COVID-19–associated Guillain-Barré syndrome: The early pandemic experience

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Abstract
Guillain-Barré syndrome (GBS) is an inflammatory polyradiculoneuropathy associated with numerous viral infections. Recently, there have been many case reports describing the association between coronavirus disease-2019 (COVID-19) and GBS, but much remains unknown about the strength of the association and the features of GBS in this setting. We reviewed 37 published cases of GBS associated with COVID-19 to summarize this information for clinicians and to determine whether a specific clinical or electrodiagnostic (EDx) pattern is emerging. The mean age (59 years), gender (65% male), and COVID-19 features appeared to reflect those of hospitalized COVID-19 patients early in the pandemic. The mean time from COVID-19 symptoms to GBS symptoms was 11 days. The clinical presentation and severity of these GBS cases was similar to those with non–COVID-19 GBS. The EDx pattern was considered demyelinating in approximately half of the cases. Cerebrospinal fluid, when assessed, demonstrated albuminocytologic dissociation in 76% of patients and was negative for severe acute respiratory distress syndrome–coronavirus-2 (SARS-CoV-2) in all cases. Serum antiganglioside antibodies were absent in 15 of 17 patients tested. Most patients were treated with a single course of intravenous immunoglobulin, and improvement was noted within 8 weeks in most cases. GBS–associated COVID-19 appears to be an uncommon condition with similar clinical and EDx patterns to GBS before the pandemic. Future studies should compare patients with COVID-19–associated GBS to those with contemporaneous non–COVID-19 GBS and determine whether the incidence of GBS is elevated in those with COVID-19.

KEYWORDS
coronavirus, COVID-19, electrodiagnosis, electrophysiology, Guillain-Barré syndrome, neurological diseases, SARS-CoV-2 virus

1 INTRODUCTION
Coronavirus disease-2019 (COVID-19), caused by the severe acute respiratory distress syndrome–coronavirus-2 (SARS-CoV-2), is primarily a respiratory infection, but has been associated with a variety of neurological symptoms, including dizziness, headache, confusion,
myalgia, and loss of taste and smell. Reports are emerging of several neurological illnesses that co-occur with COVID-19 such as encephalitis and, particularly, stroke. Guillain-Barre syndrome (GBS) is an acute, generalized polyradiculoneuropathy that is preceded by a symptomatic infection such as Campylobacter jejuni, Epstein-Barr virus, influenza, or cytomegalovirus in about two thirds of cases. GBS has been associated with influenza infections and vaccinations and, recently, an increased incidence of GBS was reported during the Zika virus outbreak in South America. GBS associated with COVID-19 is now widely reported, but the strength and mechanism of the association and the clinical and electrodiagnostic (EDx) patterns remain unclear. We undertook a review of the current literature to clarify what is known about GBS-associated COVID-19 during this early stage of the pandemic.

2 | METHODS

This work is a retrospective review of published literature in English of COVID-19–associated GBS identified by a Medline search via PubMed up to June 22, 2020. We accepted a priori the diagnostic criteria for GBS and details of subtype classification (acute inflammatory demyelinating polyneuropathy [AIDP], acute motor axonal neuropathy [AMAN], acute motor sensory axonal neuropathy [AMSAN], and Miller Fisher syndrome [MFS]) used by the authors of the articles, because formal review and classification of the patients was limited by the lack of availability of complete data. We then applied the Hadden electrophysiological criteria for GBS (P.N., R.C.) to each case, depending on data availability, and compared the original diagnosis to the Hadden criteria diagnosis. Descriptive statistics were used. Varying denominators represent the number of patients for whom the data were available.

3 | RESULTS

3.1 | Clinical presentation and course

A total of 45 patients from 29 published articles (see Table S1 online) were available for analysis. One series of eight patients was excluded due uncertainty about the diagnosis of COVID-19 and incomplete neurological data leaving 37 patients from 28 publications in the final analysis.

Table 1 provides the demographic and clinical data of the 37 patients. The mean age of the patients was 58.7 years. Most (90%) were at least age 50 years old, and 65% were male. The most common COVID-19 symptoms were cough, fever, or both, and the diagnosis was confirmed by nasopharyngeal, oropharyngeal, or fecal real time polymerase chain reaction (RT-PCR) (81%) or by SARS-COV-2 immunoglobulin G or M antibody testing (19%). Abnormalities on pulmonary imaging were noted in 24 (68.9%) patients, consisting of ground-glass opacities, interstitial pneumonitis, consolidation, or bibasilar opacities. Two patients presented with neurological symptoms. Both reported exposure to COVID-19 but did not have systemic symptoms at presentation. They had pulmonary ground-glass opacities on computed tomography (CT) of the chest, indicating asymptomatic infection. For the remainder, the mean time to onset of neurological symptoms was 11 ± 6.5 days (range, 3-28 days) from the onset of COVID-19 and a majority of patients (31 of 37, 84%) developed GBS while experiencing ongoing symptoms from COVID-19. Limb paresthesias or pain and weakness were the most common symptoms on presentation and most patients developed
varying degrees of extremity weakness during the course of the illness. Most patients developed limb weakness during the course of their illness and more than a third required mechanical ventilation. In the 16 patients for whom data were available, the mean time to nadir of neurological symptoms was 5 days (range, 1.5-10 days).

### TABLE 2  Laboratory and imaging features

| Laboratory abnormalities                              | Number (%) |
|-------------------------------------------------------|------------|
| Elevated inflammatory markers (see text)              | 15 (40.5)  |
| Lymphocytopenia                                        | 12 (32.4)  |
| Thrombocytopenia                                       | 2 (5.4)    |
| Leukocytosis                                           | 2 (5.4)    |
| Hyponatremia                                           | 1 (2.7)    |

**MRI of the spine (n = 15)**

| Normal                          | 9 (60.0) |
| Lumbosacral root enhancement    | 2 (13.3) |
| Radiculitis and brachial/lumbosacral plexitis | 2 (13.3) |
| Leptomeningeal enhancement      | 1 (6.7)  |
| Myelopathy                      | 1 (6.7)  |

**CT or MRI imaging of the brain (n = 14)**

| Normal                          | 10 (71.4) |
| Facial nerve enhancement        | 2 (14.3)  |
| Cranial neuritis                | 1 (7.1)   |
| Enlargement, T2 hyperintensity, enhancement of CN III | 1 (7.1) |

**Cerebrospinal fluid (n = 33)**

| Albuminocytologic dissociation  | 25 (75.8) |
| Normal                          | 6 (18.2)  |
| Pleocytosis                      | 2 (6.1)   |
| SARS-CoV-2 PCR (n = 18)          | 0 (0.0)   |

Abbreviations: CN, cranial nerve; CT, computed tomography; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory distress syndrome-coronavirus-2.

### TABLE 3  Guillain-Barré syndrome subtype classification

| GBS subtype per original report                     | Number (%) | GBS subtype per Hadden classification by reviewers | Number (%) |
|-----------------------------------------------------|------------|---------------------------------------------------|------------|
| AIDP                                                | 24 (64.8)  | Demyelinating                                     | 18 (48.6)  |
|                                                     |            | Equivocal                                         | 3 (8.1)    |
|                                                     |            | Unable to classify                                | 3 (8.1)    |
| Acute motor sensory axonal neuropathy              | 5 (13.5)   | Axonal                                            | 2 (5.4)    |
|                                                     |            | Unable to classify                                | 2 (5.4)    |
|                                                     |            | Demyelinating                                     | 1 (2.7)    |
| Miller Fisher syndrome                              | 5 (13.5)   | Unable to classify                                | 5 (13.5)   |
| Acute motor axonal neuropathy                       | 1 (2.7)    | Axonal                                            | 1 (2.7)    |
|                                                     |            | Unable to classify                                | 2 (5.4)    |

Abbreviations: AIDP, acute inflammatory demyelinating polyneuropathy; GBS, Guillain-Barré syndrome.

### 3.2  Diagnostic testing

Table 2 summarizes key laboratory and imaging findings. Elevated inflammatory markers, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), and D-dimer, were the most frequent laboratory abnormalities. Results of ganglioside antibody testing were reported in 17 patients (see Table S2 online), but only two patients (12%) had positive findings. One patient had an equivocal elevation of asialo-GM1 antibody and another had elevated immunoglobulin G antibodies to GD1b. Both had clinical features suggestive of Miller Fisher syndrome (MFS). MRI of the spine was abnormal in 40% of the patients in whom it was performed. Brain imaging was performed in fewer than half of the patients, and it revealed cranial nerve abnormalities in 28.6% of them. Cerebrospinal fluid (CSF) albuminocytologic dissociation was noted in more than three fourths of patients in whom lumbar puncture was performed. Protein levels in the CSF ranged from 44 to 313 mg/dL. CSF PCR testing for SARS-COV-2 was negative in all 18 patients in whom it was assayed.

Nerve conduction study data were available in 32 of 37 (86.4%) of the patients; needle electromyography was performed in 15 of 37 (40.5%). The details of the EDx evaluations were highly variable across studies (Table S2). In an attempt to standardize these findings, the Hadden criteria for EDx subtype were applied to the available data. Two thirds of the cases were amenable to this application and the remaining 12 cases could not be classified. AIDP was the most common reported EDx subtype of GBS (65%) and could be confirmed by Hadden criteria in 49% of the patients (Table 3). The next most common classification by the original authors was AMSAN, followed by MFS and AMAN. Using the Hadden criteria, fewer than 10% of all patients could be classified as axonal variants.

### 3.3  Treatments and outcomes

Thirty-three of 37 patients (89%) were treated with intravenous immunoglobulin (IVIg) at 0.4 g/kg/day for 5 days and 2 of these...
received a second course of IVIg. Three patients underwent plasma exchange (PLEX) and, of these, two received PLEX after IVIg. One patient with MFS was treated symptomatically with acetaminophen. Hydroxychloroquine was used in 12 of 37 (32.4%), 5 (13.5%) received azithromycin, and lopinavir and ritonavir were used in combination in 6 (16.2%) patients. Two patients received umifenovir, a broad-spectrum antiviral compound approved in China and Russia for the treatment of influenza. One patient was treated with oral prednisone, and another received tocilizumab in addition to hydroxychloroquine, antiretroviral therapy, and IVIg.

The response to therapy was reported in 33 of 37 (89%) patients. One patient died within 24 hours of admission due to respiratory failure.9 The period of follow-up varied substantially, so it was difficult to ascertain long-term outcomes. Varying degrees of improvement were noted in 24 of 33 (73%) patients at 5 days to 8 weeks after treatment.

4 | DISCUSSION

Despite numerous case reports of GBS associated with COVID-19, the prevalence remains unclear, as ascertainment and reporting are uneven and the total number of concurrent COVID-19 patients is not known. However, many of the reports are of single cases and we have not noticed a clear increase in GBS cases at our academic centers, so it appears to be rarely associated with COVID-19. It is also possible that GBS cases may have been incorrectly attributed to critical illness neuropathy, or undiagnosed in the setting of severe systemic illness.

Most patients reported were over age 50 years and male, which likely reflects the underlying demographics of diagnosed COVID-19 early in the pandemic; that is, older age and male gender are risk factors for more severe COVID-19, and the incidence of GBS rises with age.28,39 The male predominance is slightly higher than that reported in a large series of non–COVID-19 GBS cases,40 and it will be of interest to see if the age and gender ratios change as more young patients become infected and testing becomes more widespread.

Over one third of the patients required mechanical ventilation, which is slightly higher than the 20% to 30% that require invasive ventilation with non–COVID-19 GBS.40 This is not surprising given the concurrent pulmonary disease in the patients considered here. The nadir of the neurological illness usually occurred within 1 week of onset, sometimes as early as 2 to 3 days, and only occasionally in the second week of GBS. This is somewhat more rapid than other series, but the data regarding nadir was limited in the reviewed cases. Some degree of recovery usually occurs within weeks but the long-term prognosis is not yet clear.

All of the major GBS EDx patterns have been reported in association with COVID-19. A demyelinating pattern was the most common, similar to previous reports from Western countries.40 However, the breakdown into other categories differed between the original reports and our attempts at using the Hadden criteria for classification. Part of the discrepancy may be explained by our lack of access to the complete EDx data. Overall, the available data are insufficient to draw conclusions about whether the GBS subtype distribution is different than in non–COVID-19 patients.

Almost all of these GBS patients were treated with IVIg, which is associated with thromboembolic adverse effects.41 Because COVID-19 may be associated with a pro-thrombotic state,42 there may be concern about IVIg administration, but none of the reports described thrombotic complications. PLEX was used to treat GBS without reported complications in two patients that we reviewed, but PLEX is associated with hypotension in a small percentage of patients43 and can also affect the balance of clotting factors, potentially leading to thromboembolic events.44 Both IVIg and PLEX are suggested as treatments for the COVID-19–induced cytokine storm based on direct removal of cytokines or by promoting a shift toward a more favorable anti-inflammatory cellular and cytokine profile.45-47 PLEX challenges the tenuous hemodynamic state of critically ill patients and exposes more health-care workers for longer periods of time to SARS-CoV-2–infected patients, so, at present, it is preferable to treat COVID-19–associated GBS with IVIg unless there is a clear contraindication, such as a severe coagulopathy.

There are several potential mechanisms for the SARS-CoV-2 virus to cause profound weakness. The data collected here do not indicate a direct viral infection of peripheral nerves as occurs with West Nile virus acute flaccid paralysis.48 Similar to the direct neural infection of poliomyelitis, the paralysis syndrome most associated with West Nile virus is asymmetric and largely spares sensory function, whereas most of the GBS patients reviewed here demonstrated symmetrical and generalized patterns of weakness and sensory disturbances. CSF from these COVID-19–associated GBS patients was negative for SARS-CoV-2 by RT-PCR, and postmortem brain tissues from COVID-19 patients did not show evidence of viral infection by immunohistochemical analysis.49

GBS is a postinfectious syndrome as defined by an onset that is delayed from the acute symptoms of infection and by a mechanism that is distinct from the infection. The few cases of GBS associated with other coronaviruses, including the Middle East respiratory syndrome (MERS)-CoV virus that causes MERS, developed 1 to 3 weeks after the onset of the upper respiratory symptoms,50,51 similar to the GBS onset for COVID-19 (11 days). The postinfectious mechanism for GBS is best understood in the setting of preceding infection with Zika virus and C jejuni, where the onset of GBS occurs approximately 1 week after the onset of infection. The symptomatic period for these infections is briefer than for COVID-19, where the initial infection symptoms usually overlap with the onset of neurological symptoms.7,52

The postinfectious mechanism of GBS is also supported by the finding of autoantibodies that result from an immune response directed to an epitope of the infectious agent that then cross-reacts with a structurally similar component of peripheral nerve, resulting in delayed immune-mediated damage to peripheral nerve.53 The attachment of SARS-CoV-2 to cell surfaces is mediated by the viral spike (S) protein, which binds to angiotensin-converting enzyme 2 and also to gangliosides containing sialic acid residues, including the GalNAc residue of GM1. It has been suggested that cross-reactivity between
the viral protein–associated gangliosides and peripheral nerve gangliosides may result in molecular mimicry.\textsuperscript{54–56} Antiganglioside antibodies were uncommonly detected (12\%) in the reports analyzed here, indicating that assayed antigangliosides are in low concentration or that novel autoantibodies mediate COVID-19–associated GBS. Alternatively, the mechanism of nerve damage may be primarily facilitated by T-cell activation and release of inflammatory mediators by macrophages.\textsuperscript{57} A systematic evaluation of associations of ganglioside antibodies in GBS with COVID-19 will be needed before the mechanisms are clarified. A novel parainfectious mechanism for GBS mediated by the generalized, hyperinflammatory response that occurs with COVID-19 was suggested by some case report authors, because the acute symptoms overlap with the onset of GBS and autoantibodies were not detected in their cases. However, when all of the cases are considered, the clinical, antiganglioside testing and EDx patterns are similar to those of typical GBS cases.

Research into developing a vaccine against SARS-CoV-2 is rapidly advancing. Concerns regarding GBS associated with the swine flu vaccine raise questions regarding the risk of GBS with SARS-CoV-2 vaccines. The 1976 swine influenza vaccine was associated with a slightly increased frequency of GBS, estimated at one additional case of GBS per 100 000 vaccinated persons.\textsuperscript{58} Subsequent studies worldwide have reported varying associations (none, lower, or higher risks) between influenza vaccines other than the 1976 swine influenza vaccine and GBS.\textsuperscript{5,59–61} However, the estimated risk for GBS after influenza vaccine, based on the few studies that have demonstrated the association, is low: approximately one additional case per million persons vaccinated.\textsuperscript{59} Studies have also shown an increased risk for GBS after influenza infection, with up to 18\% of GBS patients during an influenza outbreak having serological evidence of recent influenza in one study,\textsuperscript{62} and substantially greater risks than those associated with vaccination in several others.\textsuperscript{61} These numbers, although not generalizable to COVID-19, may be useful for counseling patients regarding vaccination against SARS-CoV-2. Future studies should compare the incidence of GBS associated with COVID-19 infection with that associated with COVID-19 vaccination. The potential GBS risk of the vaccine should be weighed against the considerable morbidity and mortality of the infection.

Based on these reports, the diagnosis of GBS should be considered in known COVID-19 patients who develop global weakness during their course as a treatable alternative diagnosis to critical illness neuromyopathy. Most of the reported patients with COVID-19–associated GBS developed weakness before becoming critically ill, but both diagnostic possibilities should be considered for patients emerging from prolonged ventilation with lucid mental status but profound weakness. In two patients, GBS symptoms preceded systemic and respiratory symptoms or occurred during an otherwise asymptomatic COVID-19 infection. Therefore, testing for SARS-CoV-2 infection should be considered in all patients with suspected GBS during the pandemic and these patients should be isolated, even in the absence of respiratory and systemic symptoms, and until testing has returned negative.

Given the large number and wide geographic distribution of the GBS patients reviewed here, it is reasonable to conclude that these cases may be a representative sample. Still, conclusions from this research are limited because of the nonuniform, retrospective data collection and reporting. The lack of concurrent COVID-19 surveillance data makes it challenging to estimate the incidence of GBS associated with COVID-19 and incomplete access to the EDx data limited the utility of GBS classification by a uniform set of criteria.

GBS may be a presenting feature or occur during symptomatic infection with the SARS-CoV-2. It may be the only illness during an otherwise asymptomatic infection. The strength of the association of COVID-19 and GBS is still unclear, but a high index of suspicion should be maintained during this pandemic. COVID-19–associated GBS presents with various clinical patterns and EDx subtypes but the available data are limited by their high risk of bias. Prospective studies of COVID-19–associated GBS will provide information regarding neurological recovery in these patients compared with non–COVID-19–associated GBS, and will determine whether there are relapses of COVID-19–associated GBS. Future studies of patients with COVID-19 will help to determine whether the frequency, presentation, EDx subtype, antiganglioside antibody profile, and clinical course of COVID-19–associated GBS deviate from historical norms or contemporaneous patients with non–COVID-19 GBS.

**CONFLICT OF INTEREST**
The authors declare no potential conflicts of interest.

**ETHICAL PUBLICATION STATEMENT**
We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

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