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Sars-Cov-2 and its Relationship with the Development of Guillain Barre

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Abstract:
Guillain Barré syndrome is a rare pathology today, which attacks the peripheral nervous system and produces muscle weakness and even loss of sensitivity in patients. In recent years, a great association has been evidenced between patients admitted to the emergency service with COVID 19 disease, who later tend to develop this syndrome, which is why a bibliographic review is carried out in order to establish the relationship between the virus and the development of this pathology.

Keywords: Guillain-Barré syndrome, GBS, paralytic neuropathy, SARS-COV-2, covid 19.

Introduction

Guillain-Barré syndrome (GBS), the most common cause of paralytic neuropathy (1), is an inflammatory polyneuropathy that is characterized by acute onset, rapid progression, symmetrical muscle weakness, unstable ambulation, and hiccups or areflexia (2).

GBS has become one of the most common causes of subacute and flaccid paralysis, with a reported . However, the exact cause of GBS is unknown, but 50% to 70% of cases appear 1 to 2 weeks after a respiratory or gastrointestinal infection or other immune stimulus that induces an aberrant autoimmune response directed at peripheral nerves and their spinal roots. (3).

annual incidence of 0.5 to 2 cases per 100,000 people (4). The annual incidence rate increases

with age and it is rare to observe this syndrome in older children (5). Men are approximately 1.5 times more likely to be affected than women (6). Table 1 shows the main etiological factors associated with GBS, several studies have revealed associations with a few pathogens such as Campylobacter jejuni, which is the most frequently reported infection, being found in 25-50% of adult patients and is more frequent in Asian patients (7). In addition, other infections associated with GBS include cytomegalovirus, Epstein-Barr virus, measles, influenza A virus, and Mycoplasma pneumoniae (8), as well as enterovirus D68 (9) and Zika virus (10).

Table 1. Main etiological factors associated with Guillain-Barre syndrome

Infections	Bacteria *Campylobacter jejuni* *Mycoplasma pneumoniae* Viruses Cytomegalovirus Epstein–Barr virus Influenza A virus Enterovirus D68 Zika virus
Vaccines	Rabies vaccine Influenza A/H1N1 vaccine

GBS reaches its nadir within 2 weeks in 80% of cases, while progression beyond 4 to 5 weeks will facilitate another diagnosis (11). Sensory manifestations in the form of paresthesias can occur in 50% of patients and numbness occurs in 43%. Pain is characterized by being a relatively uncommon but recognizable manifestation in approximately 15% of cases (12). Half of the diagnosed patients develop dysfunctional autonomic diseases, the most frequent being gastrointestinal manifestations such as diarrhea and constipation in 15% of patients, followed by hyponatremia (15%), syndrome of inappropriate antidiuretic hormone secretion (5%). , bradycardia /5%) and urinary retention (4%). Other manifestations such as tachycardia, blood pressure instability, reversible cardiomyopathy, syncope and Horner's syndrome are rare (13). Cranial neuropathies can occur in up to 60% of patients and can involve multiple cranial nerves. Bulbar weakness, facial palsy, ophthalmoplegia, and hypoglossal nerve palsy are the most prevalent manifestations of cranial neuropathy (14) (Table 2).

Table 2. Clinical manifestations of GBS

Acute onset
Progressive monophasic illness up to 4 wk
Preceding infectious respiratory/gastrointestinal illness
Symmetrical upper and lower extremity weakness
Hypo/Areflexia
Paresthesias/numbness, pain (less common)
Cranial neuropathies (bulbar, facial, extraocular muscles)
Autonomic dysfunction (diarrhea/constipation, hyponatremia)

In terms of pathogenesis, Guillain-Barré syndrome is often an immune-mediated postinfectious nerve injury. There are likely to be three phenotypes D: purely demyelinating, purely axonal, and demyelinating with axonal involvement. The hypothesis about

immunopathogenesis can be seen in Figure 1. Although both elements of the immune response such as T cells and B cells play a role, the current understanding is that GBS is mediated by antibodies. Not all anti-ganglioside antibodies are neurotoxic, but antibodies that bind to GM1 or GD1 gangliosides activate complement, resulting in myelin destruction (15). The predominance of motor axonal involvement has led to the designation acute motor axonal neuropathy. Campylobacter jejuni is the main known instigator in the mechanism of infection, and molecular mimicry between C. jejuni has been found to be lipooligosaccharide and GM1 and GD1 (16). For those patients presenting with the ataxic sensory variant, the most commonly identified ganglioside antigen is GQ1b (17).

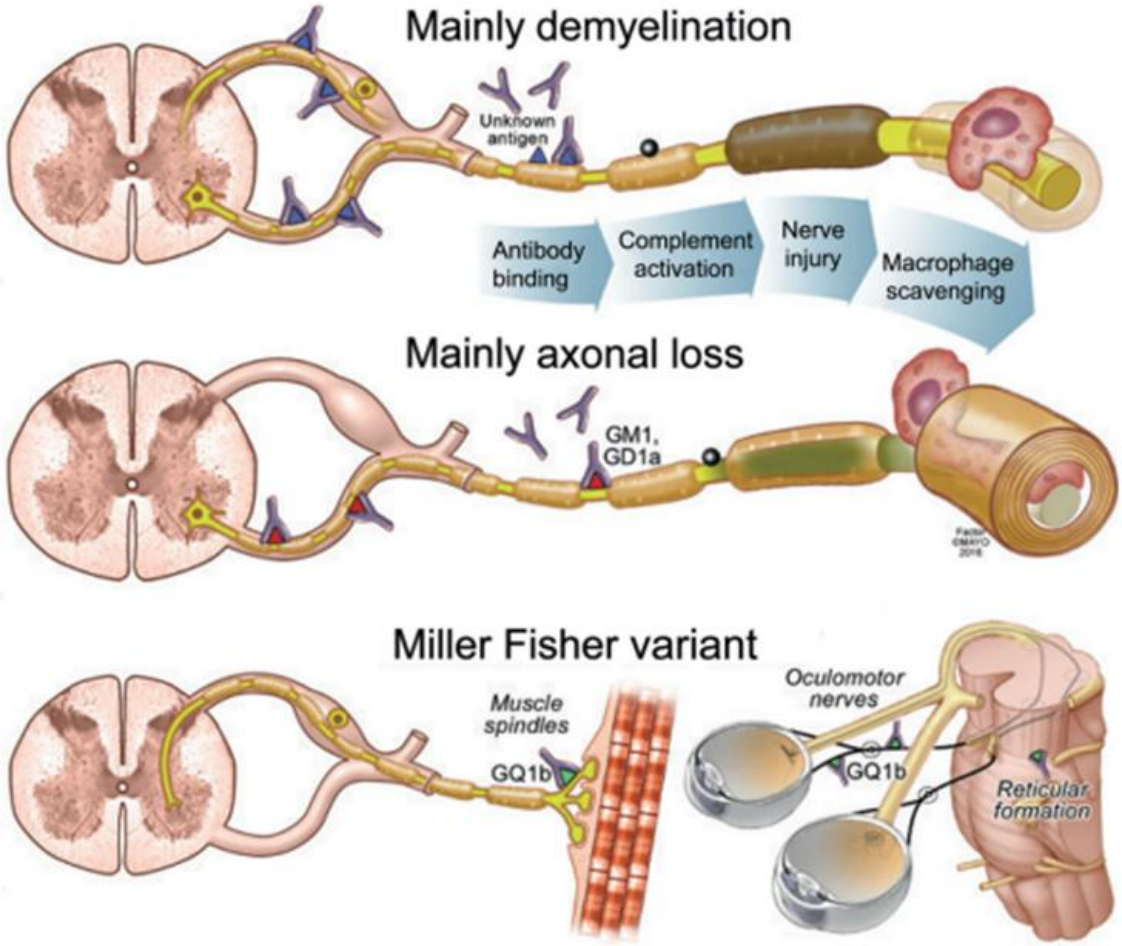

Figure 1. Current understanding of Guillain-Barré syndrome pathogenesis and clinical variants. In demyelinating Guillain-Barré syndrome, unequivocal antigens have yet to be identified but are inferred by complement activation, myelin destruction, and cleanup by macrophages. In axonal and Miller Fisher variants, specific gangliosides (GM1, GD1a, GQ1b) are targeted by immunoglobulins and share antigenic epitopes with various bacterial and viral antigens. These antigenic targets are at nodal structures, at roots, and located at the end organs. In Miller Fisher syndrome, the GQ1b antigen also exists within the brain stem. In this variant, the macrophages clean up the axon debris and come in from the nodes. Tomado de: Wijdicks, E, Klein, C. Guillain-Barré Syndrome. Mayo Clin Proc. 2017;92(3): 467-479.

Now, since the appearance of COVID-19, which includes neurological manifestations such as headache, dizziness, disorder of consciousness, acute brain disease, seizures, and ataxia in the central nervous system (CNS) (18), and likewise way it has effects on the peripheral nervous system (PNS) such as anosmia, ageusia, visual impairment, nerve pain and skeletal muscle (19). Therefore, since the start of the COVID-19 pandemic, there have been reports of the possible link between GBS and COVID-19 infection (20). The development of neurological symptoms at a time interval after infection is the classic GBS

phenotype. In most cases, the onset of GBS-related neurological symptoms was approximately 1 to 4 weeks after COVID-19 diagnosis (21). One of the most common neurological symptoms of GBS is acute muscle weakness. The pattern of muscle weakness can be helpful in diagnosing GBS (22). Therefore, limb weakness and acute flaccid quadriparesis have been observed in most GBS case reports after COVID-19 diagnosis in several studies (21). Therefore, the current study and the review of available information on the relationship between Guillain-Barre syndrome associated with COVID-19 infection is important.

Methodology

A detailed bibliographic search was carried out since 2015 of the most relevant published information in the PubMed, Scielo, Medline databases, national and international libraries specialized in the topics discussed in this review article. The following keywords were used: Guillain-Barré syndrome, GBS, paralytic neuropathy, SARS-COV-2, covid 19. The data obtained ranged from 5 to 21 records after using the keywords described above. The bibliographic search was carried out in English and Spanish, it was limited by year of publication and studies published from 2015 to the present were used.

Results

Sedaghat and Karimi in their case report describe a 65-year-old man admitted to the emergency room due to acute progressive symmetric ascending quadriparesis. The patient's neurological manifestations began with progressive acute weakness of the distal lower extremities, five days before admission. At that time, symptoms progressed from distal extremities to proximal extremities and he had been quadriplegic one day before admission. There was bilateral facial paresis. He had no urinary or fecal incontinence. Two weeks before hospitalization, the patient complained of cough, fever, and sometimes dyspnea. At that time, he was referred to an infectious disease specialist and diagnosed with COVID-19 after examining an oropharyngeal swab and a computed tomography (CT) scan of the chest. Reverse transcription polymerase chain reaction (RT-PCR) for COVID-19 was positive. At 9 days, the neurophysiological study was performed. Electrodiagnostic parameters demonstrated a decreased amplitude in the compound muscle action potential and no response in the sensory nerve action potential. Electromyography showed decreased recruitment. These findings are consistent with acute motor sensory axonal neuropathy, as can be seen in Table 3. Cerebrospinal fluid (CSF) analysis was not performed due to lack of consent. The patient received 0.40 g/kg/day of intravenous immunoglobulin for five days according to clinical manifestations related to GBS (23).

Table 3. Nerve conduction study parameters in the patient with GBS.

Nerve Stimulated	Stimulation Site	*Amplitude		Latency (ms)		Conduction velocity		F wave	
		RT	LT	RT	LT	RT	LT	RT	LT
Median (s)	Wrist	NR	NR	NR	NR	NR	NR		
Ulnar(s)	Wrist	NR	NR	NR	NR	NR	NR		
Sural (s)	Calf	NR	4.5	NR	2.00	NR	35		
Median (m)	Wrist	2.3	1.8	6.61	7.59			49	52
	AF	1.9	1.3	13.90	14.27	31	41		
Ulnar (m)	Wrist	4.7	4.4	4.17	4.69			41.9	48
	BE	4.6	3.5	8.22	8.52				
	AE	4.5	3.4	9.90	10.20	46	39		
Tibial (m)	Ankle	1.00	0.4	9.95	12.19			NR	NR
	Popliteal F.	0.90	0.4	20.63	27.03	29	21		
Peroneal(m)	Ankle	NR	NR	NR	NR	NR	NR		

*Amplitude motor = mV, Sensory= µV; m = motor study; s = sensory study; RT = right; LT = left; AF = antecubital fossa; BE = below elbow; AE = above elbow; BF = below fibula; LP = lateral popliteal fossa; NR = no response; GBS = Guillain Barre syndrome.

Tomado de: Sedaghat, Z, Karimi, N. Guillain Barre syndrome associated with COVID-19 infection: A case report. J Clin Neurosci. 2020;76: 233.235.

Bueso & et al report a case report of a 60-year-old Caucasian woman with a history of migraine who presented with fever, nonproductive cough, myalgia, and dysgeusia for 10 days. A nasopharyngeal swab for SARS-CoV-2 RT-PCR assay was positive. She was admitted due to worsening dyspnea. On her admission, chest computed tomography revealed "ground glass" opacities. She was started on supplemental oxygen, azithromycin, and hydroxychloroquine. Twenty-two days after the onset of viral symptoms, she developed lower back pain, numbness in the feet, and weakness in the legs, for which she required a walker for ambulation. Within two days, the weakness progressed symmetrically to affect her lower and upper extremities to the point that she became bedridden during her hospital stay. Her respiratory function worsened with increased oxygen requirements through a Venturi mask at 8 L/min. Cerebrospinal fluid (CSF) analysis revealed cytoalbuminological dissociation (CAD) with 197 mg/dL protein and 0 leukocytes. His clinical manifestations and laboratory findings were consistent with GBS. Treatment was started with intravenous immunoglobulin (IVIG) 0.4 g/kg/day for 5 days in addition to enoxaparin 30 mg twice daily. After one week of therapy, the patient showed improvement in both her respiratory and neurological function (24).

Discussion

During the course of the disease caused by covid 19, it has been shown that respiratory symptoms are the most predominant and cause of mortality worldwide, however, through a series of case reports, it has been shown that neurological manifestations secondary to infection caused by this virus occurs in approximately 36% of patients, being more common in those who are in serious condition. (25)

Regarding the symptoms presented, several non-specific manifestations have been described at the level of the central nervous system, such as headache, dizziness/vertigo, impaired level of consciousness, ataxia, epilepsy, acute cerebrovascular accidents and encephalopathy. On the other hand, peripheral nervous system involvement includes hyposmia, hypogeusia, neuralgia, and skeletal muscle injury with rhabdomyolysis, which occur even before the development of severe respiratory symptoms (26), which contributes to the correct diagnosis of this syndrome.

In their letter to the editor, Camdessanche et al. describe the case of a 64-year-old male patient who was admitted to the emergency department due to a fall that caused a rotator cuff tear. Following the established protocols, a SARS-CoV-2 RT-PCR was performed on a nasopharyngeal swab, which was positive, showing high fever and hypoxia, for which oxygen was administered through a nasal cannula for 5 days after admission. 11 days later, the patient reported paresthesias in the feet and hands, which progressed to severe flaccid tetraparesis, without the presence of tendon reflexes in the 4 extremities. for which he was admitted to the ICU with mechanical ventilation and intravenous immunoglobulin. On CSF analysis, the protein level was 1.66 g per liter and the cell count was normal. Antiganglioside antibodies were absent in the serum. Biological tests were not in favor of a recent infection with Campylobacter jejuni, Mycoplasma pneumoniae, Salmonella enterica, CMV, EBV, HSV1 and 2, VZV, Influenza virus A and B, HIV and hepatitis E, however, electrodiagnostic tests showed a demyelinating pattern according to the criteria for Guillain-Barré syndrome (GBS), which confirmed the diagnosis. (27)

In their case report, Otmani et al. present the case of a 70-year-old female patient who suffered from rheumatoid arthritis treated with Prednisone, who presented bilateral weakness and a tingling sensation in all four extremities, which caused total functional disability in all four limbs. 48 hours. Initially, it was determined that this episode corresponded to an exacerbation of the pathology

that this patient suffered from, however, no improvement was observed after increasing corticosteroids, which is why neurological tests were ordered that showed tetraplegia, hypotonia, areflexia and signs Bilateral positive Lasègue test. In addition, a nerve conduction study revealed a marked reduction or absence of electrical potentials in motor and sensory nerves in all four limbs, with little or no abnormalities in conduction velocities and latencies, and needle electromyography found potentials of diffuse and abundant fibrillation at rest, findings that were consistent with an acute motor and sensory axonal neuropathy subtype of Guillain-Barré syndrome. Additionally, RT-PCR was positive in an oropharyngeal swab (28), which makes it possible to associate the course of the disease due to covid 19 and the development of this syndrome.

Challenging this hypothesis, Keddie et al, in their epidemiological cohort study, in which they compared the clinical characteristics of GBS associated with COVID-19 and not associated with COVID-19, which revealed no differences in clinical and neurophysiological characteristics, the severity of illness or outcomes of GBS related to COVID-19 and not associated with COVID-19. (29)

However, authors such as Caress et al. state that the postinfectious mechanism of GBS is supported by the finding of autoantibodies that result from an immune response directed at an epitope of the infectious agent that then cross-reacts with a structurally similar component of the peripheral nerve. , resulting in delayed immune-mediated damage to peripheral nerves. The attachment of SARS-CoV-2 to cell surfaces is mediated by the viral spike protein (S), which binds angiotensin-converting enzyme 2 and also gangliosides containing sialic acid residues, including the GalNAc residue. of GM1. It has been suggested that cross-reactivity between viral protein-related gangliosides and peripheral nerve gangliosides may result in molecular mimicry. Antiganglioside antibodies are detected infrequently, indicating that the tested antigangliosides are at low concentrations or that novel autoantibodies mediate GBS associated with COVID-19. Alternatively, the nerve damage mechanism may be primarily facilitated by T cell activation and the release of inflammatory mediators by macrophages. (30) Supported by authors such as Alberti and others, who in turn affirm that there is a deregulation of the immune system mediated by systemic hyperinflammation in patients with COVID-19 with a macrophage activation syndrome. (31)

Even Curtis et al. in their case report, present an 8-year-old pediatric patient who comes to the emergency room, who underwent a covid test that was positive and who presented classic symptoms of GBS with back pain followed by symmetrical ascending weakness with loss of reflexes (32), a diagnosis that was confirmed by electrodiagnosis, confirming the suspicion of an association between the virus and the development of Guillain Barré.

Conclusion

Guillain Barré syndrome is a polyneuropathy, in which the immune system attacks the peripheral nervous system, causing demyelination and therefore triggering a series of symptoms in the patient such as muscle weakness and dependence, which in the long term in certain cases constitutes a cause of death due to the increased risk of developing respiratory complications. Despite being rare, in recent years, various studies have shown that SARS COV 2 is related to the development of this pathology in considerably high percentages, because this virus has a neurotropic nature and leads to diseases of the central nervous system. and peripheral, which makes necessary the correct treatment and monitoring of the disease of these patients, in addition to an adequate management plan by health personnel that allows rapid recognition of symptoms and therefore timely diagnosis and treatment. However, the pathophysiological association of the virus and Guillain Barré syndrome continues to be studied today.

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