

Guillain–Barré syndrome associated with SARS-CoV-2 infection. A systematic review

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Guillain–Barré syndrome (GBS) incidence can increase during outbreaks of infectious illnesses. A few cases of GBS associated with coronavirus disease 2019 (COVID-19) infection have been reported. The aim was to identify specific clinical features of GBS associated with COVID-19. PubMed, Embase and Cochrane were searched from 1 November 2019 to 17 May 2020 and included all papers with full text in English, Spanish, French or Italian, reporting original data of patients with GBS and COVID-19. Data were extracted according to a predefined protocol. A total of 18 patients reported in 14 papers were included in this review. All the patients were symptomatic for COVID-19, with cough and fever as the most frequently reported symptoms. The interval between the onset of symptoms of COVID-19 and the first symptoms of GBS ranged from –8 to 24 days (mean 9 days; median 10 days). Most of the patients had a typical GBS clinical form predominantly with a demyelinating electrophysiological subtype. Mechanical ventilation was necessary in eight (44%) patients. Two (11%) patients died. Published cases of GBS associated with COVID-19 report a sensorimotor, predominantly demyelinating GBS with a typical clinical presentation. Clinical features and disease course seem similar to those observed in GBS related to other etiologies. These results should be interpreted with caution since only 18 cases have been heterogeneously reported so far.

Introduction

Guillain–Barré syndrome (GBS) is a rare inflammatory disease of the peripheral nervous system with increasing incidence with age [1]. GBS is presumed to be triggered by preceding infections with specific pathogens [1,2]. The typical onset is characterized by weakness and sensory signs starting in the legs and progressing to arms and cranial muscles. Loss of deep tendon reflexes, dysautonomic symptoms and pain are

also common. Despite a heterogeneous clinical presentation, diagnosis is based on the patient history and neurological examination, supported by electrophysiological studies showing a motor or sensorimotor polyradiculoneuropathy and cerebrospinal fluid (CSF) examination showing increased protein level with normal cell count [2,3]. The incidence of GBS can increase during outbreaks of infectious illnesses that trigger the disease [2]. As reported by Lu *et al.* [4], in Wuhan City, Hubei Province of China, a new type of coronavirus (SARS-CoV-2, severe acute respiratory syndrome coronavirus 2 or COVID-19) was detected in December 2019. This new virus has the capacity of entering into the cell through fusion with angiotensin-converting enzyme 2 (ACE2) receptor [5]. The most recognizable feature of COVID-19 is to cause severe

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respiratory complications, which largely depend on the overall state of wellbeing of the infected patient. Age, the patient's underlying comorbidities and the condition of the immune system also play a major role in the severity of the disease [6,7]. Many signs and symptoms are associated with the infection such as fever, dyspnea, cough, headache and diarrhea [8]. Neurological manifestations are also increasingly reported, and a few cases of GBS in SARS-CoV-2 infected patients have been described. This study aims to summarize these cases into a single review to characterize GBS associated with SARS-CoV-2 infection.

Methods

Literature search, strategy and compliance with ethical standards

This review follows the guidelines set out by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [9]. A comprehensive literature search of the databases PubMed, Embase and Cochrane was designed and conducted by the authors. The keywords used for the search are shown in Table 1, which shows the primary research strategy. Initial search results were screened by checking only the title and abstract; then full-text articles from the resultant list were evaluated for inclusion. The search was supplemented by reviewing the bibliographies of the included papers to identify relevant publications. The search was limited to articles published from the period 1 November 2019 to 17 May 2020. The quality of studies has been assessed using the GRADE system by all the authors, until reaching a total agreement [10]. This study is a review of published literature and therefore is exempt from institutional review board approval.

Inclusion and exclusion criteria

The following predetermined criteria were used to screen the results: (i) original case reports or (ii) case series of patients diagnosed with GBS who tested positive for SARS-CoV-2 infection, (iii) written in English, Spanish, French or Italian.

Article data extraction

For each paper, the following data were extracted: number of patients reported, demographic characteristics, acute antecedent illness, clinical features associated with GBS including timing from antecedent illness to GBS onset, timing from GBS onset to nadir, GBS clinical subtype, Medical Research Council score

Table 1 Primary search strategy

PUBMED (NLM), searched on 17 May 2020 – Total results 224
Step 1 (((("neurologic"[All Fields] OR "neurological"[All Fields] OR "neurologically"[All Fields] OR ("neuropathies"[All Fields] OR "neuropathy"[All Fields])) OR (((("guillain-barre syndrome"[MeSH Terms] OR "guillain barre"[All Fields] AND "syndrome"[All Fields])) OR "guillain barre syndrome"[All Fields] OR ("guillain"[All Fields] AND "barre"[All Fields] AND "syndrome"[All Fields])) OR "guillain barre syndrome"[All Fields])) AND (((((((("covid 19"[All Fields] OR "covid 2019"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019 cov"[All Fields] OR "sars cov 2"[All Fields] OR "2019ncov"[All Fields] OR ("wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND (2019/12/1:2019/12/31[Date - Publication] OR 2020/1/1:2020/12/31[Date - Publication]))) OR ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronaviruses"[All Fields])) OR ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "sars cov 2"[All Fields]))
COCHRANE, searched on 17 May 2020 – Total results 7
Step 1 “Coronavirus 2019” in Keyword OR “covid19” in Keyword OR “SARS-CoV-2” in Keyword AND “neuropathy” in Keyword OR “Guillain Barre syndrome” in Keyword - (Word variations have been searched)
EMBASE, searched on 17 May 2020 – Total results 15
Step 1 (covid19:kw OR coronavirus:kw OR 'sars cov 2':kw) AND 'guillain barrè syndrome':kw AND [1-11-2019]/sd NOT [10-5-2020]/sd
Step 2 (covid19:kw OR coronavirus:kw OR 'sars cov 2':kw) AND neurological:kw AND [1-11-2019]/sd NOT [10-5-2020]/sd
Step 3 (covid19:kw OR coronavirus:kw OR 'sars cov 2':kw) AND neuropathy:kw AND [1-11-2019]/sd NOT [10-5-2020]/sd
Primary search from the three database searches combined: total of 246 candidate articles

when reported, presence of cranial nerve involvement, dysautonomic symptoms, ataxia, type of treatment, outcome, medical interventions. The results of the ancillary investigations performed for GBS diagnosis were also reported, including CSF examination, magnetic resonance imaging (MRI) and antiganglioside antibodies. GBS diagnosis was confirmed using the Brighton Collaboration criteria, specifying level of diagnostic certainty [3]. If the Brighton criteria were not reported, these were estimated based on available reported data.

The results of the electrodiagnostic studies were reviewed and, when normal control values used were also reported, the electrophysiological GBS subtype was revised using Rajabally's criteria [11]; otherwise subtype reported by the authors was included. The Rajabally criteria were chosen since they were shown to be the most appropriate for an indicative electrophysiological subtype diagnosis using a single

electrophysiological study [11]. Symptoms and signs of SARS-CoV-2 infection, diagnostic testing and treatment were also reported.

Clinical characteristics were retrieved as the number of patients in whom the variable was present in the numerator and the total number of reported cases in the denominator: n/N (%). Variables not cited were considered absent or not performed rather than missing data (e.g. symptoms or diagnostic tests).

Results

Study selection

A total of 18 patients reported in 14 papers [12–25] were included in this review. The 14 selected papers consisted of 13 case reports and one series. Figure S1 (PRISMA diagram) summarizes the flow of the 14 articles included in the review. In total, 232 articles were excluded because they were not relevant or were not reporting information on patients. Table 2 shows the quality of evidence for each article [10].

Clinical characteristics and overall outcome

Table 3 summarizes the demographics and clinical characteristics of each case with a reported GBS associated with SARS-CoV-2. Table 4 shows the diagnostic ancillary tests, outcome and treatment. Fourteen cases were from Europe [12,16–20,22–25], one from the USA [13], one from China [14], one from Iran [15] and one from Morocco [21]. Ten patients were males whilst eight were females. Mean age was 62 years (median 64.5; range 23–77 years). In 14 patients the diagnosis of SARS-CoV-2 was confirmed by nasopharyngeal swab alone, in three patients by nasopharyngeal swab plus serological test, and in one

patient by serological test alone (Table 5). All patients except three had signs of interstitial pneumonia at lung imaging tests. Cough (14 patients) and fever (13 patients) were the most frequent observed symptoms of SARS-CoV-2 infection in these patients, followed by dyspnea, ageusia, hyposmia and diarrhea (Table 5). Two or more symptoms were present in 15 patients. None of the patients was asymptomatic for SARS-CoV-2 infection. The interval between the onset of symptoms of COVID-19 and the first symptoms of GBS ranged from –8 to 24 days (mean 9 days; median 10 days). In five patients an overlap between symptoms of COVID-19 and symptoms of GBS was reported. All patients had a typical GBS clinical form, except two patients with bilateral facial palsy, two patients with a paraparetic form and one with a pure motor GBS. Eleven patients had a cranial nerve involvement, most frequently a unilateral or bilateral facial palsy that was present in six (33%) patients, a figure not different from that observed in GBS related to other etiologies ($P = 1.000$) [26]. Three patients were ataxic and one had dysautonomic symptoms (urinary retention). The nadir of neurological symptoms was reached in a mean of 5 days (median 4 days; range 2–17 days). Eleven patients met the Brighton Collaboration criteria level 1, five patients level 2 and two patients level 3. Electrophysiological studies were performed in all but three patients. Criteria used to classify cases into the different electrophysiological subtypes were reported in only seven patients. In three cases, the normal control values used for nerve conduction studies were reported and the electrophysiological subtype was revised: in two patients an acute inflammatory demyelinating polyneuropathy (AIDP) subtype was confirmed as reported by the authors, whilst in another an AIDP subtype (not specified by the authors) was defined.

Table 2 Quality of evidence

Author, year	Journal	Study center	Type of article	Quality rating [10]
Toscano <i>et al.</i> , 2020 [12]	<i>New England Journal of Medicine</i>	Italy	Case series	4
Virani <i>et al.</i> , 2020 [13]	<i>IDCases</i>	USA	Case report	5
Zhao <i>et al.</i> , 2020 [14]	<i>The Lancet Neurology</i>	China	Case report	5
Sedaghat and Karimi, 2020 [15]	<i>Journal of Clinical Neuroscience</i>	Iran	Case report	5
Alberti <i>et al.</i> , 2020 [16]	<i>Neurology: Neuroimmunology and Neuroinflammation</i>	Italy	Case report	5
Camdessanche <i>et al.</i> , 2020 [17]	<i>Revue Neurologique</i>	France	Case report	5
Padroni <i>et al.</i> , 2020 [18]	<i>Journal of Neurology</i>	Italy	Case report	5
El Otmani <i>et al.</i> , 2020 [19]	<i>Revue Neurologique</i>	Morocco	Case report	5
Coen <i>et al.</i> , 2020 [20]	<i>Brain, Behavior, and Immunity</i>	Switzerland	Case report	5
Galán <i>et al.</i> , 2020 [21]	<i>Neurología</i>	Spain	Case report	5
Marta-Enguita <i>et al.</i> , 2020 [22]	<i>Neurología</i>	Spain	Case report	5
Scheidl <i>et al.</i> , 2020 [23]	<i>Journal of the Peripheral Nervous System</i>	Germany	Case report	5
Ottaviani <i>et al.</i> , 2020 [24]	<i>Neurological Sciences</i>	Italy	Case report	5
Juliao Caamaño <i>et al.</i> , 2020 [25]	<i>Journal of Clinical Neuroscience</i>	Spain	Case report	5

Table 3 Reported demographic and clinical characteristics of Guillain-Barré syndrome associated with SARS-CoV-2 infection

Patients	Age (years)	Sex	Time from COVID-19 symptom onset to GBS symptom onset (days)	Time from neurological illness onset to nadir (days)	MRC	GBS clinical subtype	Cranial nerve involvement	Facial palsy (unilateral or bilateral)	Ataxia	Dysautonomic symptoms
1 [12]	77	F	7	4	NR	Typical	+			
2 [12]	23	M	10	5	NR	Bilateral facial palsy with paraesthesias	+	+	+	
3 [12]	55	M	10	2	NR	Typical	+	+		
4 [12]	76	M	5	5	NR	Pure motor	+		+	
5 [12]	61	M	7	4	NR	Typical	+	+		
6 [13]	54	M	10	NR	NR	Typical				+
7 [14]	61	F	-8	4	4/5 UL, 3/5 LL	Typical	+			
8 [15]	65	M	15	NR	2/5 proximal UL, 3/5 distal UL, 1/5 proximal LL, 2/5 distal LL	Typical	+	+		
9 [16]	71	F	A few days	4	3/5 UL, 2/5 LL	Typical				
10 [17]	64	M	11	3	2/5 arms, 3/5 forearms, 4/5 hands, 2/5 LL	Typical	+			
11 [18]	70	F	24	4	4/5 UL and LL	Typical			+	
12 [19]	70	F	3	2	NR	Typical				
13 [20]	43	M	10	2	4/5 proximal muscles and 3/5 distal muscles in the four limbs	Typical				
14 [21]	70	M	6	3	NR	Paraparetic				
15 [22]	76	F	8	11	0/5 proximal muscles LL, 2-3/5 distal muscles LL	Typical	+			
16 [23]	54	F	21	17	3/5 proximal muscles LL and 4/5 distal muscles LL	Paraparetic	+			
17 [24]	66	F	10	3	4/5 distal muscles UL	Typical	+	+		
18 [25]	61	M	10	2	Normal	Bilateral facial palsy	+	+		
Mean 62	Ratio (M:F)	10:8	Mean 9	Mean 5		Typical GBS, 13 patients; GBS variant, 5 patients	Total n of patients 11	Total n of patients 3	Total n of patients 1	

COVID-19, coronavirus disease 2019; F, female; GBS, Guillain-Barré syndrome; LL, lower limbs; M, male; MRC, Medical Research Council scale; NR, not reported; UL, upper limbs.

Table 4 Ancillary tests, treatment and outcome of reported Guillain-Barré cases associated with SARS-CoV-2 infection

Patients	Brighton criteria level	CSF findings	EDX subtype	Reason for meeting the EDX subcategory	Antiangiioside antibodies	MRI results	Treatment for GBS	Medical interventions	Follow-up (days) from GBS onset	Reported outcome
1 [12]	1	Protein level 101 mg/dl; white cell count 4 per mm ³ ; negative PCR assay for SARS-CoV-2	AMSAN		Negative	Enhancement of caudal nerve roots	IVIg	NIV	30	Poor outcome including persistence of severe UL weakness, dysphagia, and LL paraplegia
2 [12]	1	Protein level 123 mg/dl; no cells; negative PCR assay for SARS-CoV-2	AMSAN		NP	Enhancement of facial nerve bilaterally	IVIg		30	Mild improvement including decrease in ataxia and facial weakness
3 [12]	1	Protein level 193 mg/dl; no cells; negative PCR assay for SARS-CoV-2	AMAN		Negative	Enhancement of caudal nerve roots	IVIg	IV	30	Poor outcome including ICU admission owing to neuromuscular respiratory failure and flaccid tetraplegia
4 [12]	2	Normal; negative PCR assay for SARS-CoV-2	AIDP		NP	Head and spine normal	IVIg		30	Improved but unable to stand after 1 month
5 [12]	2	Normal; negative PCR assay for SARS-CoV-2	AIDP		Negative	Spine normal	IVIg, PEx	IV	30	Poor outcome
6 [13]	3	NP	EMG not performed		NP	Spine normal	IVIg	NIV	NR	Improvement with liberation from mechanical ventilation, normal UL strength, persistent LL weakness
7 [14]	1	Protein level 124 mg/dl; no cells	AIDP Ω	F-wave absence in two nerves with distal CMAP $\geq 20\%$ LLN with DML > 150% ULN in one other nerve	NP	NP	IVIg		30	After 1 month normal muscle strength
8 [15]	2	NP	AMSAN		NP	Head and spine normal	IVIg		NR	NR
9 [16]	1	Protein level 54 mg/dl; 9 cells per mm ³ ; negative PCR assay for SARS-CoV-2	AIDP		NP	NP	IVIg	IV	Died	Died

(continued)

Table 4 (Continued)

Patients	Brighton criteria level	CSF findings	EDX subtype	Reason for meeting the EDX subcategory	Antiganglioside antibodies	MRI results	Treatment for GBS	Medical interventions	Follow-up (days) from GBS onset	Reported outcome
10 [17]	1	Protein level 166 mg/dl; no cells	AIDP Ω	MCV < 70% LLN in three nerves	Negative	NP	IVIg	IV	NR	NR
11 [18]	1	Protein level 48 mg/dl; white blood cells $1 \times 10^6/L$ (normal $0-8 \times 10^6/L$)	AIDP Ω	MCV < 70% LLN in two nerves plus DML > 150% ULN in two nerves	NP	NP	IVIg	IV	4	NR
12 [19]	1	Protein level 100 mg/dl; no cells	AMSAN		NP	NP	IVIg		17	No improvement after 1 week with persistence of quadriplegia
13 [20]	2	NP	AIDP		NP	NP	IVIg		NR	Improvement
14 [21]	1	Albuminocytological dissociation without intrathecal IgG synthesis	AIDP		Negative	Spine normal	IVIg		11	Rapid improvement
15 [22]	3	NP	EMG not performed		NP	NP	NP		Died	Died
16 [23]	1	Protein level 140 mg/dl; normal cell count; negative PCR assay for SARS-CoV-2	AIDP		NP	Spine normal	IVIg		14	Complete recovery
17 [24]	1	Protein level 108 mg/dl; no cells; negative PCR assay for SARS-CoV-2	AIDP		Negative	NP	IVIg	IV	NR	NR
18 [25]	2	Normal; negative PCR assay for SARS-CoV-2	EMG not performed		NP	Head normal	NP		NR	Notable improvement

Ω , electrophysiological subtype revised according to Rajabally's criteria [11]. AIDP, acute inflammatory demyelinating polyneuropathy; AMSAN, acute motor axonal neuropathy; AMAN, acute motor axonal neuropathy; CMAP, compound muscle action potential; CSF, cerebrospinal fluid; DML, distal motor latency; EDX, electrophysiological; EMG, electromyography; GBS, Guillain-Barré syndrome; ICU, intensive care unit; IgG, immunoglobulin G; IV, invasive ventilation; IVIg, intravenous immunoglobulin; LL, lower limbs; LLN, lower limit normal; MCV, motor conduction velocity; MRI, magnetic resonance imaging; NIV, non-invasive ventilation; NP, not performed; PCR, polymerase chain reaction; PEx, plasma exchange; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; UL, upper limbs; ULN, upper limit normal.

Table 5 Clinical characteristics, ascertainment and treatment of SARS-CoV-2 infection

Patients	Diagnostic SARS-CoV-2 testing		Screening for other infective agents	Fever	Cough	Dyspnea	Ageusia	Hyposmia	Diarrhea	Lung imaging	Treatment
	NP swab, IgG Ω	NT									
1 [12]	NP swab, IgG Ω	NT		+	+					IP	
2 [12]	NP swab	NT		+						Normal	
3 [12]	NP swab	NT		+	+					IP	Azithromycin
4 [12]	NP swab, IgG Ω	NT		+	+		+			Normal	
5 [12]	IgG Ω	Negative for CJ, EBV, CMV, HSV, VZV, influenza, HIV		+	+		+			IP, then acinetobacter pneumonia	
6 [13]	NP swab	Positive for CD and rhinovirus		+	+					IP	Amoxicillin, steroids, hydroxychloroquine
7 [14]	NP swab	NT		+	+					IP	Arbidol, lopinavir, ritonavir
8 [15]	NP swab	NT		+	+					IP	Hydroxychloroquine, lopinavir, ritonavir, azithromycin
9 [16]	NP swab	NT		+	+					IP	Lopinavir, ritonavir, hydroxychloroquine
10 [17]	NP swab	Negative for CJ, MP, SE, CMV, EBV, HSV-1, HSV-2, influenza virus A and B, HIV, hepatitis E		+	+					IP	Paracetamol, heparin, lopinavir, ritonavir
11 [18]	NP swab	Negative for MP, CMV, LP, SP		+	+					IP	Hydroxychloroquine, azithromycin
12 [19]	NP swab	NT		+						IP	Hydroxychloroquine, lopinavir, ritonavir, amoxicillin, steroids
13 [20]	NP swab	NT							+	IP	
14 [21]	NP swab, IgG ^a	Negative for CMV, EV, HSV-1, HSV-2, HHV-6, HP, VZV, EC, HI, LM, NM, SA, SP, CN in the CSF									
15 [22]	NP swab	NT		+	+					IP	Amoxicillin, azithromycin
16 [23]	NP swab	Negative for LD, CJ and HIV		+			+			Normal	
17 [24]	NP swab	NT		+	+					IP	Hydroxychloroquine, lopinavir, ritonavir
18 [25]	NP swab	NT		+	+					IP	Hydroxychloroquine, lopinavir, ritonavir

Ω SARS-CoV-2 IgG (chemiluminescence immunoassay, Maglum). CD, *Clostridium difficile*; CJ, *Campylobacter jejuni*; CMV, cytomegalovirus; CN, *Cryptococcus neoformans*; CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; EC, *Escherichia coli*; EV, enterovirus; HHV, human herpesvirus; HI, *Haemophilus influenzae*; HIV, human immunodeficiency virus; HP, human parechovirus; HSV, herpes simplex virus; IgG, immunoglobulin G; IP, interstitial pneumonia; LD, Lyme disease; LM, *Listeria monocytogenes*; LP, *Legionella pneumophila*; MP, *Mycoplasma pneumoniae*; NM, *Neisseria meningitidis*; NP, nasopharyngeal; NT, not tested; SA, *Streptococcus agalactiae*; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SE, *Salmoneella enterica*; SP, *Streptococcus pneumoniae*; VZV, varicella zoster virus. ^aSerum anti-SARS-CoV-2 IgA and IgG ELISA (EUROIMMUN, Seekamp, Germany).

The most frequent electrophysiological subtype was AIDP (10 patients), followed acute motor and sensory axonal neuropathy (four patients) and acute motor axonal neuropathy found in one patient. CSF was examined in all except four of the patients. Increased protein level and albuminocytological dissociation with normal cell count were present in 11 (61%) patients. Antiganglioside antibodies were tested in six patients, being negative in all. In 10 patients, head and/or spine MRI was performed, showing enhancement of caudal nerve roots in two patients and of facial nerve bilaterally in one. Only six patients were tested for other infections that have been associated with GBS or acute polyradiculopathy (Table 5). All tested cases were negative for a recent or ongoing non-COVID-19 infection except for one patient who was diagnosed with *Clostridium difficile* colitis and resulted positive for rhinovirus at nasopharyngeal swab. In the CSF, the polymerase chain reaction (PCR) test for SARS-CoV-2 was carried out for nine patients, being negative in all. All the patients except two were treated with intravenous immunoglobulin (IVIg); two received a second course of IVIg and one also plasma exchange. Outcome was reported in all the patients except four. Mechanical ventilation was necessary in eight (44%) patients (all except one of them with a documented interstitial pneumonia at lung imaging). In all the patients mechanical ventilation was started after GBS onset. Compared to GBS related to other etiologies, frequency of mechanical ventilation was not significantly different ($P = 0.1788$) [27]. Intensive care unit admission was necessary in six patients. Two patients died. Death was reported to be caused by progressive respiratory insufficiency in both these patients, although it was not specified whether this was due to GBS or COVID-19. Frequency of death was not significantly different from that observed in GBS related to other etiologies ($P = 0.1045$) [28]. In eight patients an improvement after treatment for GBS was observed, whereas in four patients a poor outcome or lack of improvement was reported. In 11 patients, treatment for COVID-19 was initiated. The duration of follow-up was reported only in 10 patients and ranged from 4 to 30 days (mean 23 days; median 30 days).

Discussion

Our systematic review shows that published cases of SARS-CoV-2 related GBS generally report a sensorimotor, predominantly demyelinating GBS with a typical clinical presentation. Clinical features and disease course seem similar to those observed in GBS related to other etiologies.

COVID-19 has infected almost 5 million individuals worldwide and killed over 314 319 people so far at the writing of this paper [29]. Neurological symptoms associated with SARS-CoV-2 infection have been observed by Mao *et al.* [30], but none of the 214 patients reported in their series had GBS. Serial electrophysiology has been suggested as more accurate than a single study to establish the electrophysiological subtype of GBS [11,31]. Only one of the patients included in this review underwent a second electrophysiological study. In three patients it was possible to revise the electrophysiological results using Rajabally's criteria [11]. The time between onset of infectious illness and the first neurological symptoms, the lack of cells in the CSF, the negative PCR assay for SARS-CoV-2 in the CSF performed in half of the patients, and the reported improvement after IVIg suggests a post-infectious dysimmune underlying pathological mechanism rather than a direct effect of the virus. Dysregulation of the immune system due to COVID-19 has been reported [32]. Positivity of nasopharyngeal swab and the presence of interstitial pneumonia in most of the patients may suggest a 'parainfectious' time pattern of GBS. However, if it is considered that the incubation period of SARS-CoV-2 is about 1 week [33] and may be as long as 24 days in some patients [34], a post-infectious mechanism seems more likely. This could also explain the reason for GBS predating COVID-19 symptoms in one patient [14]. These results should be interpreted with caution, however, since the cases included in this systematic review are variable in diagnostic ascertainment and reporting of variables. Only few of the patients were tested for other infectious agents that are known to be associated with GBS. One patient resulted positive for *Clostridium difficile* and rhinovirus, but these infectious agents are not known to be associated with GBS [1,2] and they are commonly encountered in hospitalized patients. A coincidental association between COVID-19 and GBS remains possible. An Italian multicenter case-control study is currently ongoing to investigate this association. The mean time between the onset of the antecedent infective symptoms and the start of neurological symptoms, the age distribution of the patients, the greater male frequency, the time to nadir of neurological symptoms are all in line with previous studies on GBS [1,2]. All the patients except two fulfilled the Brighton criteria level 1 or 2. Antiganglioside antibodies were negative in all the patients who were tested. These antibodies are typically associated with the axonal variant of GBS [35], which seems to be encountered in a minority of the patients with GBS associated with SARS-CoV-2 infections. Future studies should evaluate whether patients

with GBS associated with SARS-CoV-2 are a specific subgroup with different target antigens. Most patients with COVID-19 are asymptomatic [36]. Inversely, all the patients included herein reported symptoms of COVID-19, although this may be due to an observer bias. Almost half of the patients received mechanical ventilation, a proportion that is not statistically different from that observed in GBS related to other etiologies. It is possible that the GBS-induced pulmonary dysventilation adds to the respiratory problems caused by the presence of COVID-19 pneumonia, observed in most of the patients reported. Also, the mortality (11%) of GBS related to SARS-CoV-2 infection seems similar to that observed in non-SARS-CoV-2 GBS (3%–10%). Further studies, however, are needed to confirm these findings.

The limitations of our systematic review include the scarcity of cases analyzed, the large variability of diagnostic ascertainment of GBS and SARS-CoV-2 and the short follow-up of the patients. Moreover, the electrophysiological criteria used for diagnosis were not reported in most cases and the presence of other preceding infections was investigated in only a few patients.

Published cases of GBS associated with COVID-19 report a sensorimotor, predominantly demyelinating GBS with a typical clinical presentation. Clinical features and disease course seem similar to those observed in GBS related to other etiologies. These results should be interpreted with caution since only 18 cases have been heterogeneously reported so far.

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Disclosure of conflict of interest

The authors declare no financial or other conflicts of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. PRISMA flow chart

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