Guillain Barré Syndrome associated with SARS-CoV-2 infection: a systematic review

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Abbreviations

GBS Guillain Barré Syndrome

CSF Cerebrospinal Fluid

ICU Intensive Care Unit

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Key Words: COVID-19, Coronavirus 2019 Disease, SARS-CoV-2, Guillain-Barré Syndrome, GBS

All Authors equally contributed to the review.

Abstract

Importance: Guillain-Barré syndrome (GBS) incidence may increase worldwide during the coronavirus disease 2019 (COVID-19) pandemic. Clinicians must be aware of the clinical spectrum of GBS associated with COVID-19.

Objective: To identify specific clinical features of GBS associated with COVID-19.

Evidence Review: We searched Pubmed and Cochrane from March 1, 2019 to May 5, 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.

Findings: A total of 14 patients reported in 10 papers were included in this review. All patients except one reported an antecedent illness, 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 8 days; median 10 days). Most of the patients had a typical GBS clinical form with facial palsy and an axonal electrophysiological subtype. Mechanical ventilation was necessary in 7 patients. One patient died.

Conclusions and Relevance: published cases of GBS associated with COVID-19 report a sensorimotor, predominantly axonal GBS with a typical clinical presentation and a frequent facial palsy. Disease course seems severe with half of the cases necessitating mechanical ventilation. These results should be interpreted with caution since only 14 cases have been heterogeneously reported so far.

Introduction

Guillain Barré Syndrome (GBS) is a rare inflammatory disease of the peripheral nervous system affecting mainly males with increasing incidence with age.[1] GBS is the most common cause of acute flaccid paralysis and 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 heterogenous 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 H. 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, coronavirus disease 2019) was detected in December 2019. This new virus has the capacity of entering into the cell through the fusion with angiotensin-converting enzyme 2 (ACE2) receptor.[5] The most recognizable feature of COVID-19 is to cause severe respiratory complications, which largely depends on the overall state of wellbeing of the infected patient. Age, patient's underlying comorbidities (hypertension, cardiovascular disease, and diabetes mellitus) 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 case 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 and evaluate if this differs from GBS triggered by other pathogens.

Methods and materials

Literature search, strategy and compliance with ethical standards

This review follows the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).[9] A comprehensive literature search of the databases PubMed and Cochrane was designed and conducted by the authors. The keywords “COVID 19”, “Coronavirus”, "SARS-CoV-2", “Guillain-Barré syndrome” were used in “AND” “OR” combinations and are summarized 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 March 1, 2019 to May 5, 2020**.** This study is a review of published literature and therefore is exempt from Institutional Review Board (IRB) approval.

Inclusion and Exclusion Criteria

The following predetermined criteria were used to screen the results: (1) Original case reports or (2) case series of patients diagnosed with Guillain-Barré Syndrome who tested positive for SARS-CoV-2 infection (3) written in English, Spanish, French or Italian.

Articles 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 (MRC) score when reported, presence of cranial nerve involvement, dysautonomic symptoms, ataxia, type of treatment, outcome, medical interventions. Results of the ancillary investigations performed for GBS diagnosis were also reported, including cerebrospinal fluid (CSF) exam, Magnetic Resonance Imaging (MRI), and anti-gangliosides antibodies. GBS diagnosis was confirmed using the Brighton Collaboration criteria, specifying level of diagnostic certainty.[10] If the Brighton Criteria were not reported, these were defined based on available reported data.

Results of the electrodiagnostic studies were reviewed and, when normal control values used were also reported, we revised the electrophysiological GBS subtype using the Rajabally's criteria[11], otherwise subtype reported by the authors was included. We chose to use the Rajabally's criteria 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 14 patients reported in 10 papers[12–21] were included in this review. The 10 selected papers consisted in 9 case reports and one series. Figure 1 (PRISMA Diagram) summarizes the flow of 10 articles included in the review. One article was excluded because not relevant and other two because not reporting information on patients.

Clinical Characteristics and Overall Outcome

Table 2 summarizes the patients' demographics and clinical characteristics of the GBS. Table 3 shows the ancillary tests, outcome and treatment for GBS reported for each case. Eleven cases were from Europe, one from the US,[13] one from Iran,[15] and one from Morocco[19]. Nine of the patients were males while 5 were females. Mean age was 61 years (median 64; range 23-77 years). In 10 patients, diagnosis of SARS-CoV-2 were confirmed by nasopharyngeal swab alone, in 3 patients by nasopharyngeal swab plus serological test for the virus, and in one patient by serological test alone (Table 4). All patients had signs of interstitial pneumonia at lung imaging tests except one. Cough (11 patients) and fever (10 patients) were the most frequent observed symptoms of SARS-CoV-2 infection in these patients, followed by dyspnea, ageusia, anosmia, and diarrhea (Table 4). Two or more symptoms were present in 10 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 8 days; median 10 days). In four patients an overlap between symptoms of COVID-19 and symptoms of GBS was reported. All patients had a typical GBS clinical form, except one patient with bilateral facial palsy with paraesthesias, one patient with a pure motor GBS, and another with a paraparetic GBS form. Seven patients had a cranial nerve involvement (most frequently an unilateral or bilateral facial palsy), three patients were ataxic and one had dysautonomic symptoms (urinary retention). The nadir of neurological symptoms was reached in a mean of 3.5 days (median 4 days; range 2-

5 days). Nine patients met the Brighton Collaboration criteria level 1, four patients level 2, and one patient level 3. Electrophysiological studies were performed in all patients but one. Criteria used to classify cases into the different electrophysiological subtypes were reported in only 7 patients. In three cases, normal control values used for nerve conduction studies were reported and the electrophysiological subtype was revised: in one patient we confirmed an acute inflammatory demyelinating polyneuropathy (AIDP) subtype as reported by the authors, in one patient the subtype was changed from AIDP to acute motor and sensory polyneuropathy (AMSAN), while in another we defined an AMSAN subtype (not specified by the authors). The most frequent electrophysiological subtypes were AMSAN and AIDP (6 patients each), followed acute motor axonal neuropathy (AMAN) found in one patient. CSF was examined in all the patients except three. Increased protein level and albuminocytological dissociation with normal cell count were present in 9 patients. Anti-gangliosides antibodies were tested in 5 patients, resulting negative in all. In eight 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 five patients were tested for other infections that have been associated with GBS or acute polyradiculopathy (Table 3). All tested cases were negative for recent or ongoing infection except one patient who was diagnosed with Clostridium difficile colitis and resulted positive for Rhinovirus at nasopharyngeal swab. In the CSF, polymerase chain reaction (PCR) test for SARS-CoV-2 was tested in 6 patients, resulting negative in all. All the patients 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 three. Mechanical ventilation was necessary in 7 patients (all of them, except one, with a documented interstitial pneumonia at lung imaging). Intensive care unit (ICU) admission was necessary in five patients. One patient died.

In 6 patients, an improvement after treatment for GBS was observed whereas in 4 patients a poor outcome or lack of improvement was reported. In 8 patients, specific treatment for COVID-19 was initiated. The duration of follow-up was reported only in 9 of the patients and ranged from 4 to 30 days.

Discussion

COVID-19 has infected over 3.4 million individuals worldwide and killed over 239,614 people so far at the writing of this paper.[22] Neurological symptoms associated with SARS-CoV-2 infection have been observed by Mao et al,[23] but none of the 214 patients reported in their series had GBS. Our systematic review shows that published cases on SARS-CoV-2 related GBS typically present with a sensorimotor polyneuropathy with symmetrical involvement of all four limbs and facial palsy. Most patients seem to have an axonal electrophysiological subtype. Serial electrophysiology has been suggested as more accurate than a single study to establish the electrophysiological subtype of GBS.[11] None of the patients included in this review underwent a second electrophysiological study. In three patients we were able to revise 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 some patients, and the reported improvement after IVIg suggest a post-infectious dysimmune underlying pathological mechanism rather than a direct effect of the virus. Dysregulation of the immune system due to COVID-10 have been reported.[24] Although positivity of nasopharyngeal swab and the presence of interstitial pneumonia in most of the patients at the start of GBS may suggest a 'parainfectious' time pattern, if we consider that the incubation period of SARS-CoV-2 is about one week[25] a post-infectious mechanism seems more likely. These results should however been interpreted with caution 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. 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 one fulfilled the Brighton criteria level 1 or 2. Anti-gangliosides antibodies were negative in all the patients who were tested. These antibodies are often associated with the axonal variant of GBS, which seems the more frequently encountered in patients with GBS associated with SARS-CoV-2 infections.[26] Future studies should evaluate whether patients with GBS associated with SARS-CoV-2 are a specific subgroup with different target agents. Most patients with COVID-19 are asymptomatic.[27] Inversely, all the patients herein reported antecedent infectious, although this may be due to an observer bias. Half of the patients reported herein received mechanical ventilation, a proportion that is higher than expected (22%) by previous literature.[2,28] This data might indicate that GBS associated with SARS-CoV-2 infection is more severe than that associated with other infectious agents observed so far. A possible explanation is that the GBS-induced pulmonary disventilation adds to the respiratory problems caused by the presence of COVID-19 pneumonia, observed in most patients in the patients reported herein. Further studies are needed to confirm this finding. Disease course is reported to be severe in most patients, although the short follow-up of the patients. Limitations of our systematic review include the scarcity of cases analyzed, the large variability of diagnostic ascertainment of GBS and SARS-CoV-2, the short follow-up of the patients.

Moreover, the electrophysiological criteria used for diagnosis were not reported in most cases and presence of other preceding infections was investigated only in a few patients. Taking these limitations into account, published reports on SARS-CoV-2-related GBS generally report a sensorimotor, predominantly axonal GBS with a typical clinical presentation and a frequent facial palsy. Disease course seems severe and half of the cases necessitate mechanical ventilation.

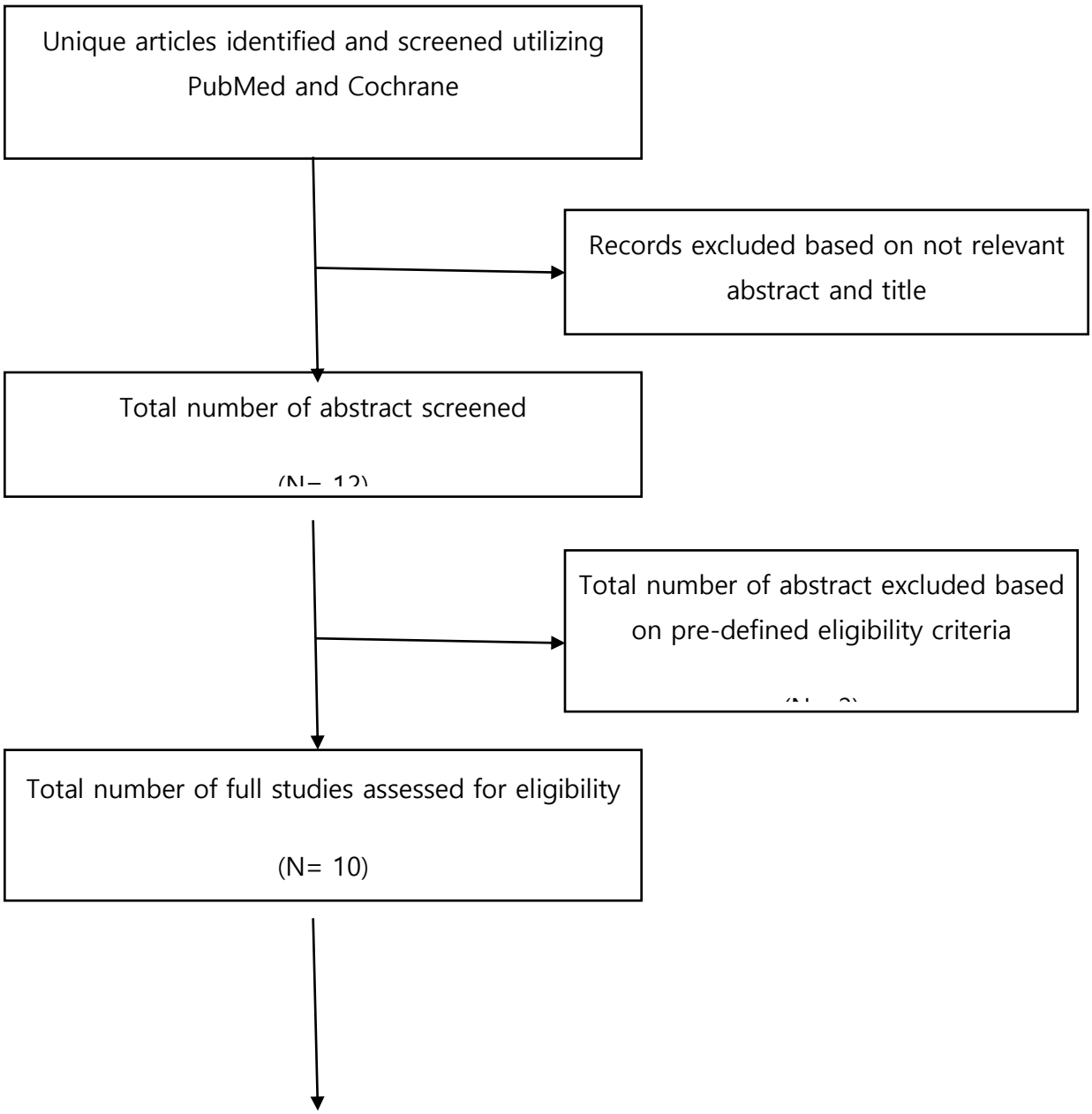
Disclosures

The authors have nothing to disclose.

Table 1. Primary Search Strategy

PUBMED (NLM), searched on May 5, 2020 - Total results: 10
(((((((((("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 ncov"[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])) AND ("Guillain"[All Fields] AND "Barre"[All Fields])
Covid 19: "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-nCoV"[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[PDAT] OR 2020[PDAT]))
Coronavirus: "coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronaviruses"[All Fields]
SARS-CoV-2: "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 May 5, 2020 - Total results: 0
Coronavirus 2019 in Keyword OR covid19 in Title Abstract Keyword AND "Guillain Barré syndrome" in Title Abstract Keyword - (Word variations have been searched)

Supplementary Fig. 1 PRISMA flow chart



Total number of studies included as evidence

(N= 10)

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