SYSTEMATIC REVIEW

COVID-19 and Guillain-Barre Syndrome: a systematic review of case reports [version 1; peer review: awaiting peer review]

Rodrigo M. Carrillo-Larco 1,2, Carlos Altez-Fernandez 3, Sabrina Ravaglia 4, Joaquín A. Vizcarra 5

1Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, United Kingdom of Great Britain and Northern Ireland, W2 1PG, UK
2CRONICAS Centre of Excellence in Chronic Diseases, Universidad Peruana Cayetano Heredia, Lima, Peru
3Facultad de Medicina Alberto Hurtado, Universidad Peruana Cayetano Heredia, Lima, Peru
4IRCCS C., Mondino Foundation, Pavia, Italy
5Department of Neurology, Emory University, Atlanta, USA

Abstract

Background: Guillain-Barre Syndrome (GBS) is a neurological autoimmune disease that can lead to respiratory failure and death. Whether COVID-19 patients are at high risk of GBS is unknown. Through a systematic review of case reports, we aimed to summarize the main features of patients with GBS and COVID-19.

Methods: Without any restrictions, we searched MEDLINE, Embase, Global Health, Scopus, Web of Science and MedXriv (April 23rd, 2020). Two reviewers screened and studied titles, abstracts and reports. We extracted information to characterize sociodemographic variables, clinical presentation, laboratory results, treatments and outcomes.

Results: Eight reports (n=12 patients) of GBS and COVID-19 were identified; one was a Miller Fisher case. Overall, the median age was 62.5 (interquartile range (IQR)=54.5-70.5) years, and there were more men (9/102). GBS symptoms started between 5 and 24 days after those of COVID-19. The median protein levels in cerebrospinal fluid samples was 101.5 mg/dl (IQR=51-145). None of the cerebrospinal fluid samples tested positive for COVID-19. Six patients debuted with ascendant weakness and three with facial weakness. Five patients had favourable evolution, four remained with relevant symptoms or required critical care and one died; the Miller Fisher case had successful resolution.

Conclusions: GBS is emerging as a disease that may appear in COVID-19 patients. Although limited, preliminary evidence appears to suggest that GBS occurs after COVID-19 onset. Practitioners and investigators should have GBS in mind as they look after COVID-19 patients and conduct research on novel aspects of COVID-19. Comparison with GBS patients in the context of another viral outbreak (Zika), revealed similarities and differences that deserves further scrutiny and epidemiological studies.

Keywords

COVID-19, Guillain-Barre Syndrome, neurological complications, pandemic
Introduction
COVID-19 is a disease for which practitioners and researchers are still learning signs/symptoms, risk factors, co-morbidities and outcomes. Although COVID-19 research is rapidly evolving, novel findings deserve in-depth scrutiny to formulate new hypothesis and make solid conclusions. This is the case of COVID-19 presenting along Guillain-Barre Syndrome (GBS), for which there are a few case reports1-6.

GBS is a neurological autoimmune disease that can deteriorate hastily, thus requiring high clinical suspicion, early identification and appropriate management. In the past, also in the context of a viral disease outbreak, it has been pinpointed that Zika virus may be a risk factor for GBS7-10. Whether COVID-19 patients are also at high risk of GBS, is largely unknown. However, the extensive evidence between Zika virus and GBS7-10, makes it relevant to study and decipher if COVID-19 is also associated with GBS. Consequently, to understand the characteristics of patients with COVID-19 and GBS, and to identify potential patterns, we conducted a systematic review of case reports of COVID-19 and GBS.

Methods
Protocol and eligibility criteria
We conducted a systematic review (protocol registration: CRD42020182015) and adhered to the PRISMA guidelines (Extended data: Table S11). We searched case reports of COVID-19 and GBS, both as defined by case report. There were no exposures, interventions, comparison groups or specific outcomes, as we aimed to summarize and describe all case reports of COVID-19 and GBS. The patients could have been studied from any healthcare facility.

Information sources and search
We used six data sources (searched on April 23rd, 2020): MEDLINE, Embase, Global Health, Scopus and Web of Science (the first three through OVID); we also searched MedRxiv. The search terms are available in Extended data: Table S21. The search did not include any restrictions. Active surveillance of key neurological journals and academic news helped identify additional sources after the search was conducted.

Study selection and data collation
Titles, abstracts and full-texts were studied by two reviewers independently (RMC-L and CA-F). Two authors (RMC-L and CA-F) agreed on a data extraction form and piloted it with one report. Extracted information included epidemiological background; disease onset and initial signs/symptoms; laboratory tests and case resolution. The extraction form was not modified during data collection. Data was collected by one reviewer (CA-F) and complemented by others (SR and JV-P).

Synthesis of results
The extracted information was synthesized qualitatively. Because of the limited number of reports and patients, we did not conduct a quantitative synthesis (e.g., meta-analysis).

Ethics
This is a systematic review of published case reports. The original reports, nor this work, provided any personal information of the patients. No human subjects were involved in this research. We did not seek authorization by an Ethics Committee.

Results
Selection process
We found 4 reports in OVID and 1 in MedXriv (Figure 1)1-4,12. We did not find any results in Scopus or Web of Science (Figure 1). In addition, we included 4 reports not yet available in the search results5-6. Finally, we selected 8 reports (n=12)1-4,6,13,14. Notably, one patient was a GBS variant: Miller Fisher6.

Evidence synthesis
The patients were from China (n=1)4, France (n=1)14, Iran (n=1)1, Italy (n=7)2,6,13, Spain (n=1)15, and US (n=1)2; the Spanish team reported the Miller Fisher case1.

The median age across the 12 patients was 62.5 (interquartile range (IQR)=54.5-70.5) years, and there were more men (9/12) than women; the median age in men was 61 (IQR=54-65) whereas in women this was 70 (IQR=61-77) years (Table 1).

In all but one patient, COVID-19 was diagnosed with molecular tests; one patient had the diagnosis made with serological tests (Table 1)7. In all but one patient, GBS was confirmed with cerebrospinal fluid tests or electromyography (Table 1). The Miller Fisher case was diagnosed with serum GD1b-IgG (Table 1)6.

GBS symptoms started between 5–24 days after those of COVID-19 in all but one patient; conversely, in one case, COVID-19 symptoms started 7 days after GBS onset (Table 1)4. In the Miller Fisher case, COVID-19 symptoms began 5 days before (Table 1)6.

The earliest cerebrospinal fluid protein levels ranged from 40 mg/dl to 193 mg/dl (median=101.5, IQR=51-145); protein levels in the Miller Fisher patient was 80 mg/dl (Table 1). All patients whose cerebrospinal fluid was tested for COVID-19, received a negative result (Table 1).

Among GBS patients, 6 debuted with ascendant weakness and 3 with facial weakness (Table 1); in addition, 7 patients evolved to respiratory failure between 4 and 6 days after GBS onset (Table 1).

GBS patients received intravenous immune globulin at 400 mg/kg, and so did the Miller Fisher patient (Table 1). Regarding COVID-19 treatment, three patients received hydroxychloroquine or other medications, including lopinavir and azithromycin (Table 1).

Five patients had a favourable outcome with symptoms remission or mild persistent symptoms, four remained with relevant
symptoms or required critical care, and one patient died (Table 1). The Miller Fisher case had successful resolution (Table 1).

Discussion
Main findings
GBS is emerging as a relevant disease that may appear in COVID-19 patients. Male predominance of GBS in COVID-19 patients seems to follow reports about more severe presentation versus its female counterparts. GBS in COVID-19 patients shows heterogeneous presentations both clinical (e.g., ascending or cranial nerve paralysis) and electrophysiological (e.g., axonal or demyelinating). Temporal correlation of GBS seems to occur after COVID-19 onset. Unlike individual case reports, this synthesis of several cases appears to suggest that GBS occurs after COVID-19 onset; nonetheless, this hypothesis deserves further verification with strong epidemiological evidence. Finally, it is too early to determine if the association between GBS and COVID-19 is related to direct viral neurotoxicity, autoimmunity, or both since no validated serological or polymerase chain reaction cerebrospinal fluid tests are commercially available.

GBS in the context of other viral disease
Although the viral characteristics differ greatly, it is still relevant to make initial comparisons with cases of GBS and Zika virus (Table 2), where there also appears to be a male predominance and the age profile seems similar\(^{15,16}\). In both contexts – COVID-19 and Zika – GBS variants with bilateral facial paralysis. On the other hand, cerebrospinal fluid protein levels seem higher in COVID-19 (Table 2).

The experience and management of Zika virus and GBS has provided relevant evidence. It taught us that GBS can be a potential complication during or (shortly) after a viral disease onset. As clinicians receive COVID-19 patients, a neurological examination should not be overlooked at admission and thereafter. Moreover, acknowledging that GBS can be a potential complication of COVID-19 should allow to secure resources (e.g., treatment) to successfully meet the needs of a GBS and COVID-19 patient.

Research needs
It is still premature to determine a predominance of any of the sociodemographic and clinical features herein summarized. Studies with larger samples and more rigorous design (e.g., retrospective cohorts) are needed to explore this potential association in greater detail to advance the evidence on sociodemographic profiles, clinical presentation and laboratory tests regarding GBS and COVID-19. This way, prognostic factors could be pinpointed so that people at greater risk can be timely managed.

Research comparing GBS associated with COVID-19 and GBS free of COVID-19\(^{15}\) will also be relevant. We encourage

![Figure 1. Selection process.](image-url)
Table 1. Data extracted from the original case reports.

<table>
<thead>
<tr>
<th>First Author</th>
<th>Country / City</th>
<th>Sex</th>
<th>Age</th>
<th>Previous comorbidities</th>
<th>Concurrent diseases</th>
<th>Drugs used before GBS onset</th>
<th>COVID-19 symptoms onset</th>
<th>GBS diagnosis</th>
<th>Method of COVID-19 diagnosis</th>
<th>Autonomic symptoms</th>
<th>Blood count</th>
<th>Other lab values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virani†</td>
<td>Pittsburgh / USA</td>
<td>Male</td>
<td>54</td>
<td>Not reported</td>
<td>Clostridium difficile colitis 2 days before GBS onset</td>
<td>None</td>
<td>10 days before GBS onset</td>
<td>Clinical diagnosis only</td>
<td>RT-PCR</td>
<td>Urinary retention</td>
<td>WBC: 8.6x10^9/L (Hb: 15.4g/dl; PC: 211 x 10^3/L)</td>
<td>Prolactin: 0.15mg/ml</td>
</tr>
<tr>
<td>Zha†</td>
<td>Jinzhou / CHINA</td>
<td>Female</td>
<td>61</td>
<td>Not reported</td>
<td>Arterial hypertension, atrial fibrillation</td>
<td>Ritonavir, Azithromycin, amlodipine, ramipril</td>
<td>7 days after GBS onset</td>
<td>Clinical + CSF analysis + Nerve conduction studies</td>
<td>RT-PCR</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Sedaghat†</td>
<td>Tehran / IRAN</td>
<td>Male</td>
<td>65</td>
<td>None</td>
<td>Clostridium difficile colitis 2 days before GBS onset</td>
<td>None</td>
<td>7 days before GBS onset</td>
<td>Clinical + CSF analysis + Electrophysiological studies</td>
<td>RT-PCR</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Toscano‡</td>
<td>Padova / ITALY</td>
<td>Male</td>
<td>23</td>
<td>Not reported</td>
<td>Arterial hypertension, atrial fibrillation</td>
<td>None</td>
<td>10 days before GBS onset</td>
<td>Clinical + CSF analysis + Electrophysiological studies</td>
<td>RT-PCR</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Toscano‡</td>
<td>Brescia / ITALY</td>
<td>Male</td>
<td>55</td>
<td>Not reported</td>
<td>Arterial hypertension, atrial fibrillation, pericarditis of presumed tubercular origin, 27 years before</td>
<td>None</td>
<td>7 days before GBS onset</td>
<td>Clinical + CSF analysis + Electrophysiological studies</td>
<td>RT-PCR</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Toscano‡</td>
<td>Padova / ITALY</td>
<td>Male</td>
<td>76</td>
<td>Not reported</td>
<td>Arterial hypertension, thrombotic event</td>
<td>None</td>
<td>5 days before GBS onset</td>
<td>Clinical + CSF analysis + Electrophysiological studies</td>
<td>RT-PCR</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Toscano‡</td>
<td>Brescia / ITALY</td>
<td>Male</td>
<td>61</td>
<td>Not reported</td>
<td>Arterial hypertension, thrombotic event</td>
<td>None</td>
<td>7 days before GBS onset</td>
<td>Clinical + CSF analysis + Electrophysiological studies</td>
<td>RT-PCR</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Gutiérrez-Orozco†</td>
<td>Madrid / SPAIN</td>
<td>Male</td>
<td>50</td>
<td>Not reported</td>
<td>None</td>
<td>None</td>
<td>3 days before GBS onset</td>
<td>Clinical + CSF analysis + Electrophysiological studies</td>
<td>RT-PCR</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Padroni†</td>
<td>Romagna / ITALY</td>
<td>Male</td>
<td>90</td>
<td>None</td>
<td>None</td>
<td>Lisinopril</td>
<td>11 days before GBS onset</td>
<td>Clinical + CSF analysis + Electrophysiological studies</td>
<td>RT-PCR</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Camdessanche†</td>
<td>Saint-Etienne / FRANCE</td>
<td>Male</td>
<td>64</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>7 days before GBS onset</td>
<td>Clinical + CSF analysis + Electrophysiological studies</td>
<td>RT-PCR</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Alberti†</td>
<td>Monza / ITALY</td>
<td>Male</td>
<td>71</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>7 days before GBS onset</td>
<td>Clinical + CSF analysis + Electrophysiological studies</td>
<td>RT-PCR</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

**Method of COVID-19 diagnosis**

- RT-PCR
- RT-PCR + CT
- RT-PCR
- RT-PCR
- RT-PCR
- RT-PCR
- RT-PCR
- RT-PCR
- RT-PCR
- RT-PCR
- RT-PCR
- RT-PCR
- RT-PCR
- RT-PCR
- RT-PCR
- RT-PCR
<table>
<thead>
<tr>
<th>First Author</th>
<th>Virani</th>
<th>Zhao</th>
<th>Sedaghat</th>
<th>Toscano</th>
<th>Toscano</th>
<th>Toscano</th>
<th>Toscano</th>
<th>Gutierrez-Ortiz</th>
<th>Padroni</th>
<th>Camdessanche</th>
<th>Alberti</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GBS course</strong> Ascendant weakness with respiratory failure by COVID-19</td>
<td>Ascendant weakness with no respiratory failure.</td>
<td>Ascendant weakness and facial bilateral palsy with no respiratory failure.</td>
<td>Flaccid areflexic tetraplegia evolving to facial weakness, upper-limb paraesthesia (36 hr), and respiratory failure (day 6)</td>
<td>Facial diplegia and generalized areflexia evolving to lower limb paraesthesia with ataxia (day 2)</td>
<td>Flaccid tetraparesis and facial weakness evolving to areflexia (day 2) and respiratory failure (day 5)</td>
<td>Flaccid areflexic tetraparesis and ataxia (day 4)</td>
<td>Facial weakness, flaccid areflexic paraplegia (days 2–3), and respiratory failure (day 4)</td>
<td>Miller Fisher variant: right internuclear ophthalmoparesis and right fascicular oculomotor palsy; gait ataxia and loss of tendon reflexes</td>
<td>Not reported</td>
<td>Ascendant weakness with respiratory failure complicated by COVID-19 pneumonia</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Neuropathy type</strong></td>
<td>Demyelinating</td>
<td>Axonal</td>
<td>Axonal</td>
<td>Axonal</td>
<td>Axonal</td>
<td>Demyelinating</td>
<td>Demyelinating</td>
<td>Not reported</td>
<td>Demyelinating</td>
<td>Demyelinating</td>
<td>Demyelinating</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COVID-19 management</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IVIG (dosing not reported)</td>
<td>400mg/kg IVIG (2 cycles) + temporary mechanical non-invasive ventilation</td>
<td>400mg/kg IVIG (2 cycles) + mechanical ventilation</td>
<td>400mg/kg IVIG for 5 days.</td>
<td>Azithromycin</td>
<td>None, no pneumonia, symptoms already resolved</td>
<td>None, no pneumonia</td>
<td>Complete resolution of Miller Fisher symptoms</td>
<td>Not reported</td>
<td>Arbidol, Lopinavir, Ritonavir, HCQ, Lopinavir, Ritonavir, Azithromycin.</td>
<td>None, no pneumonia</td>
<td>Not reported</td>
</tr>
<tr>
<td>COVID-19 pneumonia</td>
<td>None, no pneumonia, mild respiratory symptoms</td>
<td>None, no pneumonia</td>
<td>None, no pneumonia</td>
<td>None, no pneumonia</td>
<td>None, no pneumonia, symptoms already resolved</td>
<td>Azithromycin</td>
<td>None, no pneumonia</td>
<td>None, no pneumonia</td>
<td>None, no pneumonia, symptoms already resolved</td>
<td>Acetaminophen, Low molecular weight heparin, lopinavir/ritonavir 400/100 mg twice a day for ten days</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Upper extremities symptoms resolved. Lower extremities symptoms persisting on day 18. Patient was sent to a rehabilitation facility.</td>
<td>Symptom improvement over a 30-day course. Discharged home in day 30.</td>
<td>At week 4 had poor outcomes, including ICU admission owing to neuromuscular respiratory failure and flaccid tetraplegia.</td>
<td>At week 4: had improvements, including decrease in ataxia and mild decrease in facial weakness</td>
<td>At week 4: had poor outcomes, including ICU admission owing to neuromuscular respiratory failure and flaccid tetraplegia.</td>
<td>At week 4: flaccid tetraplegia, dysphagia (enteral nutrition), mechanical invasive ventilation</td>
<td>At week 4: had poor outcomes, including ICU admission owing to neuromuscular respiratory failure and flaccid tetraplegia.</td>
<td>Complete resolution of Miller Fisher symptoms</td>
<td>Complete resolution of Miller Fisher symptoms</td>
<td>At day 8 patient remained in ICU with mechanical invasive ventilation.</td>
<td>The patient died because of progressive respiratory failure.</td>
</tr>
</tbody>
</table>

COVID-19, coronavirus 2019 disease; CSF, cerebrospinal fluid; EMG, electromyography; ICU, intensive care unit; IVIG, intravenous immunoglobulin; RT-PCR, real-time polymerase chain reaction; GBS, Guillain-Barré syndrome; WBC, white blood cell count; PC, platelet count; HB, hemoglobin; BUN, blood urea nitrogen; AST, aspartate transaminase; ALT, alanine transaminase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DM, diabetes mellitus; OSAS, obstructive sleep apnea syndrome; CT, computed tomography; BAL, bronchoalveolar lavage.
Table 2. Comparison of GBS in the context of COVID-19 and Zika virus infections.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>GBS and Zika virus</th>
<th>GBS and COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal relationship</td>
<td>Zika symptoms paralleled GBS in 48% of cases16.</td>
<td>In all but one case, COVID-19 symptoms preceded GBS by 5–24 days.</td>
</tr>
<tr>
<td>Possible mechanism</td>
<td>Other periinfection mechanisms may be present.</td>
<td>Possible post-inflammatory syndrome.</td>
</tr>
<tr>
<td>GBS phenotype</td>
<td>GBS variants with bilateral facial paralysis14,15.</td>
<td>GBS variants with bilateral facial paralysis.</td>
</tr>
<tr>
<td>CSF testing</td>
<td>In 10% of patients RT-PCR was positive in cerebrospinal fluid16.</td>
<td>All cases had a negative RT-PCR in cerebrospinal fluid.</td>
</tr>
<tr>
<td>CSF protein levels</td>
<td>Median cerebrospinal fluid protein level: 116mg/dl (IQR=67-171).</td>
<td>Cerebrospinal fluid protein level ranged from 40mg/dl to 193mg/dl (median=101.5; IQR= 51-145).</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Disability at 6 months: mainly facial16.</td>
<td>Not reported.</td>
</tr>
<tr>
<td>Other body fluids</td>
<td>Related to long periods of viruuria16.</td>
<td>Not reported.</td>
</tr>
</tbody>
</table>

RT-PCR, real-time polymerase chain reaction; GBS, Guillain-Barre Syndrome; CSF, Cerebrospinal fluid; IQR, Interquartile range.

clinicians looking after patients with GBS and COVID-19 to report their experiences; furthermore, we invite them to build networks with colleagues and those whose reports were herein summarized, so that they can conduct more robust studies.

**Limitations**

Despite searching six databases, we found few case reports. As it was the case with Zika virus17, more cases may appear later in the pandemic. As the COVID-19 pandemic progresses, clinicians should be aware that GBS and other variants are possible and relevant complications. Our review provides an important first step to better understand the presentation, clinical characteristics and outcomes of COVID-19 and GBS. Epidemiological studies can build on the evidence herein summarised to conduct more robust research.

**Conclusions**

GBS is emerging as a relevant neurological disease in COVID-19 patients. Its pathophysiology and both clinical and electrophysiological characteristics remain to be further studied. The GBS onset appears to occur after the COVID-19 presentation by several days. Practitioners and investigators should have GBS in mind as they look after COVID-19 patients and conduct further research on novel aspects of COVID-19.

**Data availability**

**Underlying data**

All data underlying the results are available as part of the article and no additional source data are required.

**Extended data**


This project contains the following extended data:
- Table S1: PRISMA checklist.
- Table S2: Search terms.

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

**References**


