LUMEN ET VIRTUS

Mechanisms Underlying Co-Infection Between COVID-19 and Guillain-Barré Syndrome: Susceptibility, Disease Progression, and Clinical Impact – A Systematic Review

https://doi.org/10.56238/levv15n39-191

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ABSTRACT

Objective: To analyze the complex synergistic interaction between Covid-19 and Guillain-Barré Syndrome (GBS), exploring the clinical and epidemiological implications of this co-infection. It also seeks to evaluate the diagnostic and therapeutic challenges faced by co-infected patients and to discuss public health strategies. Methodology: It is a systematic review focused on understanding the main aspects of Covid-19 co-infection and Guillain-Barré Syndrome (GBS). The research was guided by the question: 'What are the biological and immunological mechanisms underlying the interaction between SARS-CoV-2 and GBS and how do they affect susceptibility, disease progression and clinical manifestations of patients?'. To find answers, we searched the PubMed database using four descriptors combined with the Boolean term "AND": Guillain-Barre Syndrome, COVID-19, SARS-CoV-2, and COVID-19 Vaccines. This resulted in 562 articles. 14 articles were selected for analysis. Results: The reviewed evidence shows a significant association between COVID-19 and the development of Guillain-Barré Syndrome (GBS), especially in older men. The pathogenesis suggests that the inflammatory response triggered by COVID-19 may contribute to the emergence of GBS. The infection aggravates respiratory complications in patients with GBS, increasing the need for early ventilation. Immunomodulatory therapies, such as intravenous immunoglobulin (IVIg), are effective and safe in the management of these patients Conclusion:The review highlights the importance of early diagnosis and close clinical monitoring to improve outcomes.

Keywords: COVID-19, Guillain Barré Syndrome, Complications.

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INTRODUCTION

SARS-CoV-2 is a positive-stranded RNA virus, surrounded by a lipid layer, belonging to the Coronaviridae family and the genus Betacoronavirus. Related SARS-CoV-2, SARS-CoV-1, and MERS-CoV share several characteristics, including severe disease outcomes. SARS-CoV-2 has a genome of approximately 30 Kb that encodes 29 proteins, four of which are structural proteins (envelope, membrane, nucleocapsid, and spike), 16 non-structural proteins, and nine accessory proteins. On December 31, 2019, the World Health Organization (WHO) contacted China to clarify reports that were being circulated about a cluster of viral pneumonias in Wuhan. These pneumonias have been attributed to a new strain of coronavirus, called SARS-CoV-2. The rapid worldwide spread of SARS-CoV-2 led the World Health Organization (WHO) to declare the SARS-CoV-2 outbreak a global pandemic on March 11, 2020 (MAKHLUF; MADANY, 2021) (PIMENTEL et al., 2023).

SARS-CoV-2 infections usually manifest with a variety of clinical symptoms ranging from fever and chills, cough, shortness of breath, loss of taste and smell, to fatigue, pain and persistent chest pressure, difficulty breathing, culminating in severe acute respiratory syndrome and death. After the emergence of COVID-19, the world faced an unprecedented pandemic. The repercussions of this disease in the short, medium and long term are still being investigated. There is increasing and widespread attention to the neurological complications associated with SARS-CoV-2 infections, which include symptoms such as headache, dizziness, altered mental status, seizures, ataxia, smell and taste deficits, and Guillain-Barré syndrome (GBS) (MAKHLUF; MADANY, 2021) (PIMENTEL et al., 2023).

Guillain-Barré Syndrome (GBS) is characterized as a post-infectious immune-mediated syndrome affecting the peripheral nerves and nerve roots, and is estimated to affect 1.1–1.8 per 100,000 people per year. This is due to molecular mimicry triggered by a previous infection, which results in the formation of anti-ganglioside antibodies that attack proteins present in the axonal membrane. This aggression causes a rapidly progressing ascending flaccid paresis, which can affect the sensory fibers and cranial nerves. It is considered a demyelinating disease because the lesions mainly affect the myelin of the peripheral nerves, causing paresis, muscle weakness, and even bilateral ascending paralysis. If the nerve injury reaches the diaphragmatic nerves, the patient may experience respiratory symptoms ranging from mild respiratory failure to the need for invasive ventilatory support (PIMENTEL et al., 2023) (GITTERMANN et al., 2020).

An overall GBS prevalence of 0.15‰ is reported in the COVID-19 population (including hospitalized and non-hospitalized patients), corresponding to 15 GBS cases per 100,000 SARS-CoV-2 infections. The estimated prevalence of GBS among total hospital and neurological admissions associated with COVID-19 was 0.4% and 7.6%, respectively. In addition, an approximately threefold

increase in the likelihood of AIDP has been documented among patients infected with SARS-CoV-2 compared to contemporary or historical uninfected controls (PALAIODIMOU et al., 2021).

GBS-associated COVID-19 cases followed a similar epidemiological pattern, with older men, with an average age of 61 years, being affected more frequently than women, in a ratio of almost 2:1 in case series (Pimentel et al., 2023). Similarly, the interval between COVID-19 infection and the onset of GBS symptoms is, on average, 14 to 19 days (GOMEZ et al., 2023).

The spectrum of features presented related to COVID-19-induced GBS can range from respiratory symptoms specific to COVID-19 disease to neurological features that may be sequelae resulting from the development of GBS in the context of previous COVID-19 infection. These include fever, dyspnea, cough, headache, diarrhea, weakness, dysphagia, altered sensations, loss of reflexes. Atypical features, such as dysautonomia, asymmetric pain distribution, and ataxia, may also raise initial suspicions (SHEIKH et al., 2021).

Angiotensin-converting enzyme 2 (ACE2) acts as a functional receptor for SARS-CoV-2 in human tissues. Considering the similarity in the sequencing of the spike proteins of SARS-CoV and SARS-CoV-2, it has been suggested that SARS-CoV-2 also uses ACE2 as a functional receptor. Potential mechanisms by which SARS-CoV-2 can cause neurological damage include the virus's binding to ACE2 at the blood-brain barrier, allowing it to enter the central nervous system, as well as the existence of hematogenic, transcriptional, and neuronal retrograde spread pathways (GITTERMANN et al., 2020).

The aim of this article is to analyze the complex synergistic interaction between SARS-CoV-2 infection and GBS, exploring the clinical and epidemiological implications of this co-infection. It also seeks to evaluate the diagnostic and therapeutic challenges faced by co-infected patients, seeking to ensure the improvement of clinical outcomes.

METHODS

This is a systematic review that seeks to understand the main aspects of the co-infection present between SARS-CoV-2 and GBS, as well as to demonstrate the pathophysiological mechanisms and clinical manifestations that appear concomitantly with the condition, aiming to ensure a greater clinical elucidation of these pathologies. For the development of this research, a guiding question was elaborated through the PVO (population, variable and objective) strategy: 'What are the biological and immunological mechanisms underlying the interaction between SARS-CoV-2 and GBS and how do they affect susceptibility, disease progression and clinical manifestations of patients?'

The searches were carried out through searches in the PubMed Central (PMC) databases. Four descriptors were used in combination with the Boolean term "AND": Guillain-Barre Syndrome,

COVID-19, SARS-CoV-2, and COVID-19 Vaccines. The search strategy used in the PMC database was: (Guillain-Barre Syndrome) AND (COVID-19), (Guillain-Barre Syndrome) AND (SARS-CoV-2) and (Guillain-Barre Syndrome) AND (COVID-19 Vaccines). From this search, 562 articles were found, which were subsequently submitted to the selection criteria. The inclusion criteria were: articles in English, Portuguese and Spanish; published in the period from 2019 to 2024 and that addressed the themes proposed for this research, in addition, review, observational and experimental studies, made available in full. The exclusion criteria were: duplicate articles, available in the form of abstracts, that did not directly address the proposal studied and that did not meet the other inclusion criteria.

After associating the descriptors used in the searched databases, a total of 562 articles were found. After applying the inclusion and exclusion criteria, 33 articles were selected from the PubMed database, and a total of 14 studies were used to compose the collection.

DISCUSSION

A significant finding was that SARS-CoV-2 acts through angiotensin-converting enzyme-2 (ACE2), which is expressed in type II pneumocytes, vascular endothelium, cardiomyocytes, smooth muscle cells, and enterocytes. This enzyme functions as a receptor for the virus to enter host cells; thus, the ability of SARS-CoV-2 to infect cells in vitro is thought to depend on ACE2 expression. The S protein in its RBD-binding domain demonstrates high affinity for human ACE2, giving it a high potential for infection by this route. By penetrating the host cell, SARS-CoV-2 initiates preparation for active replication. With the release of new viral copies, this process causes pyroptosis in the infected cell and, consequently, the release of damage-associated molecular patterns (DAMPs) (PIMENTEL et al., 2023).

This infectious process causes lung cell death due to the activation of a local immune response, which begins with the sensitization of macrophages and monocytes that react to the release of cytokines and through adaptive T and B lymphocytes. Thus, if the process is not effective, subsequent pyroptosis causes the DAMPs and PAMPs to be recognized and thus the inflammatory process to be prolonged. This process leads to increased secretion of the pro-inflammatory cytokines IL-6, IFNɣ, MCP1 and IP-10, which further recruit the immune system and thus aggravate the inflammatory process. For this reason, this high degree of cytokine secretion in response to SARS-CoV-2 infection uncontrols the immune system, which can result in a cytokine storm and sepsis symptoms, which are the cause of death in 28% of infected individuals. Many human viruses (including coronaviruses) possess tropism and neuronal invasion properties with the potential to cause other disorders. In addition, regarding the inflammatory aspect of a cytokine storm, it has also

been shown that the neurological manifestations of COVID-19 arise from inflammatory cascades, that is, from the presence of a cytokine storm (PIMENTEL et al., 2023).

The transmigration of SARS-CoV-2 to the nervous system implies serious neurological pathologies, such as ischemic changes of neurons, demyelination of nerve fibers, and diseases such as polyneuropathy, encephalitis, and aortic ischemic stroke. In recent months, there have been increasing reports showing the association and parainfectious nature between Guillain-Barré syndrome (GBS) and SARS-CoV-2. COVID-19 is postulated to trigger the onset of GBS in a similar way to cytomegalovirus, Epstein-Barr virus, Middle East Respiratory Syndrome (MERS), Hepatitis E, and Zika virus, contributing to the etiology of GBS through autoimmune dysregulation and increased cytokine release storm (CRS) (BENTLEY et al., 2022).

GBS is an acute monophasic paralyzing disease, usually caused by a previous infection. It occurs all over the world and affects all age groups. Several mechanisms have been proposed in the pathogenesis of GBS. One proposed mechanism for GBS is that an antecedent infection evokes an immune response, which in turn cross-reacts with peripheral nerve components due to the sharing of cross-reactive epitopes (molecular mimicry). The end result is acute polyneuropathy. This immune response can be directed at the myelin or peripheral nerve axon. The second proposed mechanism is immune reactions directed against epitopes on the surface membrane of Schwann cells or in myelin, which can cause AIDP. Both cellular and humoral immune responses participate in the process. Invasion by activated T cells is followed by macrophage-mediated demyelination, with evidence of complement and immunoglobulin deposition in myelin and Schwann cells. The third proposed mechanism is immunological reactions against epitopes contained in the axonal membrane that cause the acute axonal forms of GBS: AMAN and AMSAN. The pathophysiology of these variants is better understood than that of AIDP (ELZOUKI et al., 2021).

There are four types of Guillain-Barré syndrome that present in different forms. The first is AIDP (Acute Inflammatory Demyelinating Polyneuropathy). The demyelinating inflammatory process is suspected to begin at the level of the nerve roots, leading to the slowing of electrophysiological conduction with conduction blockages, causing extreme muscle weakness. Remyelination can occur in the peripheral nerves. It is the most common subtype of this syndrome. The second variant is Acute Motor Sensory Axonal Neuropathy (AMSAN), which is the most severe form of AMAN (Acute Motor Axonal Neuropathy). The sensory fibers of the motor neuron are more likely to be affected, with axon degeneration, causing delay and incomplete recovery, which may be reversible or irreversible. Clinically, it resembles Acute Motor Axonal Neuropathy, but with more sensory symptoms (PATNAIK, 2021).

The third is Miller Fisher Syndrome (MFS), which is characterized by the presence of hyporeflexia, accompanied by bilateral ophthalmoplegia and ataxia. Other less common

presentations include facial diplegia or pharyngeal-cervico-brachial paresis. Antibodies against GQ1b (a ganglioside component of the nerve) are present in most patients of this variant. Anti-GQ1b ganglioside is commonly an antigenic target that is not proportionately evident in the motor nerves innervating the extraocular muscles. The last variant is AMAN (Acute Motor Axonal Neuropathy), which is distinguished from Acute Inflammatory Demyelinating Polyneuropathy by the selective involvement of motor nerves and the electrophysiological pattern of axonal involvement. (PATNAIK, 2021) (GOMEZ et al., 2023).

Regarding the distribution of electrophysiological variants of GBS, it was evidenced that GBS associated with COVID-19 manifests predominantly with IADP. In addition, there were reports, albeit to a lesser extent, of AMAN, AMSAN, SMF, and PCB (PIMENTEL et al., 2023) (SRIWASTAVA et al., 2021).

The clinical features of Guillain-Barré after COVID-19 are generally similar to those presented by patients who have developed this syndrome from other causes. In this context, the patients analyzed had decreased strength, predominantly distal, of the limbs with an upward evolution, in addition to paresthesia, tactile and painful hypoesthesia, hyporeflexia or areflexia, and changes in the cranial nerves (PIMENTEL et al., 2023).

The diagnosis of GBS is established based on criteria proposed by the US National Institute of Neurological Disorders and Stroke (NINDS), which defines findings as mandatory, strongly associated with the disease and, finally, those that should cause diagnostic doubt when present. The mandatory characteristics for the diagnosis to be made are progressive weakness of the limbs, accompanied by decreased reflexes in the affected limb. Factors supporting diagnosis involve progression of up to four weeks, symmetry of motor and sensory deficit, mild sensory involvement, cranial nerve involvement (mainly VII), onset of recovery four weeks after cessation of progression, autonomic dysfunction, absence of fever at onset, albuminocytologic dissociation in CSF, and slow or blocked nerve conduction for several weeks on electroneuromyography. Among the factors that cast doubt on the diagnosis are marked asymmetric weakness, initial or persistent visual and/or intestinal dysfunction, elevated CSF lymphocyte count, and well-demarcated sensory level. Isolated sensory involvement or explanation of the best condition by another neuropathy excludes the diagnosis (PIMENTEL et al., 2023).

The overlap of respiratory paralysis in GBS and COVID-19 infection makes it extremely important for clinicians to diagnose and treat GBS early in all COVID-19 patients, recognizing that respiratory compromise due to GBS can be rapidly progressive but treatable with a high success rate in COVID-19 patients (SRIWASTAVA et al., 2021).

In Spain, investigations reported 11 cases of GBS among 71,904 patients treated in 61 different Spanish emergency departments, again indicating a higher relative frequency of GBS of

0.15% in patients with COVID-19 compared to 0.02% in non-COVID-19 patients. With the increase in the number of case reports in the literature and in an effort to examine the strength and clinical characteristics of the link between GBS and COVID-19, studies have performed a detailed analysis of 37 cases of GBS associated with COVID-19. In this retrospective review, 37 patients were evaluated, of whom 65% were male and 90% were 50 years of age or older. More than a third required mechanical ventilation. The time to peak of neurological symptoms in 16 patients with available data ranged from 1.5 to 10 days, with a mean of 5 days (MAKHLUF; MADANY, 2021).

In a study conducted, five patients with GBS after the onset of Covid-19 were analyzed. Early signs included weakness and paresthesia in the lower extremities in four patients and facial diplegia, followed by ataxia and paresthesia in one patient. In summary, flaccid tetraparesis or tetraplegia evolved from 36 hours to 4 days in four patients; three required mechanical ventilation. The interval between the onset of Covid-19 symptoms and the first signs of GBS ranged from 5 to 10 days. This interval is similar to that seen in GBS that occurs during or after other infections. As in previous studies, the authors suggest that a possible link between these two diseases is the fact that COVID-19, by stimulating inflammatory cells, produces several inflammatory cytokines, resulting in immune-mediated processes (MEDEIROS et al., 2021).

The majority of patients with concomitant COVID-19 and GBS were male and older than 40 years, which likely reflects the underlying demographics of COVID-19 diagnosed early in the pandemic; i.e., older age and male gender are risk factors for more severe COVID-19, and the incidence of GBS increases with age. In addition, men have an increased susceptibility to binding of the SARS-CoV-2 spike glycoprotein (S) and angiotensin-converting enzyme 2 (ACE2) receptors on host cells, causing downregulation in ACE2. ACE2 downregulation may be detrimental to patients who may already be ACE2 deficient (BENTLEY et al., 2022) (CARESS et al., 2020)

SARS-CoV-2 is reported to cause highly lethal acute pneumonia in 15% of cases, with clinical features similar to those reported for SARS-CoV and MERS-CoV, but with different phenotypes and varied presentation. In addition, a proportion (30%) of patients with SARS-CoV-2 pneumonia may share clinical and physiological features with severe ARDS: severe hypoxemia, low respiratory system compliance (<40 mL/cmH2O), and diffuse bilateral infiltrates on CT scan. In patients with GBS, the rapid development of severe diaphragmatic weakness may result in the appearance of areas of basal atelectasis, leading to reduced pulmonary compliance and increased intrapulmonary shunt. These changes, associated with COVID-19 pneumonia, can cause a rapid worsening of respiratory mechanics and hypoxemia, with the appearance of alveolar hypoventilation and hypercapnia. Therefore, in patients with SARS-CoV-2 infection, when the diagnosis of GBS is established or even suspected, the evaluation of the respiratory muscles is essential from a clinical point of view to decide the timing of tracheal intubation. A VC of less than 20 mL/kg, a maximal

inspiratory pressure (MIP) of less than –30 cmH2O, a maximal expiratory pressure of less than 40 cmH2O, or a reduction in VC of more than 30% in 24 hours are good indicators of the need for invasive procedures such as MV (GALASSI; MARCHIONI, 2020).

The basic treatment of GBS is immunomodulation, mainly through removal of immunoglobulins by plasmapheresis (PLEX) or increased degradation with intravenous immunoglobulins (IVIG). Both demonstrated practically equal efficacy, improving the speed of recovery, but not necessarily the progression of the disease (GOMEZ et al., 2023).

IVIG is used to treat patients with GBS associated with thromboembolic complications, as COVID-19 is linked to a prothrombotic state. Plasma exchange therapy (PLEx) is also used to treat GBS; however, PEx may affect the balance of clotting factors, possibly resulting in thromboembolism. IVIg and PEx are the two therapies recommended as a treatment for SARS-CoV-2-induced cytokine storm by directly removing cytokines from the body. Healthcare workers are exposed for a longer time to COVID-19 infected patients during PLEx therapy due to the risk of hemodynamic conditions in critically ill patients. Therefore, it is now preferable, unless there are evident contradictions such as severe coagulopathy, to treat GBS associated with COVID-19 patients with IVIg therapy. The conventional IVIg protocol of 0.4 g/kg/day for 5 days is often preferred due to its simplicity and availability. (SHARMA et al., 2023).

CONCLUSION

Based on the reviewed evidence, it is possible to observe a relevant association between COVID-19 infection and the development of Guillain-Barré Syndrome (GBS). The studies analyzed indicate that GBS may occur more frequently in patients with COVID-19 than in those without the infection, especially in older and male individuals. The proposed pathogenesis suggests that COVID-19, through the stimulation of inflammatory cells, triggers immune responses that may contribute to the development of GBS. In addition, COVID-19 aggravates respiratory complications in patients with GBS, increasing the need for early mechanical ventilation. Immunomodulatory therapies, such as intravenous immunoglobulin (IVIg), are preferred for the management of these patients, given their efficacy and safety, especially in a prothrombotic setting. The systematic review emphasizes the importance of early diagnosis and close clinical monitoring to improve outcomes in these patients.

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