic Reviews and Meta-Analysis.	
Guillain-Barré Syndrome in the COVID-19 Pandemic. (Tawakul et al., 2021)	Discuss the association between GBS and COVID-19, diagnostic criteria, clinical, laboratory and imaging features, management, complications and death related to COVID-19 infection with concomitant GBS.	Retrospective review that examined articles published from April 1, 2020 to May 8, 2021 in English, in PubMed Central, PubMed, Google Scholar, Cochrane, science direct and Ovid databases.	The clinical picture of post-COVID-19 GBS was not different from the other classified etiologies, but there was a greater respiratory involvement. In addition, some patients had antiglycoside antibodies, which suggested the immune-mediated theory, while others did not have positive tests for antiglycosides, leading us to think about the mechanism of direct infection of the nervous system. A post-infectious pattern was observed in most cases.
The Significance of COVID-19 Immune Status in Severe Neurological Complications and Multiple Sclerosis — A Literature Review (Kulikowska et al., 2021).	To summarize the knowledge acquired so far of severe neurological complications in COVID-19 infection and the serological status of individuals with neurological diseases.	Literature review	Of the 36 cases in which the presence of anti-ganglioside antibodies was analyzed, only 5 had the antibodies, but no association was found between anti-GM1 and classical GBS and between anti-GQ1b and the Miller-Fisher variant, which was seen in about 88% of GBS cases before the Sars-

			Cov-2 pandemic. In addition, in the pandemic scenario, the number of reported cases of GBS was higher and the mean age of those affected by the syndrome was higher.

According to Finsterer et al. (2021), 220 patients with GBS and 41 with other neuropathies were identified. Of this total of 261, the age of 244 of them ranged between 8 and 94 years; 253 were gender-revealed, 179 male and 74 female. 257 had the neuropathy classified, of which 220 patients were diagnosed with GBS and of these, 118 were identified with the AIDP form. The study further suggests that the GBS associated with COVID-19 infection is due to a secondary immune reaction, not direct damage by the virus to the patient's peripheral nervous system.

Paliwal et al. (2020), brings 34 studies with 39 patients affected by GBS after COVID-19 aged between 21 and 85 years, but with an average of 60 years. Of the 39 patients, 35 were gender-revealed, and of these, 26 (74%) are men and the mean time of onset of GBS symptoms was 13.9 days, with variations from 3 days to 4 weeks. 43% of patients had significant respiratory failure secondary to pulmonary involvement. Of the 32 patients in whom the syndrome form was investigated, 24 (75%) had a demyelinating pattern and only 7 (22%) had axonal involvement. Furthermore, the article mentions that most patients had a para-infectious process and the minority had a post-infectious syndrome.

According to Patnaik (2021), the first reports of Guillain-Barré syndrome in patients with COVID-19 were described in Italy after infection by COVID-19. In most cases of Guillain-Barré syndrome, patients presented characteristics of the lower limbs involving weakness and paresthesias, which may present with fever, cough, dyspnea, anosmia, ageusia and diarrhea. According to the author, due to the small incidence of GBS cases associated with COVID-19, its pathophysiology remains unknown. Therefore, tests for Sars-Cov-2 serology and case-control studies should be performed to determine the correct association between COVID-19 infection and GBS.

In the systematic review of 94 cases, Sheikh et al. (2021) showed that the clinical picture of GBS associated with COVID-19 has some clinical features that increase the suspicion of the diagnosis, such as bilateral weakness of the legs and arms, sensory loss, paresthesia, hyporeflexia and gait problems, in addition to the attributes of GBS classic. Of the 94 patients analyzed, with a mean age between 40 and 72 years, the neurological presentation was preceded by respiratory symptoms in 72.35% of the patients (68 of 94), with paresthesia being the most typical neurological symptom, being present in about half of the patients. of individuals. The authors recognize GBS as one of the many presentations of COVID-19 infection, although

the common form is AIDP, which can lead to complications, other variants are also possible, but more studies are needed to focus on these variants.

According to Abu-Rumeileh et al. (2020), symptomatic and asymptomatic patients with COVID-19 developed GBS, with a predominance of the male population (68.5%), in the classic sensorimotor form and in acute inflammatory demyelinating polyneuropathy, with an increase in pediatric cases also being observed, resulting from the wide age range of Sars-Cov-2. In the clinical picture presented by GBS, about 2 weeks after viral infection, all cases, except one, had lower limb areflexia or generalized, 37.5% gait ataxia, 76.4% flaccid tetraparesis, 84.7% symptoms persistent sensory deficits, 36.5% developed respiratory symptoms, with 1/5 requiring mechanical ventilation. A post-infection immunomediated pathophysiological mechanism was observed when some predisposing factors were observed, namely: neurological symptoms after Sars-Cov-2 infection, improvement of the clinical picture of GBS with immunomodulators and absence of viral RNA in the cerebrospinal fluid.

The article by Koike et al. (2021) pointed out that studies carried out in Spain during the peak of the pandemic between March and April 2020 showed a higher frequency of GBS in patients with COVID-19 than in patients without COVID-19 (0 .15% and 0.02%, respectively), in addition to a study carried out in Italy in the same period of 2020, which showed that the incidence of GBS cases was higher in this period (2.43/1,000,000) when compared to the same period in 2019 (0.93/1,000,000). The cases of GBS associated with COVID-19 present electrophysiological findings characteristic of demyelination, more compatible with the acute inflammatory demyelinating polyneuropathy (AIDP) form, but did not exclude the axonal forms Acute Axonal Motor Neuropathy (AMAN) and Acute Axonal Motor and Sensory Neuropathy (AMSAN). In addition, the study cites a systematic review from January to June 2020 with 36 patients that showed that the median interval between the onset of GBS symptoms and the onset of COVID-19 symptoms was 11.5 days and cites another study. with 30 patients with GBS associated with COVID-19 who had clinical characteristics in common, including the prevalence of the AIDP form, more severe muscle weakness and hypotension when compared to individuals who do not acquire COVID-19.

According to Shoraka et al (2021)., the rate of development of neurological symptoms in patients positive for COVID-19 ranges from 3.5 to 84%, with the absence of Sars-Cov-2 RNA in the cerebrospinal fluid (CSF) in most cases. part of the cases. GBS, which affects the peripheral nerves, was more prevalent in older patients, around 60 years of age, and genetic and environmental factors may be involved in the development of this condition, which may be due to post-infection or parasitic pathophysiological mechanisms. infection. However, the exact pathogenesis is still not fully known, but findings in the biopsy, CSF and proteins (hexapeptides) contained in Sars-Cov-2, which are associated with autoimmune neuropathies, predispose to the immune-mediated pathophysiological mechanism. It has been observed that the cytokine storm caused by the virus may play an important role in the development and progression of GBS, as some cytokines recur between diseases.

According to D et al. (2021), 240 studies with 190,785 patients were analyzed to seek a causal relationship between COVID-19 infection and the manifestation of neurological disorders, which were separated into nonspecific, central nervous system and nervous system peripheral. With regard to GBS, all forms of

neuropathy have been reported. In addition, demyelination was the main association between patients with COVID-19 and GBS, with the syndrome having a more severe presentation in individuals infected with COVID-19 when compared to a group of individuals who were not infected by the viral condition. The meta-analysis showed a significant involvement of GBS in patients infected with COVID-19, with pooled proportion data of 6.9% (2.3-13.7).

In the study by Palaiodimou et al. (2021), a prevalence of 15 GBS cases per 100,000 Sars-Cov-2 infections was evidenced, including patients who required hospitalization and those who did not need to be hospitalized, exceeding the average infection rate in the general population. In addition, it was observed that patients had an average interval of 14 days between the symptoms of COVID-19 and the appearance of GBS, associated with a threefold increase in the development of acute inflammatory demyelinating polyradiculoneuropathy among patients infected with Sars-Cov-2, with probable immune-mediated etiology.

The study by Gittermann et al. (2020) was performed with 30 patients, of which 25 had their sex revealed, 14 men and 11 women. Within this group, there was a higher prevalence of older patients (mean age 60 years) presenting with GBS compared to the ages of presentation of the syndrome before the pandemic, which used to be a mean age of 40 years. In addition, the most frequent symptoms were muscle weakness of the lower limbs, areflexia and involvement of cranial nerves, denoting facial paralysis, for example. The study points to the involvement of cranial nerves associated with a demyelinating neuropathy, a presentation that, before the pandemic, was less frequent, in about 5% of reported GBS cases, but, after the syndrome related to COVID-19, became more common. be more present, with 47% of the patients in the study presenting cranial nerve involvement. Finally, the article points out that there is strong evidence that there is an association between GBS and COVID-19, with the presentation of the syndrome associated with Sars-Cov-2 being more severe.
Dalakas (2020) observed in his study that patients with neurological symptoms related to acute paralytic disease, with or without systemic symptoms, mainly associated with anosmia or ageusia and lymphocytopenia or thrombocytopenia, could indicate initial manifestations of COVID-19. GBS peaked between the 5th and 10th day after the first viral symptoms, which may help to differentiate from other neuropathies. It was observed that among the risk factors, patients with autoimmune diseases, when well controlled, did not present a higher risk when compared to the general population.

According to Freire et al. (2021), there is a possibility of a para-infectious process between GBS and COVID-19. The analysis was performed through 3 mechanisms of neurological pathogenesis: direct damage, exacerbated inflammatory response and antibody-mediated injury. In direct harm, a meta-analysis showed that the mean number of days from COVID-19 infection to onset of GBS symptoms was 11 days, shorter than the mean for other etiologic agents. The uncontrolled inflammatory response has its share of importance in the process, given that the increased inflammatory cytokines are characteristics already mentioned in other forms of GBS that are not related to COVID-19 and that the immune-mediated pathology is strongly associated with the AIDP type (73 %), according to a systematic review. With regard to antibody-mediated injury, only 6 of 58 had positive anti-ganglioside antibodies, which indicates that there was no significant difference. Thus, the short interval of days between the onset of GBS and COVID-19 suggests a para-infectious rather than a post-infectious process.

In the study published by Caress et al. (2020), AIDP was the most commonly reported subtype of GBS (65%). Male predominance is slightly higher than reported in a large case series of GBS not associated with COVID-19. In two patients, symptoms of GBS preceded systemic and respiratory symptoms or occurred concurrently with asymptomatic COVID-19 infection. Thus, based on the reports, the diagnosis of GBS should be proposed in COVID-19 positive patients who developed global weakness during the clinical course, which is important for alternative diagnoses.

The results published by Mohammadian et al. (2021) identified two cases with GBS manifestations as early manifestations of COVID-19, later developing viral symptoms. In contrast, most cases did not show viral signs associated with SBG. Thus, the most common symptoms that preceded the syndrome were fever and dry cough, with a higher prevalence of the demyelinating sensorimotor subtype. The study indicated the male sex as a risk factor, with 2.5 men for 1 woman, in addition to the HLA polymorphism related to GBS, which was found in some individuals who developed the disease.

According to Hasan et al. (2020), the IPD (individual participant data) meta-analysis performed indicates that GBS associated with Sars-Cov-2 infection resembles the classic presentation of GBS. According to the authors, reports published during the current GBS-related COVID-19 pandemic are not sufficient to suggest an association between Sars-Cov-2 and GBS infection taking into account the total number of Sars-Cov-2 infections, in contrast to the number of reported cases of GBS. However, a study in Italy during the peak of Sars-Cov-2 infection, which occurred in March and April 2020, observed a 5.4-fold increase in the incidence of GBS in this period.

As for Uncini et al. (2020), the large number of GBS cases reported during the COVID-19 outbreak worldwide may suggest a possible pathogenic link between Sars-Cov-2 and GBS. Studies show that most patients (80.5%) had electrophysiological features of acute inflammatory demyelinating polyradiculoneuropathy (AIDP). However, all GBS variants and subtypes were described in the analyzed cases. The median interval between the onset of symptoms of COVID-19 and GBS, when calculable, was 11.5 days, and in 26.2% of patients, GBS began when COVID-19 was clinically resolved. Respiratory failure occurred in one third of patients and ICU admission was required in 40% of cases.

In the article published by Tawakul et al. (2021), among the types of GBS, acute inflammatory demyelinating polyneuropathy (AIDP) was present in 33.33% of cases, while in 38.18% it had no specific subtype. In their pathophysiology, most patients did not have antiganglioside antibodies, such as GM1 and GM2, which strengthens the theory of pathophysiology caused by direct infection of the nervous system. In contrast, patients positive for anti-ganglioside antibodies suggested the immune-mediated theory. Of the patients evaluated, 58.1% showed a post-infection pattern and about 35% were para-infectious. It was observed that approximately 41.9% of the patients had comorbidities, 29.52% had arterial hypertension and 12.38% had type 2 diabetes mellitus, while 18% had no medical history.

The review by Kulikowska et al. (2021), brings a comparison between the presentations of GBS before and after the beginning of the pandemic, elucidating the point of a difference observed in this aspect: before antiganglioside antibodies were present in a varied way in about 88% of the forms of the syndrome, with highlighting anti-GM1 in typical GBS and anti-GQ1b for the Miller-Fisher variant. However, studies of GBS

associated with COVID-19 show that, in addition to the cases of the syndrome having increased in this period and the mean age of affected patients being higher, antibodies do not predominate in the presentation of GBS in this period. In a study with 36 cases in which the search for antibodies was performed, only 5 patients were positive, and, of these cases, no anti-GM1 cases were related to classic GBS and there were no anti-GQ1b antibodies associated with the Miller-Fisher variant. This topic reinforces the theory of an autoimmune basis for GBS associated with COVID-19, and, in addition, speaks in favor of the theory that the absence of antibodies in these conditions suggests a demyelinating picture. Despite this difference, traditional treatment with intravenous immunoglobulin was effective.

4. Conclusion

Guillain-Barré Syndrome consists of an immune-mediated neuromuscular condition usually subsequent to an infectious process, which triggers an inflammatory response followed by a molecular mimicry that causes an autoimmune response in the individual's peripheral nervous system.

Although there is no consensus in the scientific community regarding the causal relationship between COVID-19 and GBS, it is believed that infection with the new coronavirus precipitates an immune-mediated reaction that triggers this neuromuscular condition characterized by progressive, symmetrical and ascending weakness, in addition to areflexia.

The studies carried out during the pandemic converge in several aspects, starting with the increase in the incidence of GBS in the pandemic period. Furthermore, it has been seen that individuals who present the inflammatory cytokine storm are more likely to present a cross-response of defense mechanisms, causing an attack on the cells themselves, due to a deregulation in the inflammatory response. The post-COVID-19 GBS, in the various studies analyzed, showed presentations of the main variants of GBS, with demyelinating, axonal, axonal and sensory and Miller-Fisher only.

Studies show a higher incidence of GBS related to COVID-19 in males and in the elderly, who also had a worse prognosis, as they had a more severe condition. Furthermore, GBS linked to COVID-19 was classified as more severe than when caused by other etiologies. Finally, there is still no consensus on two points: with regard to the detection of antibodies, such as anti-GM1 and anti-GM2, common in presentations before the pandemic, they suggest a direct involvement of the nervous system and not by molecular mimicry; some articles brought cases of GBS infection with current infection by COVID-19 (para-infection) and others brought cases after the end of the infection, speaking in favor of a post-infectious process.

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