Guillain-Barré syndrome associated to COVID-19 infection: a review of published case reports

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Introduction. The coronavirus disease 2019 (COVID-19) pandemic is a major worldwide health disorder. There is an increasing number of neurological complications recognized with COVID-19 including patients with GBS and its variants.

Development. A review of the clinical cases of GBS associated to COVID-19 infection published in the last months has been developed. We included 48 patients (31 men, mean age 56.4 years). The most common COVID-19 symptoms were cough (60.4%) and fever (56.3%). Mean time from COVID-19 symptoms to neurologic manifestations was 12.1 days, but in nine patients (18.8%) developed GBS within seven days. Eleven patients (22.9%) presented cranial nerve involvement in the absence of muscle weakness; 36 presented the classic sensory motor variant (75%) and one had a pure motor variant (2.1%). The electrodiagnostic pattern was considered demyelinating in 82.4% of the generalized variants. The presence of hyposmia/dysgeusia was associated with a latency shorter than seven days to GBS onset of symptoms (30% vs 15.6%), and cranial nerve involvement in the absence of weakness (30.8% vs 17.1%). Most patients (87.5%) were treated with intravenous immunoglobulin. Neurological outcome was favorable in 64.6%; 29.2% had respiratory failure and 4.2% died shortly after being admitted.

Conclusions. GBS in patients with SARS-CoV-2 infection resembles clinically and electrophysiology the classical forms. Further studies are necessary to understand whether GBS frequency is actually increased due to SARS-CoV-2 infection and explore pathogenic mechanisms.

Keywords. Acute inflammatory demyelinating polyneuropathy. Acute motor axonal neuropathy. Acute motor sensory axonal neuropathy. Bilateral facial palsy. COVID-19. Guillain-Barré syndrome. Miller Fisher syndrome. SARS-CoV-2.

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Introduction

The first report of the novel coronavirus infection was on 31 December 2019 in Wuhan, Hubei Province, China [1]. Since then the virus has rapidly spread around the world, and on February 11th, 2020, the World Health Organization (WHO) named this new infection as coronavirus disease 2019 (COVID-19). At the same time, the International Committee on Taxonomy of Viruses renamed the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and in March 2020 it was defined as a pandemic. Similar to other coronaviruses, COVID-19 mainly affects the respiratory tract after an incubation period of 3 to 14 days. Depending on the patient's immune system and comorbidities, the symptoms may remain mild or lead to severe progression and even death. The most common manifestations of COVID-19 are fever, cough, dyspnea, pneumonia and respiratory complications. However, gastroenterological and neurological manifestations have been also described [2,3]. Neurologic symptoms are present in about 57% of patients, including mild symptoms such as hyposmia, dysgeusia, myalgias and headache, which appear at an early stage of the disease, and other symptoms that usually appear in patients with more advanced disease associated to moderate or severe infection (depressed levels of consciousness, confusion, seizures, stroke and encephalitis) [4]. Guillain-Barré syndrome (GBS) is an acute inflammatory polyradiculoneuropathy and the most common cause of flaccid paralysis in the world. Patients with GBS typically present with painful paresthesias and ascending symmetric weakness, with reduced or absent tendon reflexes. Patients can also have cranial nerves involvement and respiratory muscle weakness. The clinical presentation of the disease is heterogeneous, and several variants exist [5-7].

GBS pathogenesis represents an infectious-triggered autoimmune disease. Several pathogens have been associated with GBS, including virus such as influenza, enteroviruses, cytomegalovirus, Epstein-Barr, herpes simplex, hepatitis, and HIV [7]. GBS outbreaks have been also associated with viral epi-

demics, including H1N1, dengue, chikungunya and Zika virus, and with coronavirus, including the Middle East respiratory syndrome (MERS)-CoV and SARS-CoV.

The cross-immunity between viral antigens and peripheral nerve glycolipids has not been well characterized [8]. Neurotrophic characteristics of coronavirus have been described previously, but the exact mechanism of damage is yet to be elucidated [9].

Up to July 4, 2020, 47 patients have been reported with classical GBS or its variants, in association with COVID-19 infection. Moreover, it has been suggested an increase in the frequency of GBS associated with the current pandemic [10].

Development

We made a retrospective review of the published literature of GBS associated with COVID-19 infection identified via PubMed using the following search terms: 'Guillain-Barré', 'acute inflammatory demyelinating polyneuropathy', 'acute motor axonal neuropathy', 'acute motor sensory axonal neuropathy' or 'Miller Fisher' and 'SARS-CoV-2' or 'COVID'. The last article included was published on July 4, 2020. We selected articles both in English and in Spanish language, and we chose 'title' as search field. We included only patients who have had a COVID-19 infection confirmed either by reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 or with positive COVID-19 serum antibodies (IgM/IgG). We registered epidemiologic data such as gender, age, COVID-19 symptoms, COVID test performed, time gap between the COVID-19 infection and the first GBS symptom, neurological manifestations, anti-gangliosides, CSF characteristics, EMG results (when available), GBS variant, treatment and outcome.

We analized 47 patients from 37 articles and an additional patient who was admitted in our center (48 patients: 31 men, mean age 56.4 years, range 14-77 years) with GBS or its variants [11,12], associated with SARS-CoV-2 infection (Table I). The reports included 12 patients from Italy, nine from Spain, five from USA, four from France, four from Iran, two from Germany and one from Canada, Morocco, the UK, the Netherlands, Turkey and China.

COVID-19 symptoms preceded GBS in 46 patients, including cough (60.4%), fever (56.3%), hyposmia/dysgeusia (27.1%), diarrhea (25%), asthenia/myalgia (18.8%), dyspnea (12.5%), headache (10.4%), odynophagia (10.4%), unspecified respiratory symptoms (10.4%). There were two (4.2%) patients with confirmed COVID-19 disease but no systemic symptoms (asymptomatic forms).

Six patients (12.5%) developed GBS in the absence of the most classical manifestations of COVID-19 infection. Rather than presenting respiratory symptoms, they were either asymptomatic or only manifested mild fever, diarrhea, headache, asthenia or myalgia. Therefore, it is possible that GBS may occur in unsuspected and undetected COVID-19 infected patients. COVID-19 should be assessed in every patient with GBS and its variants in the context of the current pandemic. Gigli et al reported eight patients with GBS which resulted in a 5.41-fold increment of GBS patients in 2020, compared with the period 2017-2019. They hypothesized that asymptomatic or mildly symptomatic infections may not develop an antibody response strong enough to be detected. We included in this review the only patient in this group who tested positive for COVID-19 [10].

Mean latency between the onset of COVID-19 symptoms and the first neurologic manifestations was 12.1 days (range 0-28 days). In nine patients (18.8%), GBS developed within seven days of COVID-19 infection. The remaining 37 patients developed GBS between seven and 28 days after the onset of COVID-19 symptoms. Some of these patients were diagnosed with GBS before their mild COVID-19 symptoms were recognized.

COVID-19 infection was confirmed by nasopharyngeal swab RT-PCR SARS-CoV-2 in 42 patients. The remaining six patients had negative PCR and positive IgM/IgG antibodies.

CSF testing was performed in 40 patients: 31 of them had albumin cytologic dissociation, seven were normal and two had oligoclonal bands (OCBs). Eighteen CSFs were tested for COVID-19, and only one of them showed positive IgG. Mild pleocytosis, like in our patient, may be present in GBS [7].

MRI enhancement in leptomeninges, postganglionic roots or cranial nerves, were identified in nine patients. Antiganglioside testing was performed in 25 patients: two patients with Miller Fisher syndrome (MFS) tested positive, one for anti-GD1b and a second had an equivocal anti-GM1.

Overall, 11 (22.9%) patients presented with cranial nerve involvement in the absence of muscle weakness. Three patients (6.3%; 2 males, mean age 63.6 years) presented with bilateral peripheral facial palsy (PFP) and distal paresthesias. The frequency of this variant among patients with COVID-19 seems similar than previously reported (<5%) [5]. Facial palsy was simultaneous in two pa-

Table I. Demographic, clinical, CSF and neurophysiological findings in patients with GBS associated to COVID-19.

Pt #	Authors	Sex/ Age	Covid-19 symptoms	COVID test	Time gap	Neurological manifestations and outcome	Anti-ganglosides	CSF	EMG (Electrophysiological subtype)	GBS variant	Treatment
1	Zuberbühler et al	F/72	Rhino conjunctivitis	IgG+ PCR-	5 days	Bilateral PFP (Left first), dysgeusia, anosmia, LL paresthesias, ataxic gait	Neg	Mild pleocytosis PCR-	Reduced UL sensory CVs	Facial diplegia & paresthesias	Not treated
2	Chan et al [13]	M/ 58	Asymptomatic	PCR+	Contact 20 days	Bilateral PFP, dysarthria, areflexia, paresthesias distal LL	NA	ACD, PCR-	Blink reflex NR; F wave NR	Facial diplegia & paresthesias	IVIG
3	Caamaño et al [14]	M/ 61	Cough, fever	PCR+	10 days	Bilateral PFP	NA	ACD, PCR-	NA	Facial diplegia	Not treated
4	Lantos et al [15]	M/ 36	Fever, myalgias	PCR+	2 days	Cranial nerve III & VI bilateral palsy, areflexia, hypoesthesia and paresthesias LL, ataxia	Anti-GM1 + (equivocal range)	NA	NA	Miller Fisher syndrome	IVIG
5	Reyes Bueno, et al [16]	F/51	Diarrhea, odynophagia, cough	IgG+ PCR-	14 days	Left III cranial nerve paresis, diplopia, inferior bilateral facial paresis, areflexia, autonomic dysfunction	Neg	ACD	Blink reflex NR; prolonged F waves	Miller Fisher syndrome	IVIG
6	Gutierrez-Ortiz et al [17]	M/ 50	Cough, headache, fever, anosmia, ageusia	PCR+	3 days	Right ophthalmoplegia, perioral paresthesias, areflexia, gait ataxia	Anti GD1b-IgG +	NA	NA	Miller Fisher syndrome	IVIG
7	Gutierrez-Ortiz et al [17]	M/ 39	Diarrhea, fever, ageusia	PCR+	3 days	Bilateral ophthalmoplegia, areflexia	NA	ACD	NA	Miller Fisher syndrome	Not treated
8	Manganotti, et al [18]	M/50	Fever, cough, hypogeusia	PCR+	16 days	Ophthalmoplegia, areflexia, ataxia	Neg	ACD, PCR -	NA	Miller Fisher syndrome	IVIG
9	Fernández-Domínguez et al [19]	F/ 74	Bilateral pneumonia	PCR+	24 days	Gait ataxia, LL areflexia	Neg	ACD	F-wave delay UL	Miller Fisher like síndrome	IVIG
10	Assini et al [20]	M/ 55	Anosmia, ageusia, fever, cough, SARS	PCR+	20 days	Bilateral ptosis, dysphagia and dysphonia (IX-X palsy), hyporeflexia	Neg	OCB; PCR-	Demyelinating neuropathy	Cranial polyneuritis	IVIG
11	Paybast et al [21]	M/ 38	Upper respiratory tract infection	PCR+	16 days	Bilateral PFP, areflexia, ascending paresthesias, distal hypoesthesia 4L; later dysphagia (IX-X palsy)	NA	ACD, PCR-	Demyelinating neuropathy	Cranial polyneuritis	IVIG
12	Hutchins, et al [22]	M/21	Fever, cough, dyspnea, diarrhea, nausea, headache	PCR +	16 days	Bilateral PFP, hypogeusia, proximal weakness 4L, areflexia, UL paresthesias	Neg	ACD	Mixed pattern (Equivocal)	Classic sensorymotor	Plasma exchange
13	El Otmani et al [23]	F/ 70	Dry cough	PCR+	2 days	Acute flaccid areflexic tetraplegia and paresthesia	NA	ACD	Axonal neuropathy (AMSAN)	Classic sensorymotor	IVIG

Table I. Demographic, clinical, CSF and neurophysiological findings in patients with GBS associated to COVID-19 *(cont.)*.

Pt #	Authors	Sex/ Age	Covid-19 symptoms	COVID test	Time gap	Neurological manifestations and outcome	Anti-gangliosides	CSF	EMG (Electrophysiological subtype)	GBS variant	Treatment
14	Bigaut et al [24]	M/ 43	Cough, asthenia, myalgia, anosmia, ageusia, diarrhea	PCR+	21 days	Right PFP, distal weakness in LL, areflexia, paresthesia, hypoesthesia, ataxia	NA	ACD	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG
15	Bigaut et al [24]	F/ 70	Asthenia, myalgia, anosmia, ageusia, diarrhea	PCR+	7 days	Left PFP, proximal acute tetraparesis, areflexia, distal and perioral paresthesias	NA	ACD	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG
16	Sedaghat et al [25]	M/ 65	Cough, fever, dyspnea	PCR+	14 days	Bilateral PFP, acute ascending tetraparesis, areflexia, distal hypoesthesia LL	NA	NA	Axonal neuropathy (AMSAN)	Classic sensorymotor	IVIG
17	Camdesanche et al [26]	M/ 64	Cough, fever	PCR+	11 days	Dysphagia, flaccid tetraparesis, areflexia, distal paresthesias Respiratory failure (MV)	Neg	ACD	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG
18	Assini et al [20]	M/ 60	Fever, cough, SARS	PCR+	20 days	Acute distal weakness LL, areflexia, gastroparesis, arterial hypotension	Neg	OCB; PCR-	Axonal neuropathy (AMSAN)	Classic sensorymotor	IVIG
19	Scheidl et al [9]	F/ 54	Hyposmia, hypogeusia	PCR+	11 days	Acute paraparesis, areflexia, hypoesthesia & paresthesias 4L	NA	ACD	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG
20	Gigli et al [10]	M/ 53	Fever, diarrhea	IgM/G+ PCR-	NA	Paresthesias, ataxia	Neg	ACD	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG
21	Ottaviani et al [27]	F/ 66	Fever, cough	PCR+	10 days	Unilateral PFP, Paraplegia, brachial diparesis, areflexia Respiratory failure (MV)	Neg	ACD	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG
22	Zhao et al [28]	F/ 61	Arrived from Wuham asymptomatic	PCR+	0	Tetraparesis, areflexia, distal hypoesthesia	NA	ACD	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG
23	Virani et al [29]	M/ 54	Dry cough, diarrhea	PCR+	10 days	Mild tetraparesis, areflexia, paresthesias Respiratory failure (MV)	NA	NA	NA	Classic sensorymotor	IVIG
24	Coen et al [30]	M/ 70	Dry cough, myalgia, fatigue	PCR+	6 days	Flaccid tetraparesis, areflexia, distal allodynia	Neg	ACD	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG
25	Padroni et al [31]	F/ 70	Fever, dry cough	PCR+	24 days	Tetra paresis, areflexia, distal paresthesias, gait disturbances Respiratory failure (MV)	NA	ACD	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG
26	Arnaud et al [32]	M/ 64	Cough, dyspnea, diarrhea, fever	PCR+	23 days	Flaccid paraparesis, areflexia, hypoesthesia 4L	Neg	ACD	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG

Table I. Demographic, clinical, CSF and neurophysiological findings in patients with GBS associated to COVID-19 *(cont.)*.

Pt #	Authors	Sex/ Age	Covid-19 symptoms	COVID test	Time gap	Neurological manifestations and outcome	Anti-gan-gliosides	CSF	EMG (Electrophysio-logical subtype)	GBS variant	Treatment
27	Su et al [33]	M/ 72	Diarrhea, anorexia, chills	PCR+	6 days	Tetraparesis, areflexia, distal hypoesthesia, paresthesias, dysautonomia Respiratory failure (MV)	Neg	ACD, PCR-	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG
28	Toscano et al [34]	F/ 77	Fever, cough, ageusia	PCR+	7 days	Bilateral PFP, tetraplegia, areflexia, paresthesias Respiratory failure (NIV)	Neg	ACD, PCR-	Axonal neuropathy (AMSAN)	Classic sensorymotor	IVIG 2 cycles
29	Toscano et al [34]	M/ 23	Fever, odynophagia	PCR+	10 days	Bilateral PFP, areflexia, paresthesias, ataxia	NA	ACD, PCR-	Axonal neuropathy (AMSAN)	Classic sensorymotor	IVIG
30	Toscano et al [34]	M/ 76	Dry cough, anosmia	PCR+	4 days	Tetraplegia, areflexia, ataxia	NA	Normal (5 day)	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG
31	Toscano et al [34]	M/ 61	Asthenia, dry cough, anosmia, ageusia	IgG+ PCR-	7 days	Bilateral PFP, tetraplegia, areflexia, LL paresthesias Respiratory failure (MV)	Neg	Normal, PCR-	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG and plasma exchange
32	Rana et al [35]	M/ 54	Rhinorrhea, odynophagia, fever, chills	PCR+	14 days	Bilateral PFP, ophtalmoparesis, tetraparesis, areflexia, paresthesias Respiratory failure (MV)	NA	NA	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG
33	Riva et al [36]	M/ 60	Fever, headache, myalgia, ageusia, anosmia	IgG+ PCR-	20 days	Bilateral PFP, dysarthria, tetraplegia, paresthesias	Neg	Normal	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG
34	Velayos Galan et al [37]	M/ 43	Diarrhea, upper respiratory symptoms	PCR+	10 days	Bilateral PFP, dysphagia, tetraparesis, areflexia, dysesthesias	NA	NA	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG
35	Marta-Enguita et al [38]	F/ 76	Dry cough, fever	PCR+	8 days	Dysphagia, tetraparesis, areflexia, paresthesias, hypoesthesia Respiratory failure (died in <24 hs)	NA	NA	NA	Classic sensorymotor	Not treated
36	Sancho-Saldaña et al [39]	F/ 56	Fever, dry cough, dyspnea	PCR+	15 days	Bilateral PFP, oropharyngeal weakness, proximal tetraparesis, paresthesia UL, ataxia	NA	ACD, PCR-	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG
37	Paybast et al [21]	F/ 14	Upper respiratory tract infection	PCR+	14 days	Weakness LL, areflexia, paresthesias, hypoesthesia 4L, ataxia	NA	ACD	NA	Classic sensorymotor	IVIG
38	Helbok et al [40]	M/68	Dry cough, headache, fatigue, myalgia, fever, anosmia, ageusia	IgG+ PCR-	14 days	Ascending dysesthesias, proximal weakness 4L Respiratory failure (MV)	Neg	ACD, IgG+	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG (30 g), Plasma exchange

Table I. Demographic, clinical, CSF and neurophysiological findings in patients with GBS associated to COVID-19 *(cont.)*.

Pt #	Authors	Sex/ Age	Covid-19 symptoms	COVID test	Time gap	Neurological manifestations and outcome	Anti-gan-gliosides	CSF	EMG (Electrophysio-logical subtype)	GBS variant	Treatment
39	Oguz-Akarsu, et al [41]	F/53	Mild fever; bilateral pneumonia	PCR+	0	Dysarthria, areflexia in LL, paraparesis	NA	Normal PCR -	Demyelinating neuropathy (AIDP)	Classic sensorymotor	Plasma exchange
40	Kilinc et al [42]	M/50	Dry cough	PCR+ IgG+	28 days	Bilateral PFP, proximal weakness 4L, areflexia, hypoesthesia LL	Neg	Normal PCR -	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG
41	Webb, et al [43]	M/57	Cough, headache, myalgia, malaise	PCR+	7 days	Tetraparesis, areflexia, distal hypoesthesia LL Respiratory failure (MV)	Neg	Normal PCR -	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG
42	Lascano et al [44]	F/52	Dry cough, fever, odynophagia, arthralgia, diarrhoea	PCR+	15 days	Tetraplegia, areflexia, dysautonomia Respiratory failure (MV)	Neg	ACD, PCR -	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG
43	Lascano et al [44]	F/63	Dry cough, odynophagia, dyspnea	PCR+	7 days	Tetraparesis, areflexia, distal paresthesia	Neg	Normal	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG
44	Lascano et al [44]	F/61	Productive cough, fever, myalgia, syncope, diarrhoea, nausea, vomiting	PCR+	22 days	Bilateral PFP, dysphagia, paraparesis, areflexia, dysautonomia	Neg	ACD, PCR -	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG
45	Guijarro-Castro et al [45]	M/70	Bilateral pneumonia	PCR+	21 days	Tetraparesis, areflexia, distal hypoesthesia LL	Neg	ACD	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG
46	Alberti et al [46]	M/71	Fever	PCR+	7 days	Severe flaccid tetraparesis, areflexia, distal hypoesthesia 4L Respiratory failure (NIV, died in 24 hs)	NA	ACD, PCR -	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG
47	Farzi et al [47]	M/41	Cough, dyspnea, fever	PCR+	10 days	Tetraparesis, areflexia, hypoesthesia 4L	NA	NA	Demyelinating neuropathy (AIDP)	Classic sensorymotor	IVIG
48	Toscano et al [34]	M/55	Fever, cough	PCR+	10 days	Bilateral PFP, tetraplegia, areflexia, paresthesias Respiratory failure (MV)	Neg	ACD, PCR-	Axonal neuropathy (AMAN)	Pure motor	IVIG 2 cycles

4L = 4 limbs; ACD = albuminocytological dissociation; AIDP = acute inflammatory demyelinating polyneuropathy; AMAN = acute motor axonal neuropathy; AMSAN = acute motor sensory axonal neuropathy; CVs = conduction velocities; CSF = cerebrospinal fluid; EMG = electromyography; F = female; GBS = Guillain Barré syndrome; IVIG = intravenous immunoglobulin; LL = lower limbs; M = male; MV = mechanic ventilation; NA = not available; NIV = non-invasive ventilation; Neg = negative; NR = non-reactive; OCB = oligoclonal bands; PCR = polymerase chain reaction; PFP = peripheral facial paralysis; Pt = patient; UL = upper limbs.

tients, and sequential in our patient. All three had a good outcome. Six (12.5%) patients presented MFS (4 males, mean age 50 years); one patient had an overlapping MFS-GBS [16] and another one was defined by the author as a Miller Fisher like syndrome [19], since he did not present ophthalmoplegia. Two patients (4.2%) developed involvement of multiple cranial nerves and reduced reflexes and were defined as cranial polyneuritis. One patient presented with bilateral ptosis, dysphagia and dysphonia with hyporeflexia. The other patient had bilateral PFP, dysphagia and areflexia. This is a rare variant, previously reported [48], but not included in recent reviews [5-7]. The electrodiagnostic results were available in six patients: two patients with cranial polyneuritis presented demyelinating findings; the four remaining subjects had equivocal findings (Table I).

The classic sensory motor variant accounted for the majority of patients (n = 36, 75%, mean age 57.9 years) and only one patient presented with a pure motor variant (2.1%). The electrodiagnostic results were available in 34 patients: based on the authors report, 28 (82.4%) were classified as Acute Inflammatory Demyelinating Polyneuropathy (AIDP), six (17.6%) had an axonal neuropathy (five with Acute Motor Sensory Axonal Neuropathy [AMSAN] and one with Acute Motor Axonal Neuropathy [AMAN]). Percentages of demyelinating and axonal patterns may vary depending the set of criteria used for the definition, but AIDP predominated in the generalized forms [49-51].

Forty-two patients (87.5%) were treated initially with IVIG 2 g/kg; two received a second course of IVIG and two started plasma exchange sequentially. Two patients underwent plasma exchange initially (Table I). Four patients were not treated. There is a potential increased thrombotic risk using IVIG in patients with COVID-19 infection. This virus induces an enhanced inflammatory response leading to endothelial cell activation and a prothrombotic state [52,53]. Moreover, antiphospholipid antibodies as well as high D-dimer and increased fibrinogen levels occur in COVID-19, associated with both arterial and venous thrombotic events [54]. Nevertheless, these complications were not reported in the GBS patients treated with IVIG.

Short-term neurological outcome was favorable in 31 patients (64.6%), with a good neurologic recovery. Fourteen patients (29.2%) had respiratory failure, 11 of them needed mechanical ventilation (MV), one required non-invasive ventilation (NIV) and two (4.2%) patients died shortly after being admitted. Respiratory insufficiency in these patients is most likely the combined effect of muscle weakness due to GBS and lung infection due to COVID-19. No data was available from three patients.

Table II. Clinical characteristics of patients with or without hyposmia/dysgeusia.

	Hyposmia/Dysgeusia (+)	Hyposmia /Dysgeusia (–)	p^*
Patients, n (%)	13 (27.1)	35 (72.9)	
Age, mean (range)	59.6 (39-77)	55.6 (14-76)	NS
Latency COVID to neurologic symptoms, mean days (range)	10.6 (3-21)	12.7 (0-28)	NS
Latency <7 days, n (%)	4 (30.8)	5 (15.6)	NS
CNI without weakness, n (%)	5 (38.5)	6 (17.1)	NS
CNI, n (%)	10 (76.9)	18 (51.4)	NS
RF, n (%)	3 (23.1)	11 (31.4)	NS
Death, n (%)	0 (0)	2 (5.7)	NS

CNI = cranial nerve involvement; NS = non significant; RF = respiratory failure. *Mann Whitney U test

It is still unclear the main pathophysiology mechanism mediating COVID-19 nerve damage. Coronavirus may invade the neuroephitelium of the olfactory nerve. Hyposmia and dysgeusia affect up to 50-85% of patients with SARS-COV-2 infection, and also may travel via retrograde axonal transport from trigeminal and vagal endings [55-57].

We therefore compared the 13 patients who developed hyposmia, hypogeusia or both with the 35 patients without these symptoms. The first group more frequently presented: a latency between the COVID-19 infection and GBS shorter than seven days (30% vs 15.6%), cranial nerve involvement in the absence of weakness (30.8% vs 17.1%) and overall cranial nerve involvement in addition to hyposmia and ageusia (76.9% vs 51%). On the other hand, the second group presented more frequently respiratory failure (31.4% vs 23.1%) and death (5.7% vs 0%) than the first group. However, none of these differences were statistically significant (Table II).

An autoimmune post infectious mechanism is the classical pathophysiology of the neural damage seen in GBS. Favors this mechanism in COVID-19 the absence of the virus in the CSF from the majority of reported GBS patients and the apparent beneficial response to IVIG. Molecular mimicry requires a shared immunologic epitope between the virus and the host. It was recently postulated that similarities between the COVID-19 spike protein,

which anchors the virus to membrane gangliosides and peripheral nerve glycolipids leads to autoimmune neuropathy. Nevertheless, only one patient with MFS presented GD1A anti ganglioside antibody. Sequence analysis of 41 human proteins associated with immune-mediated polyneuropathies identified shared hexapeptides between the SARS-CoV-2 virus and the human heat shock proteins 60 and 90 [58]. Viral peptides could also trigger autoimmunity through direct activation of autoreactive T cells against host antigens or indirectly through activation of antigen presenting cells that stimulate preprimed autoreactive T cells in a process known as bystander activation [59].

Conclusions

Limitations of this review include the small number of reported patients and the variable information regarding their clinical and diagnostic studies. Prevalence of GBS associated with COVID-19 is still unknown and it is possible that not only mild GBS patients like ours may not be diagnosed as a GBS variant, but also severely affected patients may be confused with critical illness polyneuropathy. Nevertheless, GBS in patients with SARS-CoV-2 infection resembles clinically and electrophysiology the classical forms. Further studies are necessary to understand whether GBS frequency is actually increased due to SARS-CoV-2 infection and explore pathogenic mechanisms. Neurologists should consider testing all patients with GBS for COVID-19 infection because they may be asymptomatic or lack the classical respiratory symptoms.

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Síndrome de Guillain-Barré asociado a infección por COVID-19: revisión de casos publicados

Introducción. La pandemia por la enfermedad por coronavirus 2019 (COVID-19) es un importante problema para la salud mundial. Hay un incremento en las complicaciones neurológicas reconocidas por la COVID-19, incluyendo el síndrome de Guillain-Barré (SGB) y sus variantes.

Desarrollo. Se realizó una revisión de los casos publicados en los últimos meses de SGB asociado a infección por COVID-19. Incluimos a 48 pacientes (31 hombres; edad media: 56,4 años). Los síntomas de COVID-19 más comunes fueron tos

(60,4%) y fiebre (56,3%). El tiempo promedio entre los síntomas de COVID-19 y el SGB fue de 12,1 días, pero nueve pacientes (18,8%) desarrollaron SGB en menos de siete días. Once pacientes (22,9%) presentaron afectación de los nervios craneales en ausencia de debilidad muscular, 36 presentaron la variante clásica sensitivomotora (75%) y uno tuvo una variante motora pura (2,1%). El patrón electrofisiológico se consideró desmielinizante en el 82,4% de las variantes generalizadas. La presencia de hiposmia/disgeusia estuvo asociada con una latencia menor a los siete días hasta el inicio de los síntomas del SGB (30 frente a 15,6%) y a la afectación de los nervios craneales en ausencia de debilidad (30,8 frente a 17,1%). La mayoría de los pacientes (87,5%) fueron tratados con inmunoglobulina endovenosa. La evolución neurológica fue favorable en el 64,6%, el 29,2% tuvo insuficiencia respiratoria y hubo un 4,2% de muertes.

Conclusiones. El SGB en pacientes con infección por SARS-CoV-2 es similar clínica y electrofisiológicamente a las formas clásicas. Se requieren más estudios para comprender si la frecuencia del SGB realmente aumentó debido a la pandemia por COVID-19 y explorar los mecanismos patógenos involucrados.

Palabras clave. COVID-19. Neuropatía motora axonal aguda. Neuropatía sensitivomotora axonal aguda. Parálisis facial bilateral. Polineuropatía desmielinizante inflamatoria aguda. SARS-CoV-2. Síndrome de Guillain-Barré. Síndrome de Miller Fisher.