COVID-19-Associated Guillain-Barre Syndrome: Atypical Para-infectious Profile, Symptom Overlap, and Increased Risk of Severe Neurological Complications

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Abstract

The concurrence of COVID-19 with Guillain-Barre syndrome (GBS) can increase the likelihood of neuromuscular respiratory failure, autonomic dysfunction, and other life-threatening symptoms. Currently, very little is known about the underlying mechanisms, clinical course, and prognostic implications of comorbid COVID-19 in patients with GBS. We reviewed COVID-19-associated GBS case reports published since the outbreak of the pandemic, with a database search up to August 2020, including a manual search of the reference lists for additional relevant cases. Fifty-one (51) case reports of COVID-19 patients (aged 23–84 years) diagnosed with GBS in 11 different countries were included in this review. The results revealed atypical manifestations of GBS, including para-infectious profiles and onset of GBS without antecedent COVID-19 symptoms. Although all tested patients had signs of neuroinflammation, none had SARS-CoV-2 in the cerebrospinal fluid (CSF), and only four (4) patients had antiganglioside antibodies. The majority had a 1- to 10-day time interval between the onset of COVID-19 and GBS symptoms, and many had a poor outcome, with 20 out of the 51 (39.2%) requiring mechanical ventilation, and two deaths within 12 to 24 h. The atypical manifestations of COVID-19-associated GBS, especially the para-infectious profile and short time interval between the onset of the COVID-19 and GBS symptoms, increase the likelihood of symptom overlap, which can complicate the treatment and result in worsened disease progression and/or higher mortality rates. Inclusion of a neurological assessment during diagnosis of COVID-19 might facilitate timely identification and effective management of the GBS symptoms and improve treatment outcome.

Keywords SARS-CoV-2 · COVID-19 · Atypical · Guillain-Barre · Para-infectious · Prognosis

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Introduction

The recent outbreak of the coronavirus disease 2019 (COVID-19) has caused an unprecedented worldwide pandemic characterized by an overwhelming health burden and serious socioeconomic consequences. This disease is typified by respiratory symptoms, ranging from mild flu-like symptoms to a severe highly lethal pneumonia [1, 2]. The current coronavirus pandemic is caused by the newly identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is a highly pathogenic coronavirus that is associated with rapid infectivity rates. The structure of SARS-CoV-2 and its mechanism of infection are similar to those associated with other coronaviruses, including the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) [1, 3]. In this regard, SARS-CoV-2 has a 75–80% identical genome sequence with MERS-CoV and SARS-CoV [4, 5], but it is far more

transmissible [6] and causes more deaths than these two coronaviruses.

Although the neuropathogenic mechanisms associated with SARS-CoV-2 infection are still unclear, a recent study found that 78/214 (36.4%) of COVID-19 patients presented with neurological symptoms [7]. Among the most devastating neurological conditions triggered by SARS-CoV-2 is Guillain-Barre syndrome (GBS) [2, 8, 9]. GBS is a rare autoimmune disorder [10] characterized by inflammatory demyelinating and/or axonal neuropathy, resulting in rapidly progressive paralysis with either reduced or absent reflexes [11], which may also be associated with cranial neuropathy and pain [12]. One of the prominent assumptions about the underlying pathological mechanisms of GBS is molecular mimicry, a process in which antibodies formed against the virus or other pathogens bind to gangliosides on the surface membranes of peripheral motor and sensory neurons and cause an immune-mediated damage to the myelin sheath and/or axons [13] (Fig. 1). The SARS-CoV-2 infection triggers an adaptive immune response in which T cell-B cell interactions result in the production of SARS-CoV-2-specific antibodies [14], but a similarity in viral and ganglioside peptide sequences or structure (molecular mimicry) [15] can result in a loss of self-tolerance [16]. Under these circumstances, the gangliosides, which are predominantly located on the membranes of neurons and the Schwann cells [17], which form the myelin sheath, may act as receptors for antiganglioside antibodies, which neutralize the neurons' complement inhibitory activity [18] and turn them into targets for an autoimmune-mediated destruction of myelin sheaths or axons [16, 19] (Fig. 1). Depending on the nature of the damage, an individual may experience either the demyelinating or axonal GBS subtype, which not only differ in the symptom manifestations but also in the likelihood of recovery [20].

GBS has a worldwide annual incidence of 1.2–2.3 per 100,000 [25] that increases to 3.3 per 100,000 in adults over 50 years [26], and it is associated with significant complications, mortality, and severe residual functional disability [27, 28]. Of particular interest during the COVID-19 pandemic, GBS is one of the leading causes of neuromuscular respiratory failure, necessitating mechanical ventilation in approximately 17 to 30% of afflicted patients [29]. Respiratory failure is most common in patients with a rapid rate of disease progression, autonomic dysfunction, bulbar dysfunction, or bilateral facial weakness [30]. Since respiratory failure is also a prominent feature of COVID-19, the GBS-COVID-19 comorbidity could exacerbate severe respiratory dysfunction and increase the overall symptom burden and need for mechanical ventilation.

One of the most concerning features of COVID-19-associated GBS is the recently reported para-infectious profile [31], which involves concurrent manifestation of symptoms for these two conditions. Typically, GBS is regarded as a post-

infectious disorder, with two-thirds of patients experiencing respiratory or gastrointestinal infection 2 to 3 weeks prior to the onset of GBS symptoms [32, 33]. The para-infectious profile suggests that the onset of the symptoms occurs during active infection, and the overlap between the COVID-19 and GBS respiratory symptoms can complicate treatment and potentially lead to higher mortality. Thus, the quest for identifying the best medical countermeasures or procedures for improving COVID-19 treatment outcome requires understanding of the onset and manifestation of the GBS-related neurological symptoms and how they influence the prognosis of COVID-19 patients. Most of the evidence to date is based on individual case reports, which may not give a complete picture of the manifestations and extent of the detrimental effects of COVID-19-associated GBS. The purpose of the current review was to evaluate the case reports of COVID-19-associated GBS published since the outbreak of the pandemic, with the goal of assessing the onset and manifestation of COVID-19-associated GBS, its symptom profiles, neuroinflammatory mediators, and the prognosis of patients with comorbid COVID-19 and GBS.

Methods

Case Reports Identification

We searched PubMed/MEDLINE, ScienceDirect, and Google Scholar for case reports of COVID-19-associated GBS, published since the coronavirus outbreak in December 2019, as well as and Journal pre-proof articles. The search terms included “COVID-19,” “GBS,” “SARS-COV-2,” “Case Reports,” “Guillain-Barré syndrome,” “para-infectious,” and “post-infectious.” The search yielded a total of 51 COVID-19-positive patients with a clinical diagnosis of GBS.

Inclusion Criteria

For inclusion into the study, the cases must have been diagnosed with COVID-19 or found to be SARS-CoV-2 positive. The GBS symptoms had to have manifested during or after the documentation of SARS-CoV-2 infection and thus not be a preexisting condition, and the diagnosis must have been confirmed through a peer-review process of the publishing journal. All the identified cases were adults (age > 18 years), and the reviewed cases met the established criteria for the diagnosis of GBS [34, 35]. In particular, the diagnoses were based on compatible clinical features and clinical course associated with muscle weakness and absent or depressed deep tendon reflexes; supportive cerebrospinal fluid analysis with evidence of cytoalbuminological dissociation; and electrodiagnostic evidence of acute demyelination (decreased motor nerve conduction velocity, prolonged distal motor latency, increased F

Fig.1 A schematic representation of the likely pathophysiology of COVID-19-associated GBS. SARS-COV-2 has a high affinity for the angiotensin-converting enzyme 2 (ACE2) receptor [21], located on nasal and oral mucosa [22], neurons, glia cells, and blood vessels of the central nervous system [23, 24]. During an infection, SARS-COV-2 binds this receptor and is endocytosed. Due to similarity in the peptide sequences or epitopes of SARS-Cov-2 and gangliosides (molecular mimicry), the

antibodies formed against the virus, through the T Cell-B cell interactions, may bind the gangliosides located on the peripheral neurons. This may result in an autoimmune response that destroys the myelin and/or axons. The demyelination or axonal damage disrupts neural transmission, which causes the GBS symptoms such as muscle weakness, paralysis, coordination problems, breathing difficulties, and autonomic dysfunction

wave latency, conduction blocks, and temporal dispersion) or axonal GBS variant (reduced distal motor and/or sensory amplitudes or transient motor nerve conduction block). Furthermore, all the cases had to have been published or approved for publication and presented in English.

Data Extraction

For each case report, we extracted information about (1) the patient's neurological symptoms, (2) time interval between the onset of COVID-19 and GBS symptoms, (3) GBS subtype, (4) medical history, (5) results of nasopharyngeal swab and CSF analysis for SARS-CoV-2 infection, (6) CSF protein level, (7) evidence of pleocytosis, (8) antiganglioside

antibodies, (9) GBS manifestation profile, and (10) prognostic indicators.

Results

Our search yielded a total of 51 case reports of COVID-19-associated GBS with exclusion of related diagnoses, from 11 different countries including Italy ($N = 15$) [2, 8, 12, 36–41], Spain ($N = 8$) [9, 11, 42–46], the USA ($N = 9$) [22, 47–53], Iran ($N = 5$) [32, 54–56], Germany ($N = 3$) [57–59], the UK ($N = 3$) [60–62], France ($N = 4$) [63–65], Canada ($N = 1$) [66], China ($N = 1$) [31], Morocco ($N = 1$) [67], and Switzerland

($N = 1$) [40]. Figure 2 shows the patient distribution by country.

Demographic and Clinical Characteristics of the COVID-19-Associated GBS Cases

The information about sociodemographic characteristics and the medical history of the patients is summarized in Table 1, and the data on the onset of COVID-19 and GBS symptoms and laboratory test results are presented in Table 2. Table 3 shows the neurological manifestation of COVID-19-associated GBS subtypes, while Fig. 3 is a schematic illustration of the atypical manifestation of this disease, its clinical course, and prognosis. Overall, we identified 51 COVID-19-associated GBS cases which we included in this study. However, among these patients, there were five (5) cases who met the GBS symptom criteria, but did not have documentation of nerve conduction study results [9, 47, 50, 52]; as we could not conclude whether they involved demyelination or axonal neuropathy, these cases were not included in the classification of GBS subtypes.

The patients were predominantly male (76.5%). Overall, the patients were elderly with a median of 60 years and mean age ($\pm$ standard deviation) of 58.3 ± 12.8 years: 63.3 ± 11.6 for females and 56.7 ± 12.9 years for males. The overall age ranges 23–84 years. Preexisting medical conditions were reported by 45.1% of the patients and mainly involved hypertension with or without comorbid conditions, followed by type 2 diabetes mellitus.

Fig. 2 Number of COVID-19-associated GBS cases identified from each country. The number of COVID-19-associated GBS cases were highest in Italy, the USA, Spain, and Iran, which by August 2020 were among the countries hardest hit by the COVID-19 pandemic

In the majority of the cases (54.9%), the time interval between the onset of COVID-19 and GBS symptoms was 1 to 10 days, with a median of 10 and interquartile range of 12 days. Of the 51 patients, 49 tested positive for COVID-19, while two (2) had negative results, but tested positive for SARS-CoV-2 antibodies, suggesting an onset of GBS after resolution of the antecedent infection in these two cases. However, for all the 32 patients tested, there was no evidence of SARS-CoV-2 in the CSF. Of the 42 patients tested, 34 had elevated CSF protein, but none of the patients tested had an increase in the number of lymphocytes in the CSF (pleocytosis). Eight patients had normal protein levels (CSF protein may remain normal when tested acutely in GBS). Of the 30 patients tested, only four (4) had antiganglioside antibodies, including GM2 IgM, GD3 IgM, and GT1b IgG for one, and GM2 IgG/IgM for another patient with acute inflammatory demyelinating polyneuropathy (AIDP), GD1b-IgG for a patient with Miller-Fisher Syndrome (MFS), and GD1b for one patient diagnosed with acute motor axonal neuropathy (AMAN).

Table 3 shows the neurological manifestation of COVID-19-associated GBS. In the cases in which electrodiagnostic data were available ($N = 46$), the majority, 30 (65.23%) presented with acute inflammatory demyelinating polyneuropathy (AIDP), followed in 7 (15.23%) patients by acute motor-sensory axonal neuropathy (AMSAN), 3 (6.52%) with Miller-Fisher syndrome (MFS), 3 (6.52%) with an AIDP-MFS overlap, and 1 (2.17%) with acute motor axonal neuropathy (AMAN). The results also revealed rare GBS

Table 1 Sociodemographic characteristics of COVID-19-associated GBS cases published during the pandemic outbreak (January to August 2020)

Sex	Frequency (%)	Mean Age (years)	Median Age (years)	Range (years)
Female (<i>N</i> = 12)	12 (23.53)	63.33 ± 11.59	66.50	35–77
Male (<i>N</i> = 39)	39 (76.47)	56.69 ± 12.90	58.00	23–84
Total	51 (100)	58.25 ± 12.81	60.00	23–84
Age (years)				
≤ 49	11 (21.57)			
50–59	13 (25.49)			
60–69	16 (31.37)			
70–79	10 (19.61)			
80–89	1 (1.96)			
Total	51 (100)			
Medical history				
Breast cancer	1 (1.96)			
Bronchial asthma	1 (1.96)			
Hypertension	8 (15.69)			
Hypertension & obesity	1 (1.96)			
Hypertension & psoriasis	1 (1.96)			
Hypertension & AAA	1 (1.96)			
Hypertension & CAD	1 (1.96)			
Hypertension, dyslipidemia, BPH, & AAA	1 (1.96)			
Infantile strabismus	1 (1.96)			
Obesity	1 (1.96)			
Rheumatoid arthritis	1 (1.96)			
Sinusitis	1 (1.96)			
Type 2 diabetes mellitus	4 (7.84)			
None	16 (31.37)			
Not reported	12 (23.53)			
Total	51 (100)			

AAA abdominal aortic aneurysm, CAD coronary artery disease, BPH benign prostatic hyperplasia

variants including polyneuritis cranialis (PNC) and bilateral facial diplegia without blink reflexes, both of which involved cranial neuropathies. The atypical symptoms observed in this study include cognitive disturbance in the form of psychomotor agitation with confusion, dizziness with or without headache, and partial loss of consciousness, which could be a sign of possible COVID-19-associated central nervous system involvement. The neurological features indicated signs of demyelination, axonal damage, enhancement of spinal nerve roots, and impaired sensory and motor impulse transmission. Table 4 summarizes the associations between clinical GBS features and respiratory failure.

The majority of the cases (48/51; 94.12%) developed COVID-19 symptoms ranging from mild to severe and had either a post-infectious (36/51; 70.59%) or para-infectious (12/51; 23.53%) profile, while 3/51 (5.88%) were asymptomatic for COVID-19 but developed GBS symptoms. For 30/51 (58.82%) of the cases, including 11 (36.67%) with para-

infectious and 19 (63.33%) with a post-infectious profile, the time interval between the onset of COVID-19 and GBS symptoms was 1–12 days. Due to the small sample size (*N* = 48), the analysis yielded wide 95% confidence intervals, which reduces the degree of precision of the estimate, but both the odds ratios and our general observation indicate that the 1–12 day onset interval was associated with a higher likelihood for respiratory failure, admission into the intensive care unit, and use of mechanical ventilation compared to the onset GBS after a time interval longer than 12 days since the onset of COVID-19 symptoms, OR = 2.6 (95% CI 0.74–9.12). Among the 20 patients put on mechanical ventilation, 15 (75%) had a time interval of 1 to 12 days between the onset of COVID-19 and GBS symptoms, and overall, the odds were higher for the para-infectious, compared to the post-infectious profiles, OR = 1.57 (95% CI 0.42–5.85). Furthermore, 50.0% of patients with a para-infectious, and 38.89% with a post-infectious profile, were put on mechanical ventilation, with

Table 2 Time interval between the onset of COVID-19 and GBS symptoms and laboratory test results

Time Interval (days)	Frequency (%)	Median ($\pm$ IQR)	Interquartile range		Range (days)
			25th	75th	
< 1	2 (3.92)	10.00 $\pm$ 12.00	6.00	18.00	0–21
1–10	28 (54.90)				
11–20	13 (25.49)				
21–30	8 (15.69)				
Total	51 (100.00)				
Laboratory tests	Patients tested (N)	Status/results	Frequency (%)		GBS subtype
SARS-CoV-2 for COVID-19	51				
Viral Test		Positive	49 (96.08)		All
Serology Test		Positive	2 (3.92)		AIDP
SARS-CoV-2 in CSF	32	Negative	32 (100)		All
Anti-gang. antibodies	30	Absent	26 (86.67)		All
		GD1b IgG	2 (6.67)		AMAN, MFS
		GM2 IgG/IgM	1 (3.33)		GBS*
		GM2 IgM, GD3-IgM, GT1b	1 (3.33)		AIDP
CSF proteins	42	Elevated	34 (80.95)		All
		Normal	8 (19.05)		AIDP, AIDP-MFS, AMSAN
Pleocytosis	37	Absent	37 (100)		All

GBS* GBS not categorized due to absence of nerve conduction studies, Anti-gang antigangliosides

one patient in each category respectively dying within 24 and 12 h after onset of the GBS symptoms. Overall, the individuals with a para-infectious profile and those with a post-infectious profile but with a short latency between the onset of COVID-19 and the GBS symptoms were more likely to have a poor prognosis. Figure 3 illustrates the temporal relationship and clinical course of COVID-19-associated GBS.

Discussion

Our study reviewed COVID-19-associated GBS case reports published since the outbreak of the pandemic, with the main objective of examining the relationship between SARS-CoV-2-associated onset and manifestation of GBS, its neuroinflammatory features, and the prognosis of the patients presenting with para- or post-infectious profiles. The results indicate that SARS-CoV-2 infection is associated with the onset of GBS, including AIDP, AMSAN, AMAN, and MFS subtypes. We also found a rare AIDP-MFS overlap and atypical GBS variants including polyneuritis cranialis and bilateral facial diplegia without blink reflexes, which are cranial neuropathies that do not meet the diagnostic criteria for MFS or other GBS subtypes with known cranial nerve involvement. The bilateral facial diplegia without blink reflexes has not been previously reported but may be similar to the rare GBS variant with prominent facial diplegia that manifests with paresthesia [68, 69]. The majority of the cases reviewed presented with demyelinating neuropathy, which is consistent with

GBS associated with the other six pathogens, including Zika virus, hepatitis E virus, *Mycoplasma pneumoniae*, *Campylobacter jejuni*, *Cytomegalovirus*, and Epstein-Barr virus [12]. Of note, these results are not consistent with a recent review of an unspecified number of cases by Gupta et al. [70], which suggested that acute motor axonal neuropathy (AMAN) and AMSAN are the most common GBS subtypes associated with COVID-19.

The inconsistency in the proportions of GBS subtypes could be attributed to possible genetic variation, with evidence indicating a higher prevalence of AIDP in the western world, while AMAN and AMSAN are more prevalent in Asian and Southern and Central American populations [71]. Interestingly however, in this study, AMAN accounted for only 2.17% of the cases, which is even lower than the rare MFS subtype that accounted for 6.52% of the cases in this study. The rare AIDP-MFS overlap also accounted for 6.52%, which when added to the atypical bilateral facial diplegia without blink reflexes, and polyneuritis cranialis, suggests a potential for more cranial involvement of COVID-19-associated GBS, compared to GBS associated with other infections. The potential for greater cranial involvement of COVID-19-associated GBS is also reflected in the atypical neurological symptoms such as dizziness, alterations in level of consciousness, psychomotor agitation, and headache observed in this review. Although signs of vestibular dysfunction such as dizziness or disorientation have been previously reported in some GBS patients, they are rare and associated cranial neuropathy [72]. It is more likely that these symptoms

Table 3 The neurological manifestations of COVID-19-associated GBS

Subtype	Neuromuscular symptoms	Sensory symptoms	Autonomic dysfunction	Neurophysiological features
AIDP (65.23%)	<ul style="list-style-type: none"> • Ascending quadriparesis • Areflexia • Impaired movement • Facial palsy/diplegia • Oropharyngeal/hypoglossal palsy • Ophthalmoparesis • Psychomotor agitation • Fatigue • Decreased muscle tone • Ascending quadriplegia/paraplegia 	<ul style="list-style-type: none"> • Anosmia and ageusia • Dysesthesia/paresthesia • Vibratory and proprioceptive loss • Lost light touch and pinprick sensation • Stocking-and-glove hypesthesia • Distal allodynia • Low back and/or thoracic pain • Headache • Confusion • Dizziness • Loss of consciousness 	<ul style="list-style-type: none"> • Voiding dysfunction • Constipation • Respiratory failure • Dysphagia • Irregular heartbeat • Increased blood pressure • Multiple organ failure • Hypotension/hypertension 	<ul style="list-style-type: none"> • Delayed or prolonged distal motor latencies • Reduced muscle action potential amplitude • Reduced motor conduction velocities • Absent sensory nerve action potentials • Conduction blocks • Absent F waves • Absent H-reflex • A sural sparing pattern • Brainstem and cervical meningeal enhancement • Cranial neuritis (in nerves III, V, VI, VII, and VIII) • Radiculitis & plexitis on the brachial & lumbar plexus • Enhancement with lesion of cranial nerve (CN) III
MFS (6.52%)	<ul style="list-style-type: none"> • Hyporeflexia or areflexia • Ataxia • Facial palsy • Ophthalmoparesis • Oculomotor palsy • Pupillary dysfunction • Eyelid ptosis • Impaired eye movement • Hypoglossal palsy • Dysphonia • Overlap of AIPD & MFS symptoms 	<ul style="list-style-type: none"> • Anosmia and ageusia • Paresthesia • Sensory loss/numbness • Blurry vision/double vision • Dizziness on walking • Headache 	<ul style="list-style-type: none"> • Dysphagia 	
AIDP-MFS (6.52%)				
AMSAN (15.23%)	<ul style="list-style-type: none"> • Ascending quadriparesis • Quadriplegia/paraplegia • Facial paresis or palsy • Areflexia • Ataxia • Hypoglossal palsy 	<ul style="list-style-type: none"> • Paresthesia • Vibratory and Light touch loss • Neck or mastoid pain • Sensory ataxia 	<ul style="list-style-type: none"> • Gastroplegia • Respiratory failure • Dysphagia 	<ul style="list-style-type: none"> • Reduced muscle action potential amplitude • Absent sensory nerve action potential • Decrease in facial nerve cMAP amplitude • Reduced sensory action potential amplitudes • Reduced motor action potential amplitudes • Bilateral facial nerve enhancement • Enhanced caudal nerve roots • Reduced compound motor action potentials
AMAN (2.17%)	<ul style="list-style-type: none"> • Progressive tetraparesis • Tachycardia 		<ul style="list-style-type: none"> • Tachycardia • Absent heart rate variability • Dysphagia 	
PNC (2.17%)	<ul style="list-style-type: none"> • Absent heart rate variability • Diplopia • Abducens nerve palsy • Areflexia 	<ul style="list-style-type: none"> • Ageusia 		
FDBR*(2.17%)	<ul style="list-style-type: none"> • Bilateral facial nerve palsy • Unresponsive blink reflex 			

AIDP acute inflammatory demyelinating polyneuropathy, *AMSAN* acute motor-sensory axonal neuropathy, *MFS* Miller-Fisher syndrome, *AMAN* acute motor axonal neuropathy, *PNC* polyneuritis cranialis, *FDBR** facial diplegia without blink reflex

are related to COVID-19 since they are seen in many COVID-19 patients who do not develop GBS [73, 74].

Although neurological symptoms were previously reported in severe COVID-19 cases [75], in this study, we found that GBS can also occur among patients who experience mild or no prior COVID-19 symptoms, and the manifestation involves the typical post-infectious and atypical para-infectious profiles. The patients categorized as para-infectious had a concurrent manifestation of COVID-19 and

GBS symptoms, while in the case of the post-infectious profile, the GBS symptoms occurred after resolution of the COVID-19 symptoms. Typically, GBS is a post-infectious condition with symptom onset for 76% of the patients occurring in about 4 weeks after the preceding respiratory or gastrointestinal infection [76]. The para-infectious profile is an atypical feature, which was only recently reported among patients infected with Zika virus [77]. In this study, 83.3% of the para-infectious, and 50% of the post-infectious cases,

experienced an onset of GBS between 1 and 10 days, after the onset of COVID-19 symptoms. This is consistent with the previous evidence indicating an average time interval of 5 to 10 days between the onset of the COVID-19 symptoms and GBS [12, 57], but the post-infectious manifestation is contrary to the finding that the mean COVID-19 recovery time is 10 to 21 days [78]. The finding that 50% of the post-infectious GBS cases occurred before the expected time of COVID-19 recovery suggests that some of the patients in this category could still be in the active infection phase. Indeed, apart from two

patients who tested negative for SARS-CoV-2 but positive for its antibodies, all the patients tested for the virus at the onset of GBS symptoms had positive results. Furthermore, some patients (e.g., in Tiet & Alshaikh, 2020) categorized as post-infectious still had some mild COVID-19 symptoms such as cough and continued to test positive for SARS-CoV-2 weeks after the GBS diagnosis. This suggests that patients with seemingly resolved, mild, or unnoticeable COVID-19 symptoms may fit the post-infectious profile, while still in an active infection phase, and put into question the categorization of

Fig. 3 The atypical manifestation and prognosis of COVID-19-associated GBS. The results revealed that following SARS-CoV-2 infection, patients can experience GBS with or without developing COVID-19 symptoms. The GBS can manifest as a para-infectious profile, characterized by onset of symptoms during active SARS-CoV-2 infection and a COVID-19-GBS symptom overlap, while the post-infectious profile involves onset of GBS symptoms after recovering from the COVID-19.

However, some of the post-infectious profile patients may still test positive for SARS-COV-2 at the onset of GBS symptoms. The outcome ranged from mild to severe GBS symptoms, requiring admission into intensive care units, mechanical ventilation, prolonged stay in hospital, or discharge with severe residual or permanent disability, with the para-infectious profile having a higher likelihood for poor functional outcomes, due to the COVID-19-GBS symptom overlap

Table 4 Association between COVID-19-GBS onset interval, manifestation profiles, and respiratory dysfunction

COVID-19-GBS onset interval	Manifestation profile			Respiratory failure		
	Freq (%)	Para-infe. freq (%)	Post-infe. freq (%)	Yes freq (%)	No freq (%)	OR (95%CI)
1–12 days	30 (58.82)	11 (36.67)	19 (63.33)	15 (50.00)	15 (50.00)	2.6 (0.74, 9.12)
> 12 days	18 (35.29)	1 (5.56)	17 (94.44)	5 (27.78)	13 (72.22)	
None	3 (5.88)				3 (100)	
Total	51 (100)					
Manifestation profile						
Para-infectious	12 (25%)			6 (50.00)	6 (50.00)	1.57 (0.42, 5.85)
Post-infectious	36 (75%)			14 (38.89)	22 (61.11)	
Total	48 (100%)					

OR odds ratio, CI confidence interval, Infe infectious, Freq frequency

COVID-19-associated GBS patients on the basis of the resolution of the antecedent symptoms. A more accurate categorization may require laboratory analysis to confirm the serological status and whether or not the patient is still in the active infection phase and has the potential to develop symptoms associated with the antecedent infection.

An accurate identification and categorization of GBS patients is very important, since the para-infectious profile is associated with a concurrent manifestation of COVID-19 and GBS symptoms, which can complicate the treatment and may be associated with a worse prognosis. Indeed, in this study, the patients with a para-infectious profile and those with a post-infectious profile but with a short time interval between the onset of COVID-19 and the GBS symptoms were more likely to have a poor prognosis. The link between the short duration and disease severity is illustrated by our observation that 75% of the patients admitted into intensive care units or put on mechanical ventilation had a 1- to 12-day COVID-19-GBS symptom onset interval. With this short time interval, a symptom overlap was more likely, and owing to the fact that COVID-19 mainly affects the respiratory system the higher incidence of pulmonary complications, and respiratory failure in particular, is a likely occurrence. The symptom overlap may also account for the finding that these patients experienced various serious complications including progressive muscle weakness and paralysis, which in some cases spread to involve the thoracic, cranial, and abdominal regions, resulting in some atypical signs of autonomic dysfunction such as irregular heartbeat, increased blood pressure, cardiac arrest, voiding dysfunction, constipation, respiratory failure, and multi-organ failure. Some of these patients remained in intensive care units for several weeks, others were discharged into inpatient rehabilitation centers, whereas others were able to go home but with lingering neurological symptoms. One of the patients died within 12 h after the onset of GBS-related bulbar symptoms [9] and another within 24 h due to

progressive respiratory failure [2]. These findings highlight the potential devastating nature of the concurrent manifestation of COVID-19 and GBS symptoms. The short time interval of 1 to 10 days in this study, and 5 to 10 days in the previous studies [12, 57] as the duration between the onset of COVID-19 and GBS symptoms for majority of the patients, suggests that a para-infectious profile is the most likely manifestation of COVID-19-associated GBS. This is not only indicative of a potential for a poor prognosis due to symptom overlap, but also underscores the value of timely identification of neurological symptoms as part of the COVID-19 diagnostic process and specialized care for the patients with concurrent GBS symptoms.

In this study, we hypothesized that cerebrospinal fluid analysis might not only be helpful in aiding the diagnosis of COVID-19-associated GBS, but could also have some prognostic implications. The results revealed that none of the patients with reported CSF analysis had SARS-CoV-2 in the CSF, the majority of tested patients did not have antiganglioside antibodies, and most of the reviewed cases had raised protein levels in the CSF without pleocytosis (albuminocytological dissociation). Albuminocytological dissociation is a typical characteristic of GBS, found in about 90% of patients [79], and could be an important biomarker in ruling out differential diagnoses and in offering insight about the prognosis. In particular, the increase in CSF protein concentration may indicate the extent of active damage to the myelin, disease progression, and treatment response [80]. It is believed to be a consequence of antibody-mediated molecular mimicry mechanisms responsible for the erosion of the myelin sheath proteins from the axons [66], with an increase in the protein levels as evidence of the progression of demyelination [79] or other neuronal damage.

Interestingly, no antiganglioside antibodies were identified for the majority of the cases in this study, except for four patients, including one with GBS* who had anti-GM2 IgG/

IgM and another with AIDP variant with anti-GM2 IgM, anti-GD3 IgM, and anti-GT1b IgG. The third patient with MFS had GD1b-IgG, while the fourth patient with the AMAN subtype also had GD1b. Elevated of anti-GM2 IgG/IgM is a rare occurrence in GBS but may be found in different subtypes with clinical heterogeneity of IgM, while IgG is predominantly associated with cranial GBS variants, especially in patients presenting with oculomotor and vestibular dysfunction, characterized by dizziness [72]. However, in this study, neither the anti-GM2 IgG/IgM- nor the anti-GM2 IgM-positive patients had signs of cranial neuropathy, but both experienced autonomic dysfunction and were put on mechanical ventilation. The GD1b-IgG antibodies are formed against specific gangliosides on the axonal membranes [70] and thus are an atypical occurrence for MFS, which is known to mainly involve anti-GQ1b in over 90% of the patients [81] and anti-GT1a antibodies that target gangliosides on oculomotor nerves and muscle spindles [13], as well as neuromuscular junctions of cranial nerves, an underlying mechanism for ophthalmoplegia. However, evidence suggests that anti-GQ1b and anti-GT1a antibodies can also react with GD1b gangliosides [19], which may in part explain the reported GD1b-IgG antibodies in this study. The presence of antibodies is consistent with the assumption that the mechanisms for the onset of GBS could involve neuroimmunological responses to the infection, especially molecular mimicry. Further support for the immune-mediated neuropathogenesis of GBS comes from the observation in this study that most of the patients improved in response to immunoglobulin therapy.

On the other hand, the absence of antiganglioside antibodies in 86.7% of the tested patients suggests that non-immunologic mechanisms such as direct infection of the nervous system could also be involved in the onset of GBS symptoms. On the basis of absent antibodies, Lantos et al. [48] hypothesized that viral neurotropism may play a role in mediating GBS symptoms. However, the absence of a single patient with SARS-CoV-2 in the CSF in our study does not support the assumption of direct infection of the nervous system in the pathogenesis of GBS. Supporting evidence for this assumption comes from results of a study by Steininger et al. [82] indicating that the DNA of cytomegalovirus (CMV), which is the most common antecedent viral infection, was detected in the CSF of GBS patients, especially at the early stage of illness. Another study by Kuijff et al. [83] with a larger sample and comparable assay characteristics found CMV DNA in the CSF of one GBS patient. There is also a recent report of a COVID-19 patient who did not have SARS-CoV-2 RNA in the nasopharyngeal swab but did have it in the CSF [84], and SARS-CoV-2 was also found in the brain tissue of a confirmed case of COVID-19 [85]. This evidence suggests that the absence of SARS-CoV-2 RNA in the CSF should not necessarily rule out the possibility for direct viral involvement in the etiology of GBS and other neurological disorders.

Indeed, there is evidence to suggest that CSF analysis may be complicated by the decrease in the viral load to undetectable levels, before the onset of the neurological symptoms [86], and the currently available real-time reverse-transcription polymerase chain reaction (rRT-PCR) only has about 60% sensitivity [86, 87]. These might not be the only possible explanations for the absence of SARS-CoV-2 in the CSF of all the tested GBS patients in our study, and we propose further research to elucidate on this phenomenon and its implication on the prognosis of GBS.

A major limitation of our study is that, given the concurrent manifestation of the novel COVID-19 and GBS, especially for the para-infectious cases and those with a short duration between the onset of the two conditions, it remains possible that some COVID-19 symptoms could be attributed to GBS and vice versa, since both diseases affect the respiratory system. Some cases did not have all the required laboratory and neurological tests due to the overwhelming nature of the COVID-19 pandemic and the stress it exerts on the hospital environment, logistical challenges, and the demand the large patient numbers exert on the medical personnel and system. Some of the patients were reported to have been in critical condition, which also prevented the conduction of electrodiagnostic tests. Such cases without results of nerve conduction were not categorized into GBS subtypes, since it was not possible to confirm whether the symptoms were due to demyelination or axonal damage. Furthermore, there were variations in the reporting format for each patient and some case reports missed some vital information. Further research with standardized study protocols could offer more insight into the underlying neuropathological mechanisms, atypical manifestation, and prognosis of COVID-19-associated GBS.

Conclusions

Evidence from this study suggests that SARS-CoV-2 is a potential trigger of GBS, which not only manifests in patients with severe but also those with mild or absent prior COVID-19 symptoms. Although GBS is typically regarded as a post-infectious neurological disorder, a large number of COVID-19 patients present with an atypical para-infectious profile, and the majority of cases, including those with a post-infectious profile, have a short time latency between the onset of COVID-19 and GBS symptoms. This short time interval increases the likelihood for symptomatic overlap between para-infectious manifestations and a COVID-19-GBS, which not only complicates treatment but could also result in a poor prognosis characterized by severe autonomic dysfunction in the form of respiratory failure, heart failure, gastroparesis, multiple organ failure, and other signs of severe neuromuscular weakness or paralysis. These severe symptoms increase the odds for admission into the intensive care unit, need for

mechanical ventilation, extended recovery period, higher mortality rate, and permanent disability. Thus, given the high infectibility rates of the novel SARS-CoV-2, COVID-19-associated GBS should be a major public health concern. GBS symptoms can progress very rapidly, and in our study, the two fatalities occurred within 12 to 24 h mainly caused respiratory failure and multi-organ failure. Paying particular attention to potential signs of GBS among COVID-19 patients and intervening at an early stage may improve treatment outcomes and minimize on morbidity, disease burden, and fatalities. Our findings suggest that inclusion of neurological assessment in the COVID-19 diagnostic process for timely identification and effective symptom management may yield better treatment outcomes. Although the exact relationship between the novel COVID-19 and comorbid GBS remains incompletely defined, systematic follow-up of the patients could aid in the quick identification of relapse cases, given that some patients continue to test positive for SARS-CoV-2 after a prolonged period of time.

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Data Availability Not applicable.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethics approval Not applicable

Consent to Participate Not applicable; we reviewed cases from published literature.

Consent for Publication All authors have approved the publication of this work as submitted.

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