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RESEARCH ARTICLE

COVID-19 AND GUILLAIN-BARRÉ SYNDROME: A PARALLEL WITH OTHER VIRAL INFECTIONS

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ABSTRACT

Background: In view of the pandemic insurgency caused by the new coronavirus, whose clinical picture ranges from asymptomatic to respiratory failure, some clinical associations with syndromes and diseases have been raised, among them Guillain-Barré Syndrome (GBS). In order to bring more clarification, a study was carried out in order to define and analyze neurological disorders by Covid-19, in addition to making comparisons with other viral diseases. **Methods:** Integrative review based on the Pubmed database. A reading of titles and abstracts was done by 3 reviewers, in a blind and independent way, followed by a complete reading, concluded in the choice of 10 articles. These were reassessed, now by 6 evaluators, for collection, data analysis and weighting according to quality scales. **Results:** the studies seem to reveal a possible association between Covid-19 and SBG, either by a predominantly post-infectious profile, with an average latency time of 5-10 days; higher prevalence in men and with a mean age of 62.4 years. **Discussion / Conclusion:** GBS is often preceded by infectious exposure. It is possible for SARS-CoV-2 to gain entry into the central nervous system through systemic vascular dissemination or the cryptous plaque of the ethmoid bone, causing from headache to flaccid flaccid paralysis (characteristic of GBS). In Zika virus involvement, this mechanism is still not well understood. Therefore, there seems to be an association between Covid-19 and GBS with a post-infectious profile, but these are larger studies for further clarification.

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INTRODUCTION

In December of 2019, there was a disease caused by the new coronavirus (COVID-19) in China, which spread around the world, causing great international concern. Phylogenetic analysis of viruses shows that SARS-CoV-2 is a new member of the Coronaviridae family, but is distinct from acute respiratory syndrome (SARS-CoV) and Middle Eastern respiratory syndrome (MERS-CoV), although it causes similar symptoms. This potentiates the existence of a new virus in our environment with a great knowledge to be discovered about it. The clinical picture varies from asymptomatic to symptoms such as fever, sore throat, fatigue, cough and dyspnea. Regarding care, early diagnosis, social isolation and supportive treatment are essential for disease resolution.

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Coronavirus infection still hides many secrets and little is known about neurological manifestations, being first described from a serial analysis of 214 Wuhan patients (first epicenter of the disease) in 36.4% of individuals with confirmed laboratory diagnosis. Today, it is not difficult to find reports of neurological repercussions associated with Covid-19 in other countries. As for the neurological symptoms found in diagnosed patients, it can be categorized into 3 groups: manifestations of the central nervous system such as dizziness, headache, loss of sensation, acute cerebrovascular disease, ataxia and seizure; manifestations of skeletal muscle injury and peripheral manifestations, such as impaired taste, smell and vision, and neuropathies[1], such as Guillain-Barré syndrome (GBS). During the current pandemic context, cases were reported of a possible association between GBS and SARS-CoV-2, either by complication of viral infection or concomitant appearance. Therefore, the objective of this article is to analyze and describe the rare neurological impairment caused by Covid-19 and to raise possible understandings of cause and effect, in addition to drawing a

parallel between the neurological impairment by known viral infections and SARS-CoV- 2.

MATERIALS AND METHODS

Integrative literature review with research done from the Pubmed database. The basic question of the study is "Is it possible to predict any pattern between SARS-CoV-2 infection and the development of Guillain-Barre Syndrome?". The PICOS strategy was also formulated, being the population: patients with SARS-CoV-2; intervention and control do not apply to the question; object: Guillain-Barre Syndrome; study design: quantitative and qualitative studies. A previous research was carried out in order to produce a systematic review, however, due to the newness of the topic, mostly qualitative studies were found, which redesigned the study for an integrative review. The MeSh terms used were: [COVID-19 (all fields)] OR [severe acute respiratory syndrome coronavirus 2 (all fields)] AND [Guillain-Barre Syndrome (all fields)]. Identification, selection, eligibility and inclusion of articles are described in flowchart 1.

The search of articles in the database was made on May 19, 2020. Then, they were analyzed by three evaluators (reading titles and abstracts and then full reading of the texts), in a distinct and bling way. The third evaluator decided among the doubts of the first two, establishing the included articles. The studies were chosen according to the eligibility criteria: qualitative and quantitative studies; discuss some relation between GBS and SARS-CoV-2; all languages; articles of any year. The criteria were comprehensive due to the scarcity of articles on the database. There was no contact with the article's authors, because the works related to Coronavirus are available with free full versions on national and international platforms.

After the choice of the articles by the three reviewers, a new complete reading was performed, in which the 12 studies were divided between six evaluators (each evaluator with two articles). This reading aimed to collect data to make the analysis easier. The division of the articles among the evaluators was made through double draw (first of the order of the articles and after the order of the evaluators) to avoid preferences. The next step was the analysis according to evaluation scales (AMSTAR for review articles and STROBE for observational studies). The STROBE scale consists in 22 itens and the 10 observational studies obtained an average of 12 positive answers to the items.

As there is no reference score, the final quality analysis is evaluator-dependent. On the other hand, AMSTAR scale has 11 itens. Of these, the study reviews comply with 3 itens in total and 2-3 itens in partial way. The review articles were removed from the final count of included studies in the research because they are not suitable for analyzing results, being evaluated in the Discussion section. The variables found in the articles are shown in table 1. None of the included studies describes the method used to avoid biases or evaluate their risk. For this study, the double draw of evaluators and articles was used for the complete reading and data extraction and the evaluation by quality scale to avoid bias, the initial reading by the three reviewers was done blindly, in which none of the evaluators had access to the appraised titles of each to avoid bias.

RESULTS

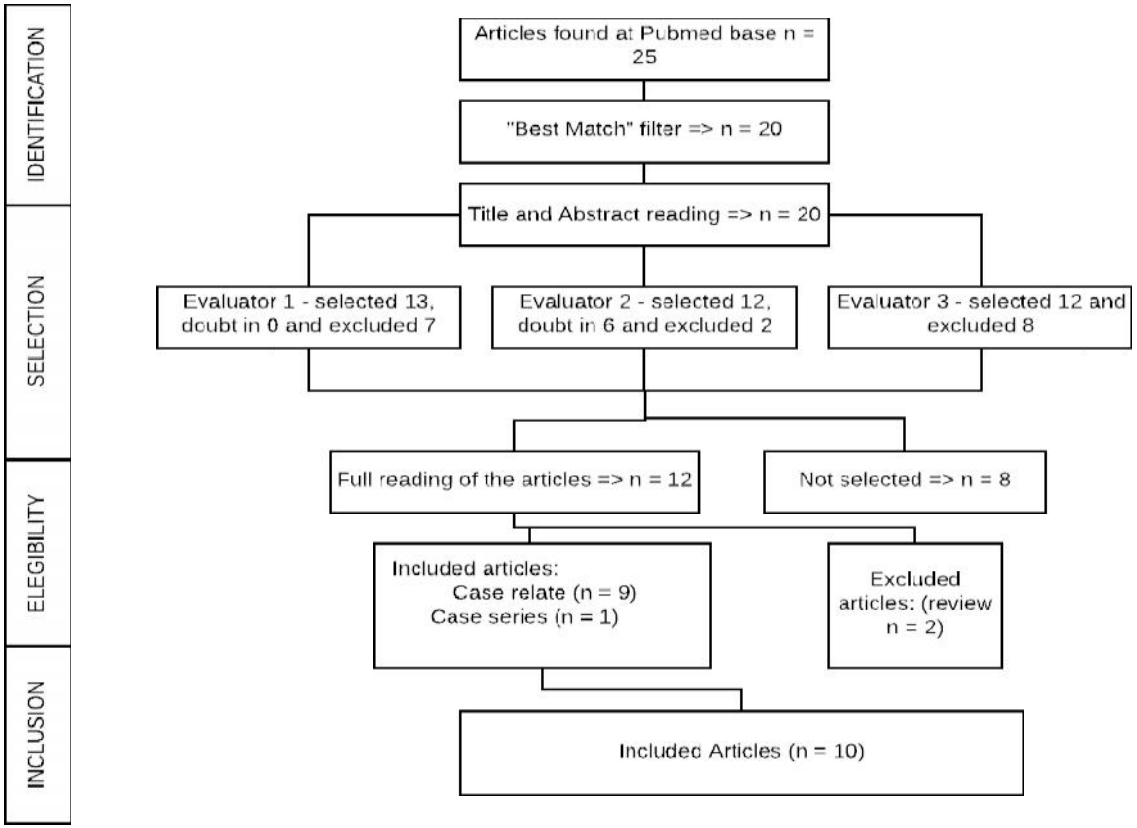
From the analysis of the studies, it was observed that there seems to be a correlation between GBS and Covid-19, either by a parainfectious process (n = 3), post-infectious (n = 5) or an atypical variant of GBS (n = 1). In the case series, it was not possible to conclude this relationship. Among the 14 patients analyzed in the studies, 71.4% are men. The mean age between reports was 62.4 years. The findings of the articles show an average latency time of 5-10 days between the onset of Covid-19 symptoms and those of GBS. Only 2 studies varied from this average (E3: 3-day latency time; E11: 15-day latency time). The E10, E12 studies did not refer to latency time. Regarding the establishment of treatment in these patients studied, the majority were treated with intravenous immunoglobulin in the articles that cited the pharmacological therapy used, having good prognosis in the majority [2-6], however 3 studies did not report the treatment for Guillain-Barré symptoms[1,7,8], one of them specified the poor prognosis in which only 1 of 5 patients was discharged with good mobility [9] and in two of them there was death of the patients mentioned in the study[10,13]. In relation to the electroneuromyographic study, the findings were: reduction or absence of the sensory action potential (SAP) and composite muscle action potential (CMAP), being evaluated the sural, tibial, common perineal and ulnar nerves; delay or prolongation of distal motor latencies. Regarding the GBS pattern, the demyelinating, mixed and axonal subtypes were found, the first and the third of these more incidents.

DISCUSSION

SARS-Cov-2 infection has been associated with neurological manifestations including consciousness deficit, polyneuropathy, myopathy, stroke and auto-immune disorders such as Guillain-Barré Syndrome, which is often present in patients with COVID-19 more severe[12,5]. GBS used to be considered a single entity characterized by lymphocytic inflammation and peripheral nervous system demyelination. Now, it is usually clinically defined as a more diverse disorder, divisible into several patterns and with various clinical repercussions[7]. GBS is often preceded by an infectious exposure or other immune stimulation which induces an aberrant autoimmune response in peripheral nerves and their spinal roots[13]. The patient's clinical condition, according to the Brighton criteria, is associated with an increasing flaccid weakness of the limbs, arreflexia, albumino-cytologic dissociation and consistent neurophysiological data. Other causes of concurrent neurotoxicities should also be excluded at the time of research, such as some infection with Campylobacter jejuni, Epstein–Barr virus, cytomegalovirus, human immunodeficiency virus (HIV), and Zika virus[9,10].
Usually, an infection eventually triggers autoantibodies directed to gangliosides in the nerve cell membrane, causing respiratory or gastrointestinal symptoms before a more obvious neurological/motor impairment. However, the mechanisms by which ZIKA virus infection, for example, causes GBS, have not yet been established; it has been suggested that the virus could exacerbate the immune response by triggering an immunopathogenic response, a process that in turn determines the onset of GBS[14,15]. Comparatively, it has been proposed that SARS-CoV-2 gains entry into the CNS in two ways: first, by systemic vascular dissemination and, secondly, more locally, through the cribriform plate of the ethmoidal bone, which may or may not have implications for

Table 1. Variables used in the articles included in the study and their frequencies

Variables	Latency time between the onset of symptoms of Covid-19 and those of GBS	Findings of head and spine MRI	Cerebrospinal fluid findings	Anti-ganglioside antibody	Treatment	Electroneuromyography	Nasopharyngeal swab	Relationship of neurological symptoms with severity of SARS-CoV-2 infection	Chest CT	Oropharyngeal swab
Number of articles	11	2	7	3	11	8	8	2	5	1



Flowchart 1. Research Prism flowchart of eligible articles

anosmia, much reported in patients with SARS-CoV-2 experience. The literature proposes that once in the systemic circulation, the virus invades neural tissue due to its neurotropic properties. Here, it binds to and interacts with angiotensin-converting enzyme 2 (ACE2) receptors in the capillary endothelium. Other plausible theories include a "macrophage activation syndrome," also known as cytokine storm, and the subsequent hyperinflammation may also be implicated in GBS pathogenesis in patients with SARS-CoV-2[8,11]. There are reports of an association between Guillain-Barré syndrome and Coronavirus infections[7-10]. Research has shown that coronaviruses have the potential to induce demyelinating disease in mice, although it is a centrally demyelinated image[9]. Regarding Zika virus, for example, there is already an established relationship with GBS and the latency of the onset GBS symptoms is, on average, 15 days. Another characteristic of Zika infection was a lower rate of anti-glycolipid antibodies, in addition to a post-infectious profile observed in cases[17]. In Covid-19, this latency time seems to be shorter (between 5-10 days) and related to more severe neurological disorders and greater respiratory depression. The reports found in the studies show a majority involvement of men (10 out of 14 patients). The youngest patient reported (male, 23 years old), had a latency time of 10 days, without worsening of neurological symptoms and improvement from the 5th day since the beginning of the same. While the oldest patient in the same study (male, 76 years), had a latency time of 5 days, worsening of neurological symptoms on the 10th day and improving around the 20th day. This pattern of worsening of neurological symptoms and reduction of latency time as older age is repeated in other patients[9]. Regarding cerebrospinal fluid (CSF) alterations, all patients tested had negative CSF PCR for SARS-Cov-2 and, when altered, hyperproteinorrhia and cellularity. So, in combination with animal models, previous reports of neurological involvement in sister viruses and current emerging reports, it appears that GBS is associated with the ongoing SARS-CoV-2 pandemic. The Covid-19 infection hides many secrets that are yet to be revealed and little is known about its neurological manifestations, due to so few published reports and the difficulty in proving a direct cause and effect relationship between a single pathogen. It can be complex to explore this subject in clinical practice[14]. In addition, the onset of Guillain-Barré syndrome symptoms in most patients overlapped with the period of SARS-CoV-2 infection. Thus, GBS associated with SARS-CoV-2 may follow the pattern of a parainfectious profile, instead of the classic postinfectious profile[4, 10]. Despite this, Gianpaolo Toscano et al was unable to determine whether severe deficits and axonal involvement are typical characteristics of the disease associated with Guillain-Barré. Julião Caamaño et al did not report a solid relationship between the two diseases, concluding the case studied as an atypical variant of GBS. And finally, the review article by Vonck et al showed a possible connection, but did not specify whether it would be a post or para-infectious condition.

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KEY POINTS

The complete understanding of the pathophysiology of SARS-Cov-2 and Guillain-Barré syndrome still requires more studies. The association of coronavirus with neurological symptoms seems to be more associated with patients who have a more severe condition. Headache is the main neurological symptom associated with Covid-19 cases, followed by anosmia, thus having fewer reports of GBS. The chronology of clinical presentation does not follow a pattern, being reported GBS before or after classic respiratory symptoms. The severity of GBS itself does not seem to be greater due to Covid-19 and cases of flaccid facial paralysis after GBS was reported. The postinfectious pattern has dominated the cases, but it would not be surprising to see a change in prevalence to the parainfectious pattern. Futher studies are needed to clarify the relationship between SARS-CoV-2 infection and GBS. The impact of COVID-19 in the context of the health system required knowledge about proper diagnosis and treatment. In addition, the current literature reveals the possible association of the disease with involvement of the central nervous system, such as the presentation of Guillain-Barré syndrome. There are still precise studies to determine and confirm a possible association to establish an early diagnosis and propose the correct treatment.

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