SARS-CoV-2-associated Guillain-Barré syndrome is a para-infectious disease

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Abstract Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been linked to the Guillain-Barré syndrome (GBS). The objective of the present study is to identify specific clinical features of cases of GBS reported in the literature associated with SARS-CoV-2 infection. We searched Pubmed, and included single case reports and case series with full text in English, reporting original data of patients with GBS and a confirmed recent SARS-CoV-2 infection. Clinical data were extracted.We identified 28 articles (22 single case reports and 6 case series), reporting on a total of 44 GBS patients with confirmed SARS-CoV-2 infection. SARS-CoV-2 infection was confirmed through serum RT-PCR in 72.7% of cases. A total of 40 patients (91%) had symptoms compatible with SARS-CoV-2 infection before the onset of the GBS. The median period between the onset of symptoms of SARS-CoV-2 infection and symptoms of the GBS was 11.2 days (range, 2-23). The most common clinical features were: leg weakness (61.4%), leg parethesia (50%), arm weakness (50.4%), arm paresthesia (50.4%), hyporeflexia/areflexia (48%), and ataxia (22.7%). 38.6% (n=17) were found to have facial paralysis. Among 37 patients in whom nerve-conduction studies and electromyography were performed, of which 14 patients (31.8%) were consistent with the acute inflammatory demyelinating polyneuropathy (AIDP) subtype of the GBS. The present retrospective analysis support the role of the SARS-CoV-2 infection in the development of the GBS, may trigger GBS as para-infectious disease，and lead to SARS-CoV-2-associated GBS.

Keywords: COVID-19; SARS-CoV-2;Guillain-Barré syndrome; Clinical features

Introduction

Guillain-Barré syndrome (GBS) is an uncommon acute immune-mediated polyradiculoneuropathy of the peripheral nervous system typically characterized by progressive, symmetric limb weakness with decreased or absent deep-tendon reflexes[1], often preceded by respiratory or gastrointestinal infections from a virus or bacteria. About 70% of patients with GBS report having had symptoms of an infectious illness in the days or weeks prior to onset of neurologic disease. Certain lines of evidence suggest that GBS is presumed to be triggered by preceding infectious agents including Campylobacter jejuni, Mycoplasma pneumoniae, cytomegalovirus, and Epstein-Barr virus and less frequently with vaccines[2-4]. The global annual GBS incidence is estimated at 1.1 to 1.8 cases per 100 000 population, which may vary depending on the regional prevalence of infectious triggers， and increase with age and varying by sex and geographic region[5].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an enveloped, single-stranded RNA virus, causing human coronavirus disease 2019 (COVID-19), has now spread into a worldwide pandemic. SARS-CoV-2 infection manifests as a pulmonary syndrome associated with fever, cough, hemoptysis, and dyspnea, among others[6, 7]. There is growing evidence of neurological complications and disease in patients with COVID-19[8-11]. Due to its worldwide distribution and multifactorial pathogenic mechanisms, COVID-19 have imposed a global threat to the entire nervous system[12]. SARS-CoV-2 infection is associated with the GBS and its variants in the peripheral nervous system.

Since the SARS-CoV-2 epidemics, numerous studies have been published on SARS-CoV-2-related GBS[13-17], but it has not been established if there is a specific clinical and electrophysiological phenotype of GBS after SARS-CoV-2 based on published cases or case series. Therefore, we have conducted a systematic and retrospective review of all published studies, which includes cases or case series, on SARS-CoV-2-related GBS, and give a comprehensive overview of clinical features, including demographic characteristics, clinical symptoms, laboratory and imageological examinations, and outcome of SARS-CoV-2-related GBS patients.

Methods

We conducted a search of the medical literature using MEDLINE (accessed from PubMed) from December 01, 2019 to Jun 26, 2020 were systematically searched for related published articles. The following search strategy was implemented and we used the following key terms:"COVID-19" OR "SARS-CoV-2" [All Fields] AND "Guillain-Barré syndrome" [All Fields].Further case reports and case series studies were obtained by reference tracing of retrieved articles. We included any article in English reporting an association between SARS-CoV-2 and GBS. At least 2 independent reviewers independently screened all publications, including title and abstract, to determine whether studies include cases. Then one reviewer independently retrieved clinical variables from the selected articles. Preprinted articles were not included. The final list of included articles was generated based on relevance to the GBS covered in this review, which includes total of 28 articles.

Results

We identified 28 articles(22 single case reports and 6 case series) (Table 1) were published between January 1, 2020 and June 26, which reported on a total of 44 GBS patients with confirmed SARS-CoV-2 infection (SARS-CoV-2-GBS). Table 1 summarized the detailed demographic and clinical characteristics of patients With SARS-CoV-2-GBS.

Of the 44 individual patients with SARS-CoV-2-GBS, their median age was 61.4 years (age range, 23-84 years), 29 patients (66%) were male, and 15 patients (34%) were female, with a male to female sex ratio of 2:1. A total of 32 (72.7%) definite cases of SARS-CoV-2 infection were those that were confirmed by a positive real-time reverse transcriptase-polymerase-chain-reaction (RT-PCR), 5 (11.4%) cases were confirmed by the presents of SARS-CoV-2 antibodies. A total of 40 patients (91%) had symptoms of SARS-CoV-2 infection in the about 2 weeks (11.2 days) preceding the onset of neurologic symptoms (Table 2). Fever (n=25,57%), cough (n=25,57%) and diarrhea (n=15,34%) was the most frequently documented antecedent symptoms of SARS-Cov-2 infection, followed fatigue (n=9,20.5%). Four patients did not report having had any systemic evidence of SARS-CoV-2 infection before the

onset of the GBS. Median time from onset of antecedent illness to onset of neurologic symptoms was 11.2 days (range, 2–23).

The clinical and laboratory features of the patients with the SARS-CoV-2-GBS are summarized in Table 1 and 3. Median time between onset of neurological symptoms and peak of GBS was 4.8 days (range, 0–23). The most frequently reported neurologic manifestations during hospitalization were upper (50.4%) or lower extremity weakness (61.4%), lower (50 %) or upper extremity paresthesia (50.4%), and hyporeflexia or areflexia (48%) (Table 3). Cranial neuropathies were present in 21 patients, with facial weakness (38.6%) being the most common. 23 (52.3%) patients reported tetraparesis. Autonomic dysfunction was present in 5 patients (11.4%).

In the 22 (50%) patients, median time between neurologic symptoms onset and neurophysiological studies was 7.4 days (range 2–14) (Table 3). 14 patients (31.8%) were determined to had acute inflammatory demyelinating polyneuropathy (AIDP) subtype of GBS, 11(25%) was interpreted as demyelinating subtype of GBS, 5 patients (11.4%) had Miller-Fisher syndrome(MFS) subtype of GBS, and 2 (4.5%) acute motor and sensory axonal neuropathy(AMSAN) subtype of GBS.

39 patients (88.6%) was performed cerebrospinal fluid (CSF) analysis (Table 1 and 3). 27 patients (27/39, 69%) with CSF data had albuminocytologic dissociation. The median protein concentration was 504 mg per deciliter (range, 21-14000) and the median white-cell count was 3.1 cells per cubic millimeter (range, 0-24).

Thirty-five patients (79.5%) were administered to specific treatment (Table 1 and 3). Of which, 29 patients (82.8%)received intravenous immune globulin (IVIG) only , one patient (3%) received plasma exchange only and three received IVIG plus plasma exchange (8.6%).The median time between onset of neurological symptoms and peak of GBS at nadir was 4.8 days(range, 0-23).Eight patients (18.2%) developed respiratory failure,.Thirty-two (77%) patients had a recorded outcome, the prognosis were good in 21 patients (47.7%), poor in 9 patients (20.5%), and two patients (4.5%) died.

Discussion

We present a clinical features of an outbreak of confirmed Guillain–Barré syndrome in the setting of a SARS-CoV-2 worldwide pandemic. To the best of our knowledge, this is one of the largest comprehensive retrospective review of all published studies, which includes cases or case series, to assess the role of SARS-CoV-2 infection in a large number of patients with Guillain-Barré syndrome diagnosed during a SARS-CoV-2 outbreak until Jun 26, 2020[18-20]. We characterized of clinical features, including demographic characteristics, diagnostic investigations, and outcome of SARS-CoV-2-related GBS patients. This updated review focusing on the clinical features may help clinicians early identify potential patients, and commence a prompt appropriate management may improving the end outcomes.

GBS is a rare autoimmune disorder that presents with a symmetric, ascending flaccid paralysis, often preceded by respiratory or gastrointestinal infections from a virus or bacteria[1]. Most of the patients with GBS have a history of suffering from a variety of infectious infectious agents, which include Campylobacter jejuni, cytomegalovirus, and ZIKA viruses among others[21], within 4-6 weeks prior to the development of symptoms with GBS, leading to the temporal profile of neurologic symptoms follow the classical postinfectious profile of the Guillain-Barré syndrome infection[1, 22].

Most cases of SARS-CoV-2-GBS appeared with a short lag time from the primary SARS-CoV-2 infection[16, 17]. Our study showed that 43 patients (98%) had neurologic symptoms during or immediately after the viral syndrome associated with SARS-CoV-2 infection. The median time from onset of antecedent illness to onset of neurologic symptoms was 11.2 days (range, 2–23).This observation suggests does not temporal profile of neurologic symptoms does not follow the classical postinfectious profile of GBS. Given the temporal association, the present study support the notion that GBS might have been triggered by humoral immune response against SARS-CoV2 in these patients[23]. The present analysis of cases with GBS substantiate the previous hypothesis that SARS-CoV-2 may trigger GBS as para-infectious or post-infectious disease as did by Zika virus[24].

The limitation of this study is that the lack of an epidemiological study to

monitor development of GBS and associated neurological disorders among acute/chronic COVID-19 patients as reported by Zika virus[24-26]. Previous study have shown an increased incidence of GBS during the COVID-19 outbreak in northern Italy, supporting a pathogenic link[27].This data suggested that increased GBS incidence during SARS-CoV-2 epidemics，which has provided a unique opportunity to further delineate the clinical features and pathophysiology of GBS. But at the same time one study have determined if clusters of the GBS have been spatially and temporally related to the current SARS-CoV-2 epidemic, the epidemiological and cohort study finds no association between COVID-19 and GBS[28].

Conclusion

In conclusion, we have characterized the clinical features of SARS-CoV-2-related GBS based on published cases and case series. The present retrospective analysis support the role of the SARS-CoV-2 infection in the development of the GBS, may trigger GBS as para-infectious disease，and lead to SARS-CoV-2-associated GBS.

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Author's contributions

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Table1. Demographic and Clinical Characteristics of Acute Neurologic Illness Among Patients With Confirmed Guillain-Barré Syndrome With Evidence of SARS-CoV-2 Infection

No	Ref	Age/ Sex	Initial viral syndrome	Diagnosis of COVID-19	TVC (days)	Neurological symptoms/ Signs	TVN (days)	CSF Findings	AAs	MRI Results	TNE (days)	Subtype of GBS	TNG (days)	Treatment for GBS	Outcome status
1	[16]	77/F	Fever, cough, ageusia	(+) RT-PCR/ NPS	NS	Flaccid areflexic tetraplegia evolving to facial weakness, upper-limb paresthesia (36 hr), and respiratory failure (day 6)	7	Day 2 (first LP): protein(N); no cells; PCR assay for SARS CoV-2(-) Day 10 (second LP): protein (101 mg/dl); WBC(4 cells/mm^3); PCR assay for SARS CoV-2(-)	Negative	Head: normal Spine: enhancement of caudal nerve roots	3	SMA	4	2 cycles of IVIG	Poor : persistence of severe upper-limb weakness, dysphagia, and lower-limb paraplegia
2	[16]	23/M	Fever, pharyngitis	(+) RT-PCR/PS:	NS	Facial diplegia and generalized areflexia evolving to lower limb paresthesia with ataxia (day 2)	10	Day 3: protein(123 mg/dl); no cells; PCR assay for SARS CoV-2(-)	Not tested	Head: enhancement of facial nerve bilaterally Spine: normal	12	SMA	2	IVIG	Good : decrease in ataxia and mild decrease in facial weakness
3	[16]	55/M	Fever, cough	(+) RT-PCR/ NPS	NS	Flaccid tetraparesis and facial weakness evolving to areflexia (day 2) and respiratory failure (day 5)	10	Day 3: protein(193 mg/dl);no cells; PCR assay for SARS CoV-2(-)	Negative	Head: normal Spine: enhancement of caudal nerve roots	11	AMA	2	2 cycles of IVIG	Poor: ICU admission owing to neuromuscular respiratory failure and flaccid tetraplegia
4	[16]	76/M	Cough,hyposmia	(+) RT-PCR/ NPS	NS	Flaccid areflexic tetraparesis and ataxia (day 4)	5	Day 5: normal protein level; no cells; PCR assay for SARS CoV-2(-)	Not tested	Head: normal Spine: normal	2	Demyelin ating	5	IVIG	Poor : mild improvement but unable to stand 1 mo after onset
5	[16]	61/M	Cough,ageusia,anosmia, asthenia	(+) RT-PCR/ serum	NS	Facial weakness, flaccid areflexic paraplegia (days 2–3), and respiratory failure (day 4)	7	Day 3: protein (40 mg/dl); WBC (3 cells/mm^3); PCR assay for SARS CoV-2(-)	Negative	Head: not performed Spine: normal	4	Demyelin ating	4	IVIG+PE	Poor : tetraplegic and ventilation dependent
6	[14]	64/M	Fever, cough	(+) RT-PCR/ NPS	2	Paresthesia in feet and hands (days 16) ; flaccid severe tetraparesia (days 19) ; swallowing disturbance	16	Protein(166 mg/dL)；cell count (N)	Negative	NA	5	Demyelin ating	3	IVIG (0,4 g/kg/d ×5 d)	NA
7	[29]	65/M	Cough,fever ,dyspnea	(+) RT-PCR/ NPS	0	Acute progressive symmetric ascending quadriparesis; began with acute progressive weakness of distal lower extremities, facial paresis bilaterally; no urinary and fecal incontinence	9	Not done	Not tested	Cervical/brain MRI: normal	9	AMAN	4	IVIG (0,4 g/kg/d×5 d)	NA

8	[30]	54/M	Cough,fever , diarrhea	(+) RT-PCR/ NPS	10	Numbness and weakness of his lower extremities; urinary retention; difficulty breathing and ascending weakness to upper extremity	8	Not done	NA	Head: normal Spine: normal	Not done	Not done	2	IVIG (0,4 g/kg/d×5 d)	Good：Upper extremity weakness resolved; Lower extremity weakness persisted
9	[17]	61/F	Denied fever, cough, chest pain, or diarrhea; On day 8:cough and fever	(+) RT-PCR/ NPS	0	Acute weakness in both legs and severe fatigue, progressing within 1 day; symmetric weakness (MRC 4/5) and areflexia in both legs and feet.	Before COV ID19	Day 4: protein(124 mg/dl); cell count (N)	NA	NA	5	Demyelin ating	3	IVIG	Good：normal
10	[31]	71/M	,Fever	(+) RT-PCR/ NPS	7	Subacute onset of paresthesia at limb extremities, followed by distal weakness rapidly evolving to a severe, flaccid tetraparesis over the previous 3 days	4	Day 0: protein(54 mg/dl); WBC (9 cells/mm^3); PCR assay for SARS CoV-2(-)	NA	NA	NA	Demyelin ating	3	IVIG (0,4 g/kg/d×5 d)	Dead
11	[32]	68/M	Fever, upper respiratory symptoms	(+) RT-PCR/ NPS	NA	Progressive gait disturbance and paresthesias of his hands and feet; bilateral facial weakness, dysphagia, dysarthria, neck flexion weakness, and inability to ambulate (days 3)	13	Day 3: protein(226 mg/dl); WBC(3 cells/mm^3); PCR assay for SARS CoV-2(-)	Negative	Head: not performed Spine: normal	Not done	Not done	8	PE	Good ： ambulate with minimal assistance
12	[32]	84/M	Fever	(+) RT-PCR/ NPS	0	Paresthesias of his hands and feet; progressive gait disturbance; bilateral facial weakness, progressive arm weakness, autonomic dysfunction, and neuromuscular respiratory failure (days 3)	16	Day 4: protein(226 mg/dl); WBC(1 cells/mm^3); PCR assay for SARS CoV-2(-)	GM2 IgG/IgM Ab↑	NA	Not done	Not done	10	PE+ IVIG	Poor: remains quadriparetic with intermittent autonomic dysfunction
13	[15]	70/F	Cough	(+) RT-PCR/ NPS	23	Bilateral weakness and tingling sensation in all four extremities	11	Day 4: protein(100 mg/dl); WBC (N); PCR assay for SARS CoV-2(-)	NA	NA	12	AMSAN	2	IVIG (2g/kg/d×5 d)	Poor ： No significant neurological improvement
14	[33]	66/F	Cough,fever pruriginous dorsal rash but had no gastrointestinal symptoms	(+) RT-PCR/ NPS	NA	Difficulty walking and acute fatigue; paraparetic with a rapidly progressive symmetric weakness in the lower limbs, leading to falls and paraplegia; initial distal weakness in the upper limbs and diffuse areflexia; progressively developed proximal weakness in all limbs, dysesthesia, and unilateral facial	7	Day ?: protein(108 mg/dl); WBC (0);	Negative	NA	10	Demyelin ating ;axo nal damage;	NA	IVIG (0,4 g/kg/d×5 d)	Poor

						palsy									
15	[34]	50/M	Cough	Fecal PCR and serum IgM and IgG for SARS-CoV-2 were all positive	NA	Progressive bilateral facial weakness, paresthesia of distal extremities and an unsteady gait	4	Day ?: protein(N); WBC (N); PCR assay for SARS CoV-2(-)	Negative Anti-GQ1b	Head: normal	Not done	Not done	11	IVIG (2g/kg/d×5 d)	Good: a mild proximal weakness in the lower extremities and facial diplegia
16	[35]	72/M	Diarrhea, anorexia, and chills	(+) RT-PCR/ NPS	7	Symmetric paresthesias and ascending appendicular weakness; dysautonomia (days 3)	6	Day 8: protein(313mg/dl); WBC (1 cells/mm^3); PCR assay for SARS CoV-2(-)	Negative	Head: not performed Spine: not performed	14	Demyelinating	7	IVIG (2g/kg/d×4 d)	Poor: remains in the ICU with severe weakness
17	[36]	54/F	Loss of smell and taste	(+) RT-PCR/ NPS	14	Acute, proximally pronounced, moderate, symmetric paraparesis, Areflexia, numbness, and tingling of all extremities were also found, with initial maintained gain ability	14	Day 8: protein(14000mg/dl); WBC (1 cells/mm^3); PCR assay for SARS CoV-2(-)	Negative	Spine: normal	NA	AIDP	23	IVIG (0,4 g/kg/d×5 d)	Good: almost complete recovery
18	[23]	68/M	Fever, cough, headache, fatigue, myalgia, persistent pelvic girdle and muscle pain of the proximal lower extremities	Anti-SARS-CoV-2-antibodies in serum (+)	10	Symmetric distal tingling in both feet followed by ascending dysesthesias up to the knees and proximal weakness, inability to walk, truncal dysesthesia; worsened with progressive weakness (MRC 1-5) in both arms (2/5) and hands (4/5) and both legs (2/5) and feet (4/5) and generalized areflexia；respiratory failure	14	Day 2: protein(64 mg/dl); cell count (N); Anti-SARS-CoV-2-antibodies in CSF (+)	Negative	Spine: normal	NA	AIDP	4	IVIG+PE	Good：improved gradually
19	[37]	70/F	Fever, cough	(+) RT-PCR/ NPS	1	Asthenia, hands and feet paresthesia and gait difculties; respiratory failure due to the worsening of muscle weakness(days 5)	23	Day 3: protein (48mg/dl); WBC(1cells/mm^3); Anti-SARS-CoV-2-antibodies in CSF (+)	Not tested	Head: not performed Spine: not performed	5	?	6	IVIG (0,4 g/kg/d×5 d)	NA
20	[38]	51/F	Diarrhea, cough , odinophagi, root-type pain in all four limbs, especially in the legs as well as dorsal and lumbar back pain	SARS-CoV-2-IgM (+)	NA	Weakness in his lower limbs which progressed to the point of preventing her from walking in a few days, associated with double binocular vision; autonomic dysfunction such as dry mouth, diarrhea and unstable blood pressure；inferior bilateral facial paresis；global areflexia	21	Day 3: protein (70mg/dl); WBC (5 cells/mm^3);	Negative	Head: not performed Spine: not performed	11	MFS	NA	IVIG (0,4 g/kg/d×5 d)+	Good：Progressive improvement in facial and limb paresis, diplopia and pain

21	[39]	61/M	Fever, cough	SARS-CoV-2-IgM (+)	NA	Bilateral facial nerve palsy	10	Day ?: protein (44mg/dl); WBC (0); PCR assay for SARS CoV-2(-)	NA	Head: normal Spine: not performed	Not done	Atypical variant	1	Oral prednisone	Good：recoverd
22	[40]	36/M	Fevers, chills, and myalgia	(+) RT-PCR/ NPS	NA	Left eye drooping, blurry vision, and reduced sensation and paresthesia in both legs; progressive ophthalmoparesis, ataxia, and hyporeflexia	2	Not done	Negative: anti-GQ1b	Head: enlarged CN III Spine: not performed	Not done	MFS	2	IVIG	Good：discharged
23	[41]	50/M	Cough, malaise, headache, low back pain, and a fever; anosmia and ageusia	(+) RT-PCR/ NPS	5	Vertical diplopia, perioral paraesthesias and gait instability; right internuclear ophthalmoparesis and right fascicular oculomotor palsy	3	Day ?: protein (80mg/dl); WBC (0 cells/mm^3); PCR assay for SARS CoV-2(-)	GD1b-IgG in serum (+).	Head CT: normal	Not done	MFS	NA	IVIG (0,4 g/kg/d×5 d)	Good：ccranial neuropathies and the ataxia improved significantly
24	[41]	39/M	Diarrhea, fever,	(+) RT-PCR/ NPS	3	Acute onset diplopia	3	Day ?: protein(62mg/dl); WBC (2 cells/mm^3); PCR assay for SARS CoV-2(-)	Not tested	Head CT: normal	NA	MFS	0	Acetaminophen	Good：recoverd
25	[42]	52/F	Cough, fever, odynophagia, arthralgia,Diarrhea	SARS-CoV-2 IgM/IgG, followed+ (+) RT-PCR/ NPS	29	Back pain, limb weakness, ataxia, distal paresthesia, dysgeusia, cacosmia. Developed respiratory failure, dysautonomia and tetraplegia with areflexia	15	Day ?: protein(60mg/dl); WBC (23 cells/mm^3); PCR assay for SARS CoV-2(-)	NA	Spine: normal	4	AIDP	4	IVIG	Good：improvement of tetraparesis. Able to stand up with assistance. GBS disability clinical score 4/6
26	[42]	63/F	Cough, shivering, odynophagia, dyspnea, chest pain	(+) RT-PCR/ NPS	9	Lower limb pain, mild weakness and normal deep tendon reflexes. Developed tetraparesis, distal paresthesia and areflexia	7	Day ?: protein(40mg/dl); WBC (2 cells/mm^3);	NA	not performed	9	AIDP	5	IVIG	Good：dismissal with full motor recovery. Persistence of lower limb areflexia and distal paresthesia. GBS disability clinical score 1/6
27	[42]	61/F	Productive cough, fever, myalgia, vasovagal syncope, Diarrhea, nausea and vomiting	(+) RT-PCR/ NPS	7	Lower limb weakness and distal paresthesia, dizziness, dysphagia, dysautonomia, areflexia. Presented worsening of bulbar symptoms and bilateral facial palsy	22	Day ?: protein(140mg/dl); WBC (24 cells/mm^3); PCR assay for SARS CoV-2(-)	NA	Spine: lumbosacral nerve root enhancement.	4	AIDP	4	IVIG	Good：improvement of tetraparesis and ability to walk with assistance. Persistence of neuropathic pain and distal paresthesia. GBS disability clinical score 3/6
28	[43]	76/M	No		NA	Tetraparesis,Dysarthria,Dysautonomia	NA	Day ?: protein(22.8 mg/dl); WBC (0.6 cells/mm^3); PCR assay for SARS CoV-2(-)	Negative	NA	NA	AMSAN	NA	NA	NA
29	[43]	70/M	Diarrhea		NA	Paraparesis,Paraesthesia,Ataxia	NA	Day ?: protein(21.6 mg/dl); WBC (0.6 cells/mm^3);	Negative	NA	NA	AIDP	NA	NA	NA

30	43	80/M	No	NA	Arthromyalgia, Paraesthesia,Paraparesis, Low back pain	NA	Day ?: protein(93.3 mg/dl); WBC (0 cells/mm^3);	NA	NA	NA	AIDP	NA	NA	NA
31	43	59/M	No	NA	Emifacial paresthesia,Facial weakness (VII c.n.),Dysarthria (XII c.n.)	NA	Day ?: protein(70.1 mg/dl); WBC (2.8 cells/mm^3);	Negative	NA	NA	MFS	NA	NA	NA
32	43	59/F	Fever,Cough Common cold	NA	Low back pain,Paraesthesia,Tetraparesis	NA	Day ?: protein(112.4 mg/dl); WBC (0.4 cells/mm^3);	Negative	NA	NA	AIDP	NA	NA	NA
33	43	82/M	Fever	NA	Asymmetric paraparesis	NA	Day ?: protein(82.7 mg/dl); WBC (0.8 cells/mm^3);	NA	NA	NA	AIDP	NA	NA	NA
34	43	53/M	Fever,Diarrhea	NA	Paraesthesia,Ataxia	NA	Day ?: protein(192.8 mg/dl); WBC (2.6 cells/mm^3);	Negative	NA	NA	AIDP	NA	NA	NA
35	43	59/F	Diarrhea	NA	Tetraparesis,Paraesthesia	NA	NA	GD1b+GT1b(+)	NA	NA	AIDP relapse	NA	NA	NA
36	44	64/M	Cough, dyspnea, diarrhea and fever	(+) RT-PCR/ NPS	7	fast progressive lower-limb weakness; generalized areflexia, severe flaccid paraparesis, mainly affecting proximal muscles, and a decreased proprioceptive length-dependent sensitivity involving the four limbs; hypoesthesia to light touch and pinprick in lower extremities	16	Day 6: protein(165 mg/dl); WBC (0 cells/mm^3); PCR assay for SARS CoV-2(-)	Negative	NA	5	Demyelinating	0	IVIG (0,4 g/kg/d×5 d)	Good：recoverd
37	45	70S/M	Cough,fatigue, myalgia,	(+) RT-PCR/ NPS	5	Paraparesis, distal allodynia, difficulties in voiding and constipation; Blad der/Bowel disturbance	6	Albuminocytologic dissociation	NA	Head: normal Spine: normal	NA	AIDP	0	IVIG (0,4 g/kg/d×5 d)	Good：recoverd
38	46	43/M	Ccough, asthenia, and myalgia in legs, followed by acute anosmia and ageusia with diarrhea the next day	(+) RT-PCR/ NPS	21	Flaccid paraparesis,generalized areflexia, lower-limb and distal upper-limb paresthesia, ataxia; right facial palsy (day 4)	21	Day 3: protein (95mg/dl); Cell count: (1 cells/mm^3); PCR assay for SARS CoV-2(-)	Negative	Spine:radiculitis and plexitis on both brachial and lumbar plexus; multiple cranial neuritis (in nerves III, VI, VII, and VIII)	9	Demyelinating	4	IVIG (0,4 g/kg/d×5 d)	Good：progressive improvement
39	46	70/F	Anosmia and ageusia, diarrhea, mild asthenia and myalgia, dyspnea and loss of ambulation	(+) RT-PCR/ NPS	10	Flaccid tetraparesis, generalized areflexia, forelimb paresthesia; respiratory failure (day 3)	10	Day 3: protein (140mg/dl); Cell count: (6 cells/mm^3); PCR assay for SARS CoV-2(-)	Negative	Head: not performed Spine: not performed	7	Demyelinating	3	IVIG (0,4 g/kg/d×5 d)	Good：progressive improvement
40	47	56/F	Fever, dry cough	(+) RT-PCR/	15	Unsteadiness and paraesthesia in	15	Day 3: protein (86 mg/dl);	Negative	Spine: brainstem and	11	Demyelin	9	IVIG	NA

		and dyspnea	NPS		both hands; lumbar pain and progressive proximal lower limb weakness(day2); global areflexia; no problems with sphincter control; bilateral facial nerve palsy, oropharyngeal weakness and severe proximal tetraparesis		WBC (3 cells/mm^3); PCR assay for SARS CoV-2(-)		cervical meningeal enhancement		ating		(2g/kg/d×5 d)	
41	[48]	60S/M	Fever, headache and myalgia followed by anosmia and ageusia	(+) RT-PCR/ NPS	28	Progressive limb weakness and distal paresthesia at four-limbs	20	Day 3: protein (86 mg/dl); WBC (3 cells/mm^3); PCR assay for SARS CoV-2(-)	Negative	Cervical spine: normal	5	AIDP	10	IVIG (0,4 g/kg/d×5 d)	Good：slow improvement
42	[49]	76/F	Cough and fever , asthenia, Lower back pain radiating to the backs of the legs	(+) RT-PCR/ NPS	7	Progressive tetraparesis with distal-onset paraesthesia, progressive tetraparesis, global areflexia, and fatal bulbar syndrome	16	Not done	Not done	Not done	Not done	Not done	5	NA	Dead
43	[50]	43/M	Diarrhea,symptoms of upper respiratory tract infection.	(+) RT-PCR/ NPS	NA	Symmetrical weakness involving all 4 limbs; bilateral facial palsy and dysphagia(day2);	10	Not done	Not tested	Not done	Not tested	AIDP	2	IVIG (0,4 g/kg/d×5 d)	Good ： Neurological and respiratory symptoms progressed favourably
44	[51]	58/M	No	(+) RT-PCR/ NPS	NA	Acute-onset bilateral facial weakness, dysarthria, and paresthesia in his feet; complete facial diplegia and areflexia in the lower extremities	NA	Day 3: protein (100mg/dl); Cell count: (4 cells/mm^3); PCR assay for SARS CoV-2(-)	Not tested	Brain: Bilateral intracranial and extracranial facial nerve enhancement	6	AIDP	NA	IVIG (0,4 g/kg/d×5 d)	Poor ： Had slight movements of his facial muscles, and the distal paresthesias of his lower extremities were unchanged

Ref.: reference; NA: not-available; M: male; F: female; (+) :Positive;TVC: Time between reported viral syndrome and confirmed COVID-19; TVN: Time between reported viral syndrome and onset of neurological symptoms (days); TNE: Time between neurological onset and EMG examination (Days); TNG: Time between onset of neurological symptoms and peak of GBS (days); AAs:Antiganglioside Antibodies; AIDP : acute inflammatory demyelinating polyneuropathy; AMAN: acute motor axonal neuropathy; AMSAN: acute motor and sensory axonal neuropathy; MFS:Miller-Fisher syndrome; PS:pharyngeal swab; NPS: nasopharyngeal swab; SMA: Sensory-Motor Axonal; AMA: Acute Motor Axonal; LP: lumbar puncture; N: normal; PE: plasma exchange;

Table 2. Clinical and Demographic Characteristics of the 44 Patients with the Guillain–Barré Syndrome.

Characteristic	Value (N =44)
Median age (range) — yr	61.4 (23–84)
Male sex — no. (%)	29 (66)
Famale sex — no. (%)	15 (34)
Duration, median (range), d	37 (84)
Time between reported viral syndrome and confirmed COVID-19 (n=23)	9.6 (0-29)
General symptoms before the onset of the Guillain-Barré syndrome — no. (%)	40 (91)
Cough	25 (57)
Fever	25 (57)
Diarrhea	15 (34)
Fatigue/asthenia	9 (20.5)
Anosmia/hyposmia	6 (13.6)
Dyspnea	5 (11.4)
Muscle pain	5 (11.4)
Ageusia	5 (11.4)
Headache	3 (7.0)
Chills	2 (4.5)
Anorexia	1 (2.3)
Rash	1 (2.3)
SARS-CoV-2 infection diagnostic category — no. (%)	
Nasopharyngeal swab/PT-PCR	32 (72.7)
SARS-CoV-2 IgM (Serum)	3 (6.8)
SARS-CoV-2 IgG (Serum)	2 (4.5)
SARS-CoV-2 antibody (CSF)	2 (4.5)
Fecal PCR	1 (2.3)
PCR for SARS-CoV-2 on CSF (Positive)	0 (0)
PCR for SARS-CoV-2 on CSF (Negative)	24 (54.5)

Table 3. Clinical and Laboratory Findings in the 44 Patients with the Guillain–Barré Syndrome.

Characteristic	Value (N=44)
Subtype of GBS— no. (%)	
AIDP	14 (31.8)
Demyelinating	11 (25.0)
MFS	5 (11.4)
SMA	2 (4.5)
AMA	1 (2.3)
AMAN	1 (2.3)
AMSAN	2 (4.5)
AIDP relapse	1 (2.3)
Duration, median (range), days	
Time between reported viral syndrome and onset of neurological symptoms (n=34)	11.2 (2-23)
Time between neurological onset and EMG examination (n=22)	7.4 (2-14)
Time between onset of neurological symptoms and peak of GBS (n=32)	4.8 (0-23)
Signs and symptoms of neurologic illness, No. (%)	
Hyporeflexia or areflexia	21 (48)
Tetraparesis	23 (52.3)
Leg weakness	27 (61.4)
Leg parethesia	22 (50.0)
Arm weakness	19 (50.4)
Arm paresthesia	19 (50.4)
Facial weakness	17 (38.6)
Facial paresthesia	1 (2.3)
Dysphagia	4 (9)
Dysarthria	4 (9)
Respiratory failure	8 (18.2)
Gait ataxia	10 (22.7)
Dysautonomia	5 (11.4)
Diplopia	3 (6.8)
Bulbar symptoms	5 (11.4)
Results of CSF analysis	
Increased protein level — no./total no. (%)	32/39 (82.1)
Proteins (mg/dL) (range)	504 (21-14000)
Increased white-cell count level — no./total no. (%)	4/35 (11.4)
Median white-cell count (range) — cells/mm^3	3.1 (0-24)
Antiganglioside Antibodies	
Negative — no./total no. (%)	22/25 (88)
Not tested — no./total no. (%)	6/44 (13.6)
Positive — no./total no. (%)	3/25 (12)
Not-available — no./total no. (%)	11/44 (25)
Treatment modality of GBS	
IVIg — no./total no. (%)	29/33 (88)
PE — no./total no. (%)	1/33 (3)
IVIg+PE — no./total no. (%)	3/33 (9)

Not-available — no./total no. (%)	9/44 (20.5)
Outcome and prognosis	
Good — no. (%)	21/44 (47.7)
Poor — no. (%)	9/44 (20.5)
Dead— no. (%)	2/44 (4.5)

AIDP : acute inflammatory demyelinating polyneuropathy; AMAN:acute motor axonal neuropathy;AMSAN: acute motor and sensory axonal neuropathy; MFS: Miller-Fisher syndrome; PS:pharyngeal swab; NPS:nasopharyngeal swab; SMA: Sensory-Motor Axonal; AMA: Acute Motor Axonal; PE: plasma exchange; IVIg:intravenous immunoglobulin;

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