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DIAGNOSIS OF GUILLAIN BARRE SYNDROME ASSOCIATED WITH SARS-COV-2 INFECTION

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ABSTRACT

The pandemic caused by the COVID-19 infection has left a large number of sequelae in different organs and tissues, these sequelae not only occurred in the respiratory system, complications were also identified in the nervous system. The increase in cases of Guillain Barré syndrome during the emerging pandemic in 2020 gave rise to the possibility that SARS-CoV-2 is a trigger for neurological manifestations.

Neurological clinical manifestations of the autoimmune type were reported, among which it was reported about patients with GBS linked to SARS-CoV-2. GBS is a polyneuropathy that affects the myelin sheath of the nerves, which is why it is considered demyelinating and has been related to infectious processes of viral and bacterial etiology, so it is possible that COVID-19 participates as a causative agent.

Therefore, it seeks to collect information regarding the association between GBS and the SARS-CoV-2 virus as well as its symptoms, diagnosis and treatment.

Key words: COVID-19, GBS, SARS-CoV-2, Guillain Barré syndrome, polyradiculoneuropathy.

INTRODUCTION

In 2020, a pandemic occurred due to SARS-Cov2, resulting in millions of deaths. SARS-Cov-2 infection, although it mostly affects the respiratory system, can cause sequelae or neurological disorders, taking into account Guillain Barre syndrome as the most frequent neurological involvement of post-infectious onset (1,2)

Guillain Barré syndrome was first described in 1834. It is a rare disease, where the immune system destroys the peripheral nerves of the individual, this in turn generates the main symptoms and signs such as: bilateral weakness in the extremities, hyporeflexia, decreased reflexes and tingling. These manifestations mostly go upwards or from distal to proximal (3).

The annual incidence of Guillain Barré syndrome according to the Pan American Health Organization, 2016, is 0.4 to 4 cases per 100,000 people. It also shows that the male population is more likely to acquire the syndrome compared to women (4).

Approximately 72 cases from 52 studies were reported in 2020 globally of patients who developed Guillain Barré syndrome after 2-33 days of presenting symptoms of SARS-Cov-2 with an average of 14 days (5). In developed countries, Guillain Barre syndrome is the most common cause of flaccid paralysis (6).

The first case worldwide of GBS (Guillain Barré Syndrome) associated with SARS-Cov-2 was published in 2020, it is a 61-year-old female patient who had made a trip to Wuhan, China. In Italy at the height of the pandemic, they increased from 0.67 to 4 cases per month of patients with GBS. There were also cases in a Latin American country such as Mexico where 7 cases of GBS with SARS-Cov-2 were reported in a health center (7).

The Ministry of Public Health of Ecuador (MSP) reported 185 to 197 patients with this syndrome in the year 2013-2014. There is currently no data on the number of people with GBS who have been infected with COVID-19. These data are necessary to be able to associate GBS with coronavirus (8). Today it is recognized that there is a link between this syndrome and SARS-Cov-2, therefore it is necessary to conduct studies in Ecuador about its incidence in order to recognize the clinic of patients infected with SARS-Cov-2 and who are presenting symptoms and signs of GBS (9).

According to the World Health Organization (WHO), 3% to 5% of patients die from complications such as myocardial infarction, paralysis of the breathing muscles, thrombosis at the pulmonary level and septicemia (10).

In patients who do not die, they may be left with a high degree of disability that affects their quality of life. Therefore, seeing an increase in cases worldwide of GBS associated with SARS-Cov-2, it is sought to properly recognize this syndrome and apply a treatment to avoid subsequent complications. What are the diagnostic methods of Guillain Barre Syndrome associated with SARS-Cov-2 infection? From the academic point of view, it will contribute to the scientific development regarding the clinical data and diagnoses of Guillain Barré syndrome due to SARS-Cov-2. It will also encourage future research on the incidence in the country.

This research seeks to obtain information about the causal relationship between SARS-Cov-2 and GBS along with its diagnosis in order to be useful in the health field in terms of epidemiological issues and early detection of this syndrome in patients infected with the coronavirus. Because the pandemic has left various sequelae and among the least studied are the neurological disorders after the nascent infection at the end of 2019, it also becomes useful to investigate this issue.

WORK DEVELOPMENT

Association of GBS and SARS-Cov-2

The SARS-Cov-2 pandemic generated an increase in cases of patients with peripheral neurological sequelae such as GBS. Approximately 73 cases from 52 studies were reported in 2020 globally of patients who developed Guillain Barré syndrome after 2 to 33 days with an average of 14 days after presenting symptoms of SARS-Cov-2 (11,12).

The first worldwide case of GBS associated with SARS-Cov-2 was published in 2020, it is a 61-year-old female patient who had made a trip to Wuhan, China whose clinical manifestations were weakness and absence of reflexes (13).

GBS manifests mainly with flaccid paralysis, this type of paralysis is symmetrical and ascending, that is, it starts from the most distal areas to the proximal regions of the organism (14). The flaccid paralysis described is accompanied by paresthesias and areflexia. The clinical picture is usually progressive, but it can generate severe symptoms within a few hours (15).

70% of GBS cases are of acute post-infectious origin, that is, this syndrome appears between 1 to 4 weeks after a gastrointestinal or respiratory infectious process. Among the main microorganisms that generate GBS are: Campylobacter Jejuni, Mycoplasma Pneumoniae, human immunodeficiency virus (HIV), Cytomegalovirus, Chikungunya virus, Zika virus, among others. So this syndrome could be triggered by COVID-19 infection (15).

There is a strong association between both diseases because patients with GBS also had active SARS-Cov-2 infection or had already overcome the infection. All this confirmed with RT-PCR tests with nasopharyngeal swab or positive IgG and IgM antibodies for COVID-19 (16).

GBS has been associated with SARS-Cov-2 mainly to a demyelinating variant, that is, it destroys the myelin sheaths of neurons and is called acute inflammatory demyelinating polyneuropathy (AIDP) and represents 33.33% of all subtypes recorded in case reports and series (16).

After AIDP the other most frequent variants of GBS were: Acute motor sensory axonal neuropathy (AMSAN) with 11.43%, Acute motor axonal neuropathy (AMAN) with 8.57% and Miller Fisher syndrome with (MFS) 6.67%. The age group in which more cases occurred was in the age range of 50 to 59 years with an average of 56 years with 27.62%. Males are the most frequent population with 59.05% (17).

Physiopathology

SARS-Cov-2 is considered neurotropic due to its neuroinvasive characteristics. An experimental study evaluated the degree of multiplication of the virus and the cellular lesion of SARS-Cov-2 in different cell types. The results described greater viral replication at the neuronal level by SARS-Cov-2 compared to SARS-Cov (18).

According to the structure of SARS-Cov-2 it has a protein called Spike (S) which binds to the membrane receptor of the host cell known as ACE II whose acronym refers to the angiotensin II converting enzyme, in this way it manages to internalize to the cells. The ACE II receptor is found in different cell lines, however these are mainly located in type II pneumocytes, enterocytes and endothelial cells (19).

In an experimental study conducted in mice, involvement of the brainstem and cerebral cortex was observed because these tissues contained a large number of ACE II receptors. Therefore, entry of the virus into the nervous system is considered feasible (20).

The virus could directly or indirectly injure the nervous system, directly infect cells and indirect injury would be generated by the inflammatory process caused by the release of pro-inflammatory cytokines such as interleukin 1 and interferon gamma. Consequently, the SARS-Cov-2 virus could affect the central nervous system and the peripheral nervous system (21).

According to several studies, the mechanism by which GBS associated with SARS-Cov-2 occurs is by a post-infectious process rather than by a para-infectious mechanism. That is, a PCR test for SARS-Cov-2 was performed in the cerebrospinal fluid (CSF) and most patients obtained a negative result and neurological symptoms such as bilateral weakness in the lower extremities and reduction in sensitivity appeared after having resolved the picture of coronavirus pneumonia (22).

One of the mechanisms by which viruses can enter the nervous system is through the invasion of the olfactory tract through its neuroepithelium, where it travels retrograde by means of axonal transport. The entry of the virus occurs through the olfactory bulb generating demyelination which translates clinically into anosmia or temporary ageusias (23).

Possibly the pathogenesis generated by GBS prior to a SARS-Cov-2 infection would be through molecular mimicry. This is based on the fact that there are autoantibodies generated by the presence of infectious antigens, which would be known as the epitope (24). Based on this, once the infectious condition generated by SARS-Cov2 is resolved, the immune system attacks neurons or peripheral nerves because these antibodies cross-destroy neurons because the latter have a component similar to the antigens of certain infectious microorganisms (25).

Autoantibodies known as ganglioside antibodies attack gangliosides of the nervous system, the latter being sphingolipids containing sialic acid. Gangliosides are mostly located in Ranvier's nodules, Schwann cells, and nerves (26).

SARS-Cov-2 also contains sialic acid residues so the immune system recognizes structures containing this component as foreign. As already described, the nervous system also contains sialic acid, therefore there is a neuronal attack by the immune system damaging the nerve sheath, the latter being important for the conduction of nerve impulses (26).

Each subtype presents a pathogenic focus and it is described in Table 1.

Table 1. Pathogenic focus according to Guillain-Barré syndrome subtype

Subtype	Pathology
AIDP	There is diffuse injury to the myelin sheath of nerves and attack on Schwann cells. There is activation of the immune system: macrophages along with lymphocyte infiltration.
LOVE	The lesion is located in Ranvier's nodules with a large number of periaxonic macrophages and few lymphocytes.
AMSAN	Similar to the AMAN subtype more lesions in the nerves and sensory roots
SMF	Insufficient cases studied. It has characteristics similar to those of AIDP.

Source: Authors.

Clinical manifestations

The main clinical manifestations were hyporeflexia with 88.57%, weakness of the lower limbs with 75.24%, sensory alterations with 51%, facial weakness with 29.52% and alteration in the cranial nerves with 20.95%. According to the patient's clinic and other complementary tests, it was determined that the most frequent variant was AIDP (27).

Studies have been conducted on the signs and symptoms present before the patient develops GBS, among which the most frequent are fever (55%), dry or wet cough (51%) and respiratory failure (27%); in addition, patients presented a severe case of pneumonia due to COVID-19 infection as a history (27).

Another symptom is pain that occurs at the level of the weakened limbs and there is also usually autonomic dysfunction where there are oscillations of blood pressure and alterations in myocardial rhythm (27). 30-40% of patients may be complicated by vegetative dysautonomia. When there is incongruity between chest imaging and the patient's respiratory failure, in these cases it should be considered as an alternative to GBS as part of the differential diagnosis (28).

In cases where there is respiratory failure, it is because the disease has injured the diaphragmatic nerves, which could force the patient to require ventilatory assistance (28).

GBS has several subtypes each with certain clinical features that are detailed in Table 2.

Table 2. Clinical picture of Guillain-Barré syndrome subtypes

GBS subtype	AIDP	LOVE	AMSAN	SMF	vFCB
Clinical picture	It is a sensory motor GBS, autonomic dysfunction or alteration and deficit in the cranial nerves.	It is a motor GBS and the deficit or involvement of the cranial nerves is rare. It does not present sensory alterations.	The clinical picture is similar to AMAN (severe), characterized by sensory deficit.	It is characterized by three classic manifestations: ataxia, ophthalmoplegia and absence of reflexes.	It is characterized by significant weakness in the facial muscles, at the level of the oropharyngeal, neck and shoulders.

Source: Authors.

Diagnosis

The diagnosis of GBS associated with SARS-Cov-2 is the same as GBS alone. The diagnosis is mostly clinical, so other complementary tests would only support the diagnostic suspicion (29).

Diagnostic criteria

For the diagnosis of GBS, the clinical criteria of Asbury & Cornblath were used, which were exposed in 1981, then reformed and published in 1990. These criteria contain the following parameters:

characteristics that are necessary, supportive, questioning and ruling out the diagnosis. However, they are no longer used due to their limited usefulness in clinical practice (30).
In 2014 the Brighton criteria emerged which are used to date and have been validated in the following countries: Malaysia, Denmark, Bangladesh, India, Iran and Japan. These criteria were studied and validated the same year, a study was conducted with the aim of identifying which are the fundamental keys of these criteria that are requirements to be met for the clinical diagnosis of GBS (30).
The results favored the validation of these criteria because the patients studied presented localized weakness in the legs, osteotendinous reflexes decreased by 91%. Nadir was achieved in 80% at 14 days, 97% at 28 days. 95% of patients had monophasic disease and only 10% were subject to a fluctuation associated with treatment. These criteria are grouped into certainty levels which are summarized in Table 3 (30).
The diagnosis of GBS is made according to the clinical history and neurological examination, it can be complemented with CSF examination and electrophysiological studies, these are the main diagnostic tools of this syndrome (30).

Laboratory studies

Laboratory tests should be performed in patients suspected of GBS, including: blood count and blood chemistry containing electrolyte, glucose, renal function, and liver function. These tests make it possible to exclude other pathologies such as infections or electrolyte and/or metabolic disorders that cause acute flaccid paralysis (31).
Tests can be performed to identify any infection prior to the neurological clinical picture, however it does not contribute to the diagnosis. In this case, this information allows us to establish a fundamental epidemiological link between the most frequent microorganisms that trigger GBS, such as Zika virus and Campylobacter jejuni (31).
The antiganglioside antibody test is quite limited because only anti-GQb1 antibodies are present and positive in 90% of cases of patients with the MFS subtype, consequently the diagnostic value of this test is elevated when it is suspected that the patient is affected with this variant of GBS and not in the classic forms or other subtypes (31).

Cerebrospinal fluid test

Regarding CSF, albuminocytological dissociation was found, in 64% the values varied based on the time of sampling the sample. Therefore, it is recommended to obtain the sample after two weeks because 88% will be positive for albuminocytological dissociation (32).
This test is also used to rule out other causes of weakness as an alternative to GBS. Classically, GBS presents albuminocytological dissociation in the CSF, that is, an increase in proteins associated with normal amounts of cells. In the first week the protein concentration is usually normal in 30% of cases and in the second week after the disease in 10% of patients. Therefore, if protein levels are in normal amounts in the CSF does not preclude diagnosis (32).
Pleocytosis of 10 to 50 μl-1 cells are values that are consistent with GBS. If the cells in the CSF are above these values, alternative diagnoses should be considered (33).
It is considered a significant or marked pleocytosis when its concentration is greater than 50 μl-1 cells and this warns of other infectious, neoplastic and inflammatory diseases of the spinal cord or nerves such as polyradiculitis (33).
During the search for an association between GBS and SARS-CoV2, CSF was studied in order to determine the mechanism by which the virus could trigger the syndrome. In the CSF we sought to determine the presence of coronavirus-19, in most studies of patients the virus was not identified, so GBS was associated as a post-viral pathology. In addition, there was cytological dissociation of albumin, which is consistent with the diagnosis of GBS that occurs 7 days after the clinical picture (33).

Electrodiagnostic studies

Electrodiagnostic studies are not necessary for the diagnosis of GBS, but it is recommended that these studies be performed if available, because they become tools that allow identifying atypical

presentations of the syndrome. Therefore, this examination in patients with GBS exposes the subtype or variant of GBS (33).

Each subtype or variant presents characteristics in the results of the electrodiagnostic study, these stand out according to the pathogenic focus developed, these characteristics are summarized in Table 4 (33).

At the beginning of the disease the results may be normal, but these begin to alter when 14 days have passed after the onset of symptoms. There are early electrodiagnostic criteria among which are: conduction block, A waves, increased motor latencies at the distal level and disorders in late responses There is no international consensus regarding which criteria adequately classify the subtypes, and one third of patients diagnosed with GBS did not fit any of the criteria and were categorized as unexcitable. Therefore conducting this examination is controversial

Possible biomarker

A recent study identified the relationship between the ratio of neutrophils and lymphocytes to Guillain Barre syndrome known as neutrophil-lymphocyte index (NLR). Where the proportion known as NLR was higher in patients with GBS than in healthy patients. So it could be considered as a parameter, however, it requires more studies to be used as a new diagnostic method of this polyneuroradiculopathy (31).

Table 4. Electrodiagnostic study

Electrodiagnosis	According to this electrophysiological study it presents as demyelinating polyneuropathy.	According to this electrophysiological study, it is presented as axonal polyneuropathy with an action potential of the sensory part without alterations.	According to this electrophysiological study, it presents as axonal polyneuropathy with an altered sensory action potential with its absence or reduction.	According to this electrophysiological study it is presented without alterations, it is normal.	According to this electrophysiological study it is presented without alterations, it is normal. However, there are cases where there is an axonal pattern.
Antibodies	Unknown	GM1a, GM1b	GM1, GM1b	GQ1b, GT1a	WG1a

GBS: Guillain Barré syndrome
AIDP: Acute Inflammatory Demyelinating Polyneuropathy
AMAN: Acute motor axon neuropathy
AMSAN: Acute sensorimotor axon neuropathy
FMS: Miller-Fisher syndrome
vFCB: Pharyngo-cervico-brachial variant

Source: Authors.

Table 3. Brighton criteria		
CD Level 1	**CD Level 2**	**CD Level 3**
Flaccid weakness with bilateral involvement in the lower extremities; **And**	Flaccid weakness with bilateral involvement in the lower extremities; **And**	Flaccid weakness with bilateral involvement in the lower extremities; **And**
Reduction of deep tendon reflexes accompanied by weakness; **And**	Reduction of deep tendon reflexes accompanied by weakness; **And**	Reduction of deep tendon reflexes accompanied by weakness; **And**
Monophasic course and time between onset of lowest point of weakness and clinical plateau after 12 hours to 28 days; **And**	Monophasic course and time between onset of lowest point of weakness and clinical plateau after 12 hours to 28 days; **And**	Monophasic course time between onset of the lowest point of weakness and clinical plateau after 12 hours to 28 days; **And**
When an optional or alternate diagnosis consistent with the	When an optional or alternate diagnosis consistent with the weakness is not under consideration; **And**	When an optional or alternate diagnosis

weakness is not under consideration; **And** Cytoalbumin dissociation (is the increase in CSF proteins* along with a white blood cell count of <50 cells/µL; And Electrophysiological studies consistent with GBS	CSF leukocytes with figures of <50 cells/µl (with or without protein elevation at the CSF level); Or electrophysiological studies consistent with Guillain Barré syndrome if it was not possible to obtain the CSF sample for study or if the sample was taken but results are not yet available.	consistent with the weakness is not under consideration;
CD: Diagnostic certainty CSF: Cerebrospinal fluid		

Source: Authors.

Treatment

GBS does not have a curable treatment, it only involves a control of signs and symptoms of the disease to prevent its progression. The recommended treatment is intravenous administration of immunoglobulin or plasmapheresis (35).

Immunoglobulin therapy involves the administration of healthy antibodies from a donor and is administered intravenously. High doses of immunoglobulins can block antibodies that damage the peripheral nervous system leading to the clinical picture of GBS.

Intravenous immunoglobulin was administered in 56% of patients at doses of 0.4 g/kg daily for five days. In one patient this procedure generated erythema and an episode of presyncope. Another patient developed dyspnea and dysphagia.

Plasmapheresis is a process where the patient's plasma is changed for a superficial plasma and consists of eliminating the antibodies that cause demyelination and axonal damage. It is recommended to perform plasmapheresis as soon as possible, in a period of less than 7 days. In the case of needing mechanical ventilation, it is recommended to perform four to five plasmapheresis, which would give a better result in the resolution of the disease (32).

The plasmapheresis administered also generated adverse effects in a patient who had a cardiac arrest, so both intravenous immunoglobulin therapy and plasma exchange are two procedures that can present adverse effects.

Intravenous immunoglobulin and plasma exchange are equally effective as treatment for GBS. Plasmapheresis treatment of a five-day cycle was the most commonly applied in these patients (9).

Intravenous immunoglobulin treatment as well as plasmapheresis remains the recommended treatment for these patients, complemented by supportive care. About 80% of patients regain the ability to walk again 6 months after the disease began. Treatment with corticosteroids does not offer many results in terms of patient improvement and may even lead to delayed recovery (1,9).

Patients who evolved suddenly and severely required mechanical ventilation and therapeutic measures from the intensive care unit. Therefore, it is important to make an early diagnosis of this syndrome in order to provide early and timely treatment due to the substantial risk of morbidity and mortality (1).

CONCLUSIONS

COVID-19 is an infectious disease that has spread globally and can affect various devices and systems. Several studies showed the neurotropic capacity of the virus that could also affect the cells of the nervous system directly and indirectly.

GBS is considered to be generated by post-infectious autoimmune mechanism since it has been observed that patients presented negative tests for SARS-CoV-2 both in immunological tests and in RT-PCR at the CSF level. The pathophysiological mechanism by which the virus can generate GBS has not yet been fully elucidated, however it is important to recognize the typical clinical picture of the syndrome to provide timely care to the patient and avoid possible complications in the short and long term.

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GLOSSARY

GBS: Guillain Barré syndrome
SARS-Cov-2: Severe acute respiratory syndrome coronavirus type 2
CSF: Cerebrospinal fluid
NLR: Lymphocyte Neutrophil Index
GBS: Guillain Barré syndrome
AIDP: Exacerbated Inflammatory Demyelinating Polyneuropathy