SYSTEMATIC REVIEW

COVID-19 and Guillain-Barre Syndrome: a systematic review of case reports [version 1; peer review: 1 approved, 1 not approved]

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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

This article is included in the Coronavirus (COVID-19) collection.

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**Competing interests:** No competing interests were disclosed.

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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 reports[1-6].

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 GBS[7-10]. Whether COVID-19 patients are also at high risk of GBS, is largely unknown. However, the extensive evidence between Zika virus and GBS[7-10], 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 S1[1]). 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 S2[1]. 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 results[5-6]. Finally, we selected 8 reports (n=12)[1-6,13,14]. Notably, one patient was a GBS variant: Miller Fisher[5].

Evidence synthesis

The patients were from China (n=1)[1], France (n=1)[4], Iran (n=1)[1], Italy (n=7)[2,6,13], Spain (n=1)[5], and US (n=1)[2]; the Spanish team reported the Miller Fisher case[5].

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). 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).[5]

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).[6] In the Miller Fisher case, COVID-19 symptoms began 5 days before (Table 1).[5]

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).[5] 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
Figure 1. Selection process.

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. 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 will also be relevant. We encourage
Table 1. Data extracted from the original case reports.

| First Author | Country / City | Sex | Age | Previous chronic conditions | Concurrent diseases | Drug used before GBS onset | COVID-19 Diagnosis Methods | GBS Diagnosis Methods | Autonomic symptoms | Blood count | Other lab values |
|--------------|----------------|-----|-----|----------------------------|--------------------|---------------------------|-----------------------------|------------------------|-------------------|-------------|-----------------|
| Sedaghat     | USA            | Male | 64  | None                        | None               | None                      | RT-PCR                      | RT-PCR                 | None              | None         | None            |
| Zhao         | CHINA          | Male | 54  | None                        | None               | None                      | None                        | None                   | None              | None         | None            |
| Padroni      | FRANCE         | Male | 61  | None                        | None               | None                      | None                        | None                   | None              | None         | None            |
| Gutierrez-Ortiz | USA       | Female | 71 | None                        | None               | None                      | RT-PCR + CT                 | RT-PCR                 | None              | None         | None            |

**Notes:**
- **Sex:** Male or Female.
- **Age:** The age of the patient.
- **Previous chronic conditions:** None or specified conditions.
- **Concurrent diseases:** None or specified conditions.
- **Drug used before GBS onset:** None or specified drugs.
- **COVID-19 Diagnosis Methods:** RT-PCR, CT, and other methods.
- **GBS Diagnosis Methods:** RT-PCR, CSF analysis, and other methods.
- **Autonomic symptoms:** None or specified symptoms.
- **Blood count:** WBC and lymphocyte count.
- **Other lab values:** Glucose, creatinine, and other tests.
| First Author | GBS course | Neuropathy type | GBS Management | COVID-19 management | Outcome |
|--------------|------------|----------------|----------------|---------------------|---------|
| Virani       | Ascendant weakness with respiratory failure. | Ascendant weakness with respiratory failure. | Ascendant weakness with respiratory failure. | Ascendant weakness with respiratory failure. | Ascendant weakness with respiratory failure. |
| Zhao         | Ascendant weakness with no respiratory failure. | Ascendant weakness and facial bilateral palsy with no respiratory failure. | Ascendant weakness with no respiratory failure. | Ascendant weakness with respiratory failure. | Ascendant weakness with respiratory failure. |
| Sedaghat     | Ascendant weakness and facial bilateral palsy with no respiratory failure. | Flaccid areflexic tetraplegia evolving to facial weakness; upper limb paralysia (36 hr), and respiratory failure (day 6). | Ascendant weakness with respiratory failure. | Ascendant weakness with respiratory failure. | Ascendant weakness with respiratory failure. |
| Toscano      | Flaccid areflexic tetraplegia evolving to facial weakness; upper limb paralysia (36 hr), and respiratory failure (day 6). | Flaccid tetraparesis and facial weakness evolving to anterior horn cell disease (days 2-3), and respiratory failure (day 5). | Ascendant weakness with respiratory failure. | Ascendant weakness with respiratory failure. | Ascendant weakness with respiratory failure. |
| Toscano      | Flaccid tetraparesis and facial weakness evolving to anterior horn cell disease (days 2-3), and respiratory failure (day 5). | Facial weakness, flaccid areflexic paraplegia (days 2), and respiratory failure (day 4). | Ascendant weakness with respiratory failure. | Ascendant weakness with respiratory failure. | Ascendant weakness with respiratory failure. |
| Toscano      | Facial weakness, flaccid areflexic paraplegia (days 2), and respiratory failure (day 4). | Facial weakness, flaccid areflexic paraplegia and right fascicular oculomotor palsy; gait ataxia and loss of tendon reflexes. | Ascendant weakness with respiratory failure. | Ascendant weakness with respiratory failure. | Ascendant weakness with respiratory failure. |
| Gutierrez-Ortiz | Ascendant weakness with respiratory failure. | Ascendant weakness with respiratory failure. | Ascendant weakness with respiratory failure. | Ascendant weakness with respiratory failure. | Ascendant weakness with respiratory failure. |
| Padroni      | Ascendant weakness with respiratory failure. | Ascendant weakness with respiratory failure. | Ascendant weakness with respiratory failure. | Ascendant weakness with respiratory failure. | Ascendant weakness with respiratory failure. |
| Camdessanche | Ascendant weakness with respiratory failure. | Ascendant weakness with respiratory failure. | Not reported. | Not reported. | Not reported. |
| Alberti      | Ascendant weakness with respiratory failure. | Ascendant weakness with respiratory failure. | Not reported. | Acetaminophen, Low molecular weight heparin, lopinavir/ritonavir 400/100 mg twice a day for 10 days. | Not reported. |

GBS, Guillain-Barré syndrome; IVIG, intravenous immune globulin; Lopinavir+Ritonavir, 400/100 mg twice a day for 10 days; HCQ, hydroxychloroquine; DM, diabetes mellitus; OSAS, obstructive sleep apnea syndrome; CT, computed tomography; BAL, bronchoalveolar lavage.

COVID-19, coronavirus 2019 disease; CSF, cerebrospinal Fluid; EMG, Electromyography; ICU, intensive care unit; IVIG, intravenous immune globulin; 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; HB, hemoglobin; DM, diabetes mellitus; OSAS, obstructive sleep apnea syndrome; CT, computed tomography; BAL, bronchoalveolar lavage.
GBS and Zika virus
Related to long periods of viruuria

GBS and COVID-19
Not reported.

Disability at 6 months: mainly facial
Not reported.

Other periinfection mechanisms may be
Possible post-inflammatory syndrome.

Median cerebrospinal fluid protein level:
Cerebrospinal fluid protein level ranged from 40mg/dl
to 193mg/dl (median=101.5; IQR= 51-145)

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

**Table 2. Comparison of GBS in the context of COVID-19 and Zika virus infections.**

| Characteristics          | GBS and Zika virus                                                                 | GBS and COVID-19                                                                 |
|--------------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Temporal relationship    | Zika symptoms paralleled GBS in 48% of cases<sup>1,2</sup>.                     | In all but one case, COVID-19 symptoms preceded GBS by 5–24 days.              |
| Possible mechanism       | Other periinfection mechanisms may be present.                                   | Possible post-inflammatory syndrome.                                           |
| GBS phenotype            | GBS variants with bilateral facial paralysis<sup>1,3</sup>.                      | GBS variants with bilateral facial paralysis.                                  |
| CSF testing              | In 10% of patients RT-PCR was positive in cerebrospinal fluid<sup>4,5</sup>.     | All cases had a negative RT-PCR in cerebrospinal fluid.                        |
| CSF protein levels       | Median cerebrospinal fluid protein level: 116mg/dl (IQR=67-171).                  | Cerebrospinal fluid protein level ranged from 40mg/dl to 193mg/dl (median=101.5; IQR= 51-145) |
| Prognosis                | Disability at 6 months: mainly facial<sup>6</sup>.                               | Not reported.                                                                  |
| Other body fluids        | Related to long periods of viruuria<sup>6</sup>.                                 | Not reported.                                                                  |

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**

Figshare: COVID-19 and Guillain-Barre Syndrome: A systematic review of case reports, https://doi.org/10.6084/m9.figshare.12317486.v2<sup>11</sup>.

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).

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Version 1

Reviewer Report 08 September 2020

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Maria Regina Fernandes de Oliveira
Centre for Tropical Medicine, University of Brasília, Brasilia, Brazil

Paper: COVID-19 and Guillain-Barre Syndrome: a systematic review of case reports.

The research question is truly relevant because of the epidemiological scenario in all the world.

Methods:
The paper conducted a review of eight reports which describe 12 patients from six countries. The authors summarize some results from 12 patients as median and IQR (ex: median age; median CSF protein levels).

Given that the reports came from different populations and different countries, and not represent a homogeneous data set, It's a methodological mistake to summarize the data in this way. Summarizing the data using these measures could be misleading. The data must be presented individually, report by report. The most acceptable is presenting the data range among the reports for the numerical variables or proportions.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
No

Are the conclusions drawn adequately supported by the results presented in the review?
No

Competing Interests: No competing interests were disclosed.
Reviewer Expertise: Health Technology Assessment; Epidemiology; Infectious diseases.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 09 Sep 2020

Rodrigo M Carrillo-Larco, Imperial College London, London, UK

Dear reviewer,

Thank you very much for taking time and reviewing our work; your input and suggestions are much appreciated.

I appreciate your major comment and understand your concern; however, may I please gently disagree on the following grounds?

1. Your major reservation suggested that our “statistical” approach was not correct, and that we should have not “pooled” the estimates and report means/medians but rather just describe the results (narratively). I think this is a very interesting comment. Nonetheless, we took sort of a “data pooling” approach, in which we summarised, using basic statistics, the main features of the patients. Notably, the individual results were also presented in tables so that the reader could have both, our summaries (means/medians) to have a broad picture of the findings, as well as the results for each patient. We argue that our approach would be similar as if we had accessed the individual-level data of these patients and delivered an individual-level meta-analysis. In that sense, we do not feel our approach was incorrect.

1. Our approach is not new in the literature, and a quick search of published systematic reviews of case reports in the last few months shows the following:
   1. [https://pubmed.ncbi.nlm.nih.gov/32840686/](https://pubmed.ncbi.nlm.nih.gov/32840686/) - this work is an updated version of our research question. And they followed a similar approach reporting, for example: “...the classical albuminocytological dissociation (cell count < 5/µl with elevated CSF proteins) was detected in 71.2% of the cases (42/59) with a median CSF protein of 100.0 mg/dl...” As we did, they presented summary measures (median).
   2. [https://pubmed.ncbi.nlm.nih.gov/32888662/](https://pubmed.ncbi.nlm.nih.gov/32888662/) - this systematic review of case reports conducted a “...exploratory factor analysis of the symptoms was performed.” This is, arguably, a more complex statistical approach than ours. This could also suggest that one can be more flexible on how to handle the statistical analysis of a systematic review of case reports, with plenty of more options than describing the findings narratively.
   3. [https://pubmed.ncbi.nlm.nih.gov/32880011/](https://pubmed.ncbi.nlm.nih.gov/32880011/) - like our work, this review also provided pooled results: “...the mean age at presentation was 69.8 years.”
   4. [https://pubmed.ncbi.nlm.nih.gov/32856065/](https://pubmed.ncbi.nlm.nih.gov/32856065/) - this work also provided pooled proportions across all reviewed patients: “...with respiratory symptoms being the predominant manifestation (70%)."
   5. [https://pubmed.ncbi.nlm.nih.gov/32871559/](https://pubmed.ncbi.nlm.nih.gov/32871559/) - similarly, this work also provided
pooled means: “...The mean age of this population was 25 years (range 2–85 years).”

I am sure there may be plenty of examples in which the authors decided to conduct a systematic review of case reports and only describe the findings, with no “statistical analysis”. However, we opted for a different approach, in which we gently summarised the findings with simple statistics to provide a broad picture of the overall findings. In addition, the individual findings are provided in tables so that the reader have both: i) a summary of the findings expressed with the aid of basic statistics; and ii) the individual results for each reviewed case (i.e., patient). I believe you raised an interesting point, but I argue that our approach is not incorrect. Moreover, we have provided a few examples suggesting that one can be flexible and conduct some statistical analysis with systematic reviews of cases reports, and this does not invalid the findings. Following these arguments, and if possible, we kindly ask for a reconsideration of your decision.

Again, thank you very much for time in reviewing this work, it is much appreciated. Wish you and your family/friends all the best in these uncertain times.

Competing Interests: No competing interests.

Reviewer Response 15 Sep 2020

MARIA OLIVEIRA, University of Brasília, Brasília, Brazil

Dear authors,

In your response you argue “that our approach would be similar as if we had accessed the individual-level data of these patients and delivered an individual-level meta-analysis", but the work didn't perform an individual-level meta-analysis. For such an aproach, please see: Richard D Riley, Paul C Lambert, Ghada Abo-Zaid, "Meta-analysis of individual participant data: rationale,conduct, and reporting". For this rationale, the authors highlight "it is inappropriate to simply analyse individual participant data as if they all came from a single study". On the other hand, there are very few patients from different countries in the reviewed reports, so I suggest not summarize the data as presented. Suppressing medians will not diminish the relevance and quality of the report.

Competing Interests: I declare no competing interests.

Reviewer Report 25 June 2020

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Hugh J Willison
Institute of Infection, Immunity and Inflammation, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK

This review represents a summary of the cases published to date of GBS following COVID-19 infection. The methodology is simply descriptive as the literature in this area is still emerging and case control studies have not been published. It does seem likely from the available reports that typical GBS can follow COVID-19 but that the frequency of this association is uncommon.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: GBS and other autoimmune neuropathy.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.