

REVIEW

Guillain-Barré syndrome in SARS-CoV-2 infection: an instant systematic review of the first six months of pandemic

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ABSTRACT

A systematic review from 1 January to 30 June 2020 revealed 42 patients with Guillain-Barré syndrome (GBS) associated with SARS-CoV-2 infection. Single cases and small series were reported from 13 countries, the majority from Europe (79.4%) and especially from Italy (30.9%). SARS-CoV-2 infection was demonstrated by nasopharyngeal swab (85.7%) and serology (14.3%). Median time between COVID-19 and GBS onset in 36 patients was 11.5 days (IQR: 7.7–16). The most common clinical features were: limb weakness (76.2%), hyporeflexia (80.9%), sensory disturbances (66.7%) and facial palsy (38.1%). Dysautonomia occurred in 19%, respiratory failure in 33.3% and 40.5% of patients were admitted in intensive care unit. Most patients (71.4%) had the classical clinical presentation but virtually all GBS variants and subtypes were reported. Cerebrospinal fluid (CSF) albumin-cytological dissociation was found in 28/36 (77.8%) and PCR for SARS-CoV-2 was negative in 25/25 patients. Electrodiagnosis was demyelinating in 80.5% and levels 1 and 2 of Brighton criteria of diagnostic certainty, when applicable, were fulfilled in 94.5% patients. Antiganglioside antibodies were positive in only 1/22 patients. Treatments were intravenous immunoglobulin and/or plasma exchange (92.8%) with, at short-time follow-up, definite improvement or recovery in 62.1% of patients. One patient died. In conclusion, the most frequent phenotype of GBS in SARS-CoV-2 infection is the classical sensorimotor demyelinating GBS responding to the usual treatments. The time interval between infectious and neuropathic symptoms, absence of CSF pleocytosis and negative PCR support a postinfectious mechanism. The abundance of reports suggests a pathogenic link between SARS-CoV-2 infection and GBS but a case-control study is greatly needed.

INTRODUCTION

SARS-CoV-2 and its associated COVID-19 were reported to originate in December 2019 in Wuhan (China) spreading rapidly around the world. On 30 January 2020, the WHO declared the SARS-CoV-2 a public health emergency of international concern and by 6 July, when this review was completed, there have been 11. 327. 790 confirmed cases of COVID-19 including 532. 340 deaths.

COVID-19 is a systemic disorder presenting typically with fever and respiratory symptoms but neurological manifestations such as acute cerebrovascular diseases, seizures, ageusia, anosmia

meningitis, encephalitis and skeletal muscle involvement were soon reported.¹ More recently, progressively increasing case reports of Guillain-Barré syndrome (GBS) in SARS-CoV-2 infection raised the concern over a possible association.

This may not surprise as approximately 70% of patients with GBS have a preceding illness and infectious agents such as *Campylobacter jejuni*, Influenza virus, *Cytomegalovirus* and recently Zika virus have been demonstrated to trigger GBS.^{2–5}

Aim of this study is, by a systematically review of the reported cases of GBS in SARS-CoV-2 infection, to clarify the clinical and electrophysiological phenotype, to discuss, on the basis of the available data, whether the disease mechanism could be para-infective or postinfective and to speculate on the possible pathogenesis.

METHODS

A PubMed search was completed on 6 July to identify papers reporting patients with GBS with SARS-CoV-2 infection and COVID-19 from 1 January to 30 June 2020 using the following terms: "Guillain-Barré syndrome", "Miller Fisher syndrome", "cranial polyneuritis", "facial diplegia", "Acute sensory ataxia", "Bickerstaff encephalitis" "acute inflammatory demyelinating polyneuropathy", "acute motor axonal neuropathy", "acute motor and sensory axonal neuropathy" combined with "SARS-CoV-2" and "COVID-19". Reference lists of articles were also examined. Full-text papers in English were analysed and those reporting sufficiently detailed information, according to a predefined list of 12 items (the headings of online supplementary table 1), were selected. Duplicated reports were searched by author names and patient's characteristics. Data were extracted from reports according to a template. 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 (%). If clinical features were reported at multiple time points, data representing the full disease course were presented. Continuous variables (age, time between infectious and neuropathic symptoms) were expressed as medians. Certainty of GBS and Miller Fisher syndrome (MFS) diagnosis was assessed, on the basis of the reported findings, by the Brighton Collaboration GBS Working Group criteria.⁶ Level 1 of Brighton criteria indicate the highest degree of diagnostic certainty supported



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by nerve conduction studies and the presence of albuminocytological dissociation in cerebrospinal fluid (CSF). A level 2 diagnosis is supported by either a CSF white-cell count of less than 50 cells/ μ l (with or without an elevated protein level) or nerve conduction studies consistent with the polyneuropathy patterns described for GBS and MFS (if the CSF is unavailable). A level 3 diagnosis is based on clinical features without support from nerve conduction or CSF studies. A diagnostic classification was also employed to categorise the different GBS and MFS presentations.⁷ This systematic review was made following, when applicable, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.⁸

RESULTS

A total of 33 papers (28 single case reports) describing GBS variants and subtypes in patients with SARS-CoV-2 infection were found. No duplicated reports were identified and overall 42 patients were included in the systematic review.^{9–41}

The demographic data, the clinical, laboratory and imaging findings of the 42 patients, are detailed in the online supplemental table 1 and summarised in tables 1 and 2. Because of the characteristics of the reports, the low number of patients and the variability in the reported features, we described the studies and summarised their results qualitatively and quantitatively rather than by a meta-analysis approach. The median age was 57.5 years, and the majority of patients were men (64.3%). The first patient, a woman who returned from Wuhan to Shanghai, was reported online on 1 April 2020.⁹ Overall, patients were reported from 13 countries but mostly from Europe (79.4%) and especially from Italy (30.9%).

Six (14.3%) patients were admitted to the hospital because of COVID-19 symptoms and developed GBS during hospitalisation; 4 (9.5%) were admitted for COVID-19, discharged and then readmitted because of the onset of neuropathic symptoms; 32 (76.2%) patients presented to the hospital because of neuropathic symptoms. The diagnosis of SARS-CoV-2 infection was made by positive RT-PCR of nasopharyngeal swab in 36 (85.7%) patients (sometimes after repeated tests) and when negative by serology in 6 (14.3%) patient (online supplementary table). Diagnosis of SARS-CoV-2 infection was made before the onset of GBS in 16 (38.1%) patients, in 21 (50%) patients during the hospitalisation for GBS and in 2 (4.8%) patients retrospectively by serology. In three patients, no information on the timing of diagnosis was given.

Other preceding infections related to GBS such as *C. jejuni*, *Cytomegalovirus*, hepatitis E, *Mycoplasma pneumoniae* and Epstein-Barr virus, varicella zoster virus, HIV were variably searched for and excluded in seven patients.

Most frequent presenting symptoms of COVID-19 were fever (73.8%) and cough (66.7%). Hypoageusia and hyposmia were reported in 38% and 26.2% of patients. One patient did not present any sign of and four were oligosymptomatic showing only mild loss of smell and taste, or dry cough and low-grade fever that resolved spontaneously in few days.^{16 25 30 32 36} Interstitial pneumonia was documented by chest RX or CT in 61.9% of patients. Specific information on treatment of COVID-19 was reported in 20 (47.6%) patients. Thirteen patients were treated with hydroxychloroquine and antiretroviral drugs (lopinavir and ritonavir) alone or in combination. Seven patients received azithromycin alone or in combination with hydroxychloroquine. In two patients, additional treatment with steroids or tocilizumab was reported.

Table 1 Demographic, geographical, clinical and laboratory features of patients with SARS-CoV-2 and Guillain-Barré syndrome (GBS)

	Number (%)
Number of patients	42
Age: years, median (IQR) (range)	57.5 (50.7–65.2) (21–77)
Gender: males:females	27 (64.3):15 (35.7)
Country	
Italy	13 (30.9)
Spain	7 (16.7)
France	5 (11.9)
USA	4 (9.5)
Switzerland	4 (9.5)
Iran	2 (4.8)
China	1 (2.4)
Canada	1 (2.4)
Germany	1 (2.4)
Turkey	1 (2.4)
Austria	1 (2.4)
The Netherlands	1 (2.4)
UK	1 (2.4)
Diagnosis of SARS-CoV-2 infection	
Nasopharyngeal swab positive	36 (85.7)
Serology positive	6 (14.3)
Presenting symptoms of COVID-19	
Asymptomatic	1 (2.4)
Oligosymptomatic	4 (9.5)
Fever	31 (73.8)
Cough	28 (66.7)
Dyspnoea	7 (16.7)
Headache	5 (11.9)
Hypoageusia	16 (38.0)
Hyposmia	11 (26.2)
Gastrointestinal	8 (19.0)
Myalgia	7 (16.7)
Interstitial pneumonia	26 (61.9%)
Relationship between onset of COVID-19 and GBS symptoms	
Not reported or not calculable	4 (9.5)
GBS as presenting feature	2 (4.8)
Time interval between onset of COVID-19 and GBS in 36 patients: days, median (IQR) (range)	11.5 (7.7–16) (3–28)
COVID-19 clinically resolved before GBS	11 (26.2)

The temporal relationship between onset of COVID-19 symptoms and GBS was not reported or not calculable in four (9.5%) patients. In the very first reported, Chinese patient, the onset of neuropathic symptoms preceded by 8 days fever, cough, pneumonia and positive nasopharyngeal swab. However, at admission, the patient presented lymphocytopenia and thrombocytopenia suggesting an antecedent SARS-CoV-2 infection.⁹ In another patient, GBS was the presenting feature and COVID-19 symptoms never developed although chest CT revealed ground glass opacities.³⁰ The mean interval between onset of COVID-19 and GBS symptoms in the remaining 36 patients was 11.5 days (IQR: 7.7–16; range: 3–28 days). In 11/42 (26.2%) patients, the COVID-19 symptomatology clinically resolved before the onset of GBS. In the remaining patients, the neuropathic symptomatology started while COVID-19 was ongoing. The most commonly reported clinical features of GBS were: limb weakness (64.3% tetraparesis, 11.9% lower limbs

Table 2 Clinical and laboratory features of patients with Guillain-Barré syndrome (GBS) associated with SARS-CoV-2 infection

	Number (%)
Total number of patients	42
Neurological features	
Confusion and agitation	1 (2.4)
Ophthalmoparesis	7 (16.7)
Facial palsy	16 (38.1) bilateral 13/16 (81.2)
Bulbar palsy	11 (26.2)
Four limbs weakness	27 (64.3)
Weakness limited to LLs	5 (11.9)
Hyporeflexia	34 (80.9)
Sensory disturbances	28 (66.7)
Ataxia	10 (23.8)
Dysautonomia	8 (19.0)
Clinical classification	
Classic GBS	30 (71.4)
Paraparetic	2 (4.8)
Facial diplegia with/without paraesthesia	3 (7.1)
Cranial polyneuritis	2 (4.8)
Miller Fisher syndrome	3 (7.1)
Acute ataxic neuropathy	2 (4.8)
Electrodiagnosis	
Not done	6 (14.3)
AIDP	29/36 (80.5)
AMAN	1/36 (2.8)
AMSAN	5/36 (13.9)
Equivocal	1/36 (2.8)
CSF	
Not done	6 (14.3)
Normal	8/36 (22.2)
Albuminocytological dissociation	28/36 (77.8)
RT-PCR for SARS-CoV-2 negative	25/25(100)
Antiganglioside antibodies	
Not done	20 (47.6)
Negative	21/22 (95.5)
GD1b (1gG)	1/22 (4.5)
MRI	
Not done	17 (41.5)
Normal/not contributory	16/25 (64.0)
Cranial nerves enhancement	5/25 (20.0)
Roots/plexus enhancement	5/25 (20.0)
Brainstem and spine leptomeningeal enhancement	1/25 (4.0)
Brighton criteria	
Not applicable	7 (16.7)
Level 1	19/35 (54.3)
Level 2	14/35 (40.0)
Level 3	2/35 (5.7)
Respiratory failure	
Non-invasive ventilation	2/14 (14.3)
Invasive ventilation	12/14 (85.7)
ICU admission	17 (40.5)
Immunotherapy	
Not reported	1 (2.4)
Not done	1 (2.4)
IVIg	35 (83.3)
PE	2 (4.8)
IVIg and PE	2 (4.8)

Continued

Table 2 Continued

	Number (%)
Oral steroids	1 (2.4)
Follow-up	
Not reported	5 (12.0)
Death	1/37 (2.7)
No improvement	4/37 (10.8)
Minimal/slight improvement	7/37 (18.9)
Definite improvement	16/37 (43.2)
Recovery	7/37 (18.9)

AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; AMSAN, acute motor and sensory axonal neuropathy; CSF, cerebrospinal fluid examination; ICU, intensive care unit; IVIG, intravenous immunoglobulin; LLs, lower limbs; PE, plasma exchange; RT-PCR, reverse transcriptase PCR.

paraparesis), hyporeflexia (80.9%), sensory disturbances (66.7%) and facial palsy (38.1%, in 81.2% bilateral). Dysautonomia occurred in 19.5% of patients. Three patients had urinary retention,^{14 18 38} three unstable blood pressure,^{31 40} one severe drug-resistant hypertension,¹⁹ one gastroplegia, paralytic ileus and loss of blood pressure control.²⁸ One patient showed transient episodes of confusion and agitation possibly imputable to the severity of COVID-19.²¹ According to the clinical diagnostic classification, most patients (71.4%) had the classic form of GBS characterised by symmetrical weakness of the limbs, sensory symptoms and reduced or absent tendon reflexes. Two patients (4.8%) had the paraparetic form, three (7.1%) facial diplegia with or without paraesthesia, two (4.8%) cranial polyneuritis, three (7.1%) MFS and two (4.8%) could be classified as an acute ataxic neuropathy. Most of patients (80.5%) had electrodiagnostic features of acute inflammatory demyelinating polyradiculoneuropathy (AIDP). Five patients (13.9%) were reported to have the acute motor and sensory axonal subtype; however, the examination of the electrophysiological results, when available, showed in at least one case increase distal motor latencies, slow conduction velocities and prolonged F wave latencies well in the demyelinating range.^{5 11} CSF examination was performed in 36 (85.7%) patients and showed albuminocytological dissociation in 28 (77.8%). The search for the viral RNA in CSF was negative in all 25 cases in whom was done. Antigangliosides antibodies were searched in 22 (52.4%) patients and IgG to GD1b was found in only one (4.5%) patient with MFS.¹³ MRI of head, spine and nerves was performed in 25 (59.5%) patients and showed thickening or contrast enhancement of cranial nerves and of nerve roots in 10 (40%) patients. A leptomeningeal brainstem and spine enhancement was described in one patient.³³ The Brighton criteria for diagnostic certainty of GBS and MFS were not applicable in the seven patients diagnosed as facial diplegia, cranial polyneuritis and acute ataxic neuropathy. In the remaining 35 patients: 54.3% reached the level 1 (the highest) of certainty, 40% the level 2 and 5.7% the level 3. Respiratory failure occurred in 14 (33.3%) patients and required invasive ventilation in 12 (85.7%). Intensive care unit (ICU) admission was required in 40.5% of patients. In 12 patients, respiratory failure developed after the diagnosis of GBS; on the other hand, two patients were already on invasive ventilation for COVID-19 pneumonia when neuropathic symptoms started.²⁸ It was often difficult to dissect in the individual subject the relative contribution of interstitial pneumonia and GBS in inducing respiratory failure. However, the presence of hypercapnia, paradox respiration, acidosis (suggesting a neuromuscular respiratory failure) or

a picture of mild interstitial pneumonia not compatible with the respiratory status could be identified in 7/14 (50%) patients indicating that in these cases GBS was the main cause for respiratory failure.^{10 12 17 27 35 37 38}

Thirty-five (87.5%) patients were treated with intravenous immunoglobulins (IVIG) and two (5%) with plasma exchange. Two (5%) patients received both. In one patient, low dosage of oral steroids was administered.²² In one patient, treatment was not reported and another with bilateral VI nerve palsy and areflexia was treated symptomatically with acetaminophen and spontaneous recovery occurred in 2 weeks.¹³

Follow-up was not reported in 5/42 (12%) patients; follow-up interval was specified in 15 patients and the median time was 14 days (IQR 10–30, range 1–60 days). No improvement was described in 4/37 (10.8%) patient, minimal or slight improvement in 7 (18.9%), definite improvement in 16 (43.2%) and recovery in 7 (18.9%). Only one patient died.¹⁹

DISCUSSION

Starting from 1 April and until 30 June 2020, 42 patients with SARS-CoV-2 infection and GBS have been reported mostly from Europe and particularly from Italy. Curiously, looking at the chronology of the online publications (online supplementary table), it seems that case reports have followed, with some delay, the virus trail: first from China, then Iran, France, Italy, Spain and USA. The classical clinical sensorimotor presentation with hyporeflexia, with or without cranial nerve involvement, was most frequent but virtually all GBS variants and subtypes were described. According to the Brighton criteria, 94% of patients fulfilled the level 1 or 2 indicating a high diagnostic certainty for GBS or MFS. Respiratory failure occurred in about one-third and ICU admission was required in at least 40% of patients. Interstitial pneumonia due to COVID-19 was reported in about two-third of patients. In some patients, it may be difficult to assess the relative role of COVID-19 and GBS in determining the disease severity and the cause of respiratory failure, above all in those in whom GBS developed during ICU stay. Some features as hypercapnia, paradox respiration, acidosis or a discrepancy with the severity of interstitial pneumonia indicated a neuromuscular respiratory failure. The great majority of patients showed the AIDP electrophysiological subtype and CSF albuminocytological dissociation. These features together with cranial nerve involvement can help to distinguish in the ICU setting GBS from critical illness neuropathy and/or myopathy that is expected to happen in patients with severe COVID-19. Patients were treated mainly with IVIG and, at a short time follow-up, 62% showed definite improvement or recovered. This information is important as suggests that GBS in SARS-CoV-2 infection should be treated in the usual way. The abundance of GBS cases reported during the COVID-19 outbreak worldwide may suggest a possible pathogenic link between SARS-CoV-2 and GBS. To date, the incidence of GBS in the 'COVID-19 era' has been analysed only in Friuli Venezia-Giulia, Italy, where an unusual cluster (eight cases) occurred in the months of March and April 2020.²³ Monthly incidence was 0.65/100.000 versus 0.12/10.000 in the same months of previous years with 5.41-fold increase. However, only one patients (twice negative at swab test) had positive serology for SARS-CoV-2 and chest CT scan showing interstitial pneumonia. SARS-CoV-2 may damage the nerves directly by invading the nerves, or by triggering a postinfectious immune response, either via systemic effects as a cytokine storm, or specific attack to neural targets.^{42 43} The frequent early, and often persistent, anosmia and ageusia reported in large cohorts,¹

and the combination with other cranial neuropathies in the cases we analysed, may suggest a neurotropism of SARS-CoV-2. Two similar coronaviruses SARS-CoV and MERS-CoV can enter the CNS via olfactory nerves or retrograde axonal transport through other cranial nerves.⁴⁴ The reported MRI studies showing enhanced oculomotor, trigeminal, facial, nerves roots and plexuses may corroborate this hypothesis but could also simply reflect a postinfectious nerve inflammation. On the other hand, the SARS-CoV-2 spike protein interacts with the GalNAc residue of GM1 and ganglioside dimers for anchoring to cell surface and an immune cross reaction between epitopes within the spike-bearing gangliosides and the sugar residues of surface peripheral nerve glycolipids is possible.⁴⁵ How SARS-CoV-2 may trigger GBS is currently debated, especially if there is a parainfectious or postinfectious (immune-mediated) pathogenesis. GBS is considered the prototype of postinfectious neuropathy usually developing 1–3 weeks after an acute infection.³ Parainfectious neuropathies, as those caused by *Borrelia burgdorferi*, *Brucella* and West Nile virus, develop during or within a few days after the infection by the direct effect of the agent or an hyperimmune response.⁴⁶ However, the distinction between parainfective and postinfective disorders solely on the basis of the time interval seems simplistic when considering the time interval between SARS-CoV-2 infection and GBS for several reasons. COVID-19 may be oligosymptomatic or even asymptomatic and the incubation period is up to 14 days making difficult the calculations of time interval between the infection and the development of GBS.⁴⁷ SARS-CoV-2 infection, in its most severe form, has been thought to evolve through a continuum of three stages: early infection, pneumonia and hyperinflammatory response.⁴⁸ The active viraemia occurs in the first two stages while the immunological and inflammatory complications were observed in the hyperinflammatory phase. In ICU patients, it is difficult to tell when and in which phase GBS develops. Moreover, respiratory symptoms, as well as lung CT scans abnormalities, may persist beyond the acute infection phase. In the cases we reviewed, the median interval between the onset of COVID-19 and GBS symptoms, when calculable, was 11.5 days and in 26.2% of patients GBS started when COVID-19 was clinically resolved. In all tested cases, CSF pleocytosis was absent and PCR for SARS-CoV-2 in CSF negative. Overall, the above findings support more a post-infective than a parainfective mechanism. Regarding a cross-reactive autoimmune pathogenesis involving the gangliosides, antibodies antigangliosides were found only in only one patient making this hypothesis unlikely. Moreover, antiganglioside antibodies are associated with axonal GBS subtypes whereas most of reported cases with SARS-CoV-2 infection were classified as AIDP. The combination of sensorimotor signs with facial palsy, respiratory insufficiency and the demyelinating electrophysiological subtype has been described in patients with GBS with other preceding virus infections, such as *Cytomegalovirus* and more recently Zika virus, suggesting that such clinical and electrophysiological profile may be the signature of an antecedent viral infection, in contrast to a bacterial infection as *Campylobacter jejuni*, that is associated with primary axonal subtypes.^{3 5 49} At last, hydroxychloroquine and antiretroviral drugs, employed in COVID-19 treatment, may rarely cause or increase the risk for peripheral neuropathy.^{50 51} Considered the duration of treatment in patients with COVID-19 infection, we think that the likelihood of inducing a neuropathy is low. Regarding differential diagnosis it should be underlined that these toxic neuropathies are axonal. Limitations of this review are the restriction to English-language publications and the not uniformity, in the considered studies, of the reported features and findings that

made possible to evaluate some features only in subgroups of patients. A general limitations of the existing literature is that the cases, understandably, were investigated on an ad hoc and retrospective basis. In addition, other preceding infections related to GBS were excluded in only few patients and most reports have a short clinical follow-up and limited description of clinical outcome. Not overlooking the difficulties due to a severe, sometimes overwhelming health emergency, to establish if a true association exists between SARS-CoV-2 and GBS a prospective standardised cohort study with a case-control design, with predefined case definition for GBS diagnosis and follow-up, and uniformity in the electrodiagnostic criteria applied is greatly necessary.

CONCLUSIONS

- ▶ Starting from 1 April until 30 June, 42 patients with SARS-CoV-2 infection and GBS have been reported.
- ▶ Most patients had the classical GBS presentation but virtually all variants and subtypes were reported.
- ▶ The great majority of patients showed the AIDP electrophysiological subtype and CSF albuminocytological dissociation.
- ▶ Levels 1 and 2 of Brighton diagnostic criteria of certainty were fulfilled in a very high percentage of patients.
- ▶ Respiratory failure occurred in one-third and ICU admission was in required in 40% of patients.
- ▶ Patients seemed to respond to the usual treatment.
- ▶ The median time interval between COVID-19 symptoms and GBS onset, normal CSF cell count and PCR for SARS-CoV-2 negative support a postinfective autoimmune disorder but antiganglioside antibodies are likely not involved.
- ▶ The abundance of GBS cases reported during the COVID-19 outbreak suggests a pathogenic link but to establish a true association a case-controlled study is greatly needed.

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