



Case report

Guillain–Barré syndrome as a parainfectious manifestation of SARS-CoV-2 infection: A case series



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ABSTRACT

The global SARS-CoV-2 pandemic posed an unprecedented challenge to almost all fields of medicine and Neurology is not an exception. Collecting information about its complications and related conditions will help clinicians to become more confident in managing this disease. Guillain-Barre Syndrome (GBS) is mostly described as a post-infectious phenomenon and its occurrence during acute phase of illness is of interest. GBS has recently been reported during the active phase of COVID-19 for the first time. Severity and fast progression of GBS associated with COVID-19 have also been shown in recent studies. Here we report three cases of GBS during the active phase of COVID-19 with severe symptoms and fast progression to quadriplegia and facial diplegia over 2 days, which led to death in one case due to severe autonomic dysfunction. We suggest SARS-CoV-2 might be associated with rather a severe, rapidly progressive and life-threatening phenotype of GBS.

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1. Introduction

Coronavirus disease 2019 (COVID-19) is defined as an illness caused by a novel coronavirus, which is now called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; formerly called 2019-nCoV). SARS-CoV-2 was first identified at an outbreak of respiratory illness cases in Wuhan City, Hubei Province, China. It was initially reported to the World Health Organization (WHO) on December 31, 2019 [1]. On January 30, 2020, the WHO declared the COVID-19 outbreak as a global health emergency [2,3].

Since August 16, 2020, the COVID-19 pandemic has resulted in more than 21 million of confirmed cases worldwide. Additionally,

Iran stands on the 11th rank in terms of infected cases by SARS-CoV-2, with more than 341,000 infected cases [4].

Guillain–Barré Syndrome (GBS) is considered mostly a post-infectious, immune-mediated disease. Symptoms of a preceding upper respiratory tract infection or gastrointestinal infection are often reported prior to the onset of GBS symptomatology. However, it might also occur during the infectious phase in some cases. The first case of GBS during the COVID-19 pandemic has recently been published, and since then investigations on its relationship to COVID-19 have started [5]. Molecular mimicry between infectious agents and gangliosides plays a crucial role in inducing these antibodies [6,7].

2. Case 1

An 88-year old woman was admitted to the emergency department in April 2020 with quadriplegia. Her symptoms started with acute paraparesis, which progressed to quadriplegia within two days. She did not report cough, dyspnea, fever, diarrhea, paresthesia or urinary symptoms. She was complaining of severe fatigue, low back pain and pain in her thighs. Her past medical history was significant for hypertension. On physical examination, she

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization; GBS, Guillain–Barré Syndrome; MRC, Medical Research Council; CSF, cerebrospinal fluid; EMG-NCS, electromyography and nerve conduction studies; AMSAN, acute motor and sensory axonal neuropathy; ICU, intensive care unit; CT, computed tomography; PCR, polymerase chain reaction; AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; IVIg, intravenous immunoglobulin; MERS, Middle East respiratory syndrome.

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was afebrile, and her oxygen saturation was 95%. She had left eye closure weakness and neck flexion weakness. An evaluation of muscle power revealed Medical Research Council (MRC) grade 2/5 in the muscles of upper limbs and MRC 3/5 in lower limbs. Deep tendon reflexes were absent in lower limbs and depressed in upper limbs. Sensory examination revealed impaired proprioception. Spinal tap was performed on day two of admission, and cerebrospinal fluid (CSF) analysis showed an elevated protein level (88 mg/dl) with no cells in accordance with albuminocytologic dissociation. Antigangliosides antibodies were not checked. She underwent electromyography, and nerve conduction studies (EMG-NCS) revealed features consistent with an acute motor and sensory axonal neuropathy (AMSAN) subtype of GBS (Table 1). She was admitted in the intensive care unit (ICU) due to autonomic instability, and plasma exchange was started. On the third day of admission, she was intubated owing to respiratory distress, and her chest computed tomography (CT) scan revealed pneumonia with a ground glass pattern suggestive of corona virus infection. COVID-19 polymerase chain reaction (PCR) returned positive; therefore, she was isolated. She was commenced on Dexamethasone, along with Hydroxychloroquine and Lopinavir/Ritonavir for the treatment of COVID-19. Minimal improvement in muscle power was achieved after 6 sessions of plasma exchange 2 weeks after commencing the treatment. She was discharged upon improvement of respiratory symptoms.

3. Case 2

Our second patient was a 47-year-old man who was admitted to the emergency department by his family with generalized weakness and dysarthria in April 2020. His family provided a history of 10 days of dyspnea and cough prior to the emergence of his dysarthria that led to hospital presentation. He appeared ill, but he was afebrile. On neurologic examinations, a mild muscle weakness and generalized hyporeflexia were found together with dysarthria. MRI brain and whole spine results were normal. The CT scan of his chest was consistent with COVID-19 infection. There was elevated CRP and leukopenia on his blood examination. The patient was admitted in an isolated ward, and Dexamethasone, Hydroxychloroquine and Lopinavir/Ritonavir were started to treat COVID-19. On the second day of admission, a neurology consult was requested as the patient developed urinary retention. The patient complained of severe low back pain. On examination, he had quadriparesis and weakness in neck flexors. He was areflexic. Based on his EMG-NCS (Table 2), an AMSAN type of GBS was diag-

nosed. Hence, treatment with plasma exchange was started. The CSF analysis revealed elevated protein with the level of 154 mg/dl and no cells. Antigangliosides antibodies were not checked. One day during his treatment, he developed bilateral facial palsy. The patient was intubated due to respiratory distress on the same day and was transferred to ICU. On the 4th day of admission and after 2 sessions of plasma exchange, the patient died from severe autonomic dysfunction.

4. Case 3

A 58-year-old man was admitted to the emergency department in April 2020, with a two-day history of progressive dyspnea, dry cough and dizziness. Vital signs on presentation were remarkable for the respiratory rate of 26 breaths per minute with oxygen saturation of 88% on room air. The patient was admitted to the hospital with the impression of COVID-19 infection. Chest CT-scan results were consistent with the diagnosis of COVID-19, which was confirmed by a positive nasopharyngeal PCR test. He was admitted to ICU for respiratory support and was treated with available suggested drugs for COVID-19 such as Remdesivir, Hydroxychloroquine, Favipiravir and Lopinavir/Ritonavir. On the 7th day of admission, he developed muscle weakness, gait disturbance and areflexia. EMG/NCV findings were suggestive of an AMSAN sub-type of GBS (Table 3). CSF was acellular with elevated protein (65 mg/dl). Antigangliosides antibodies were not checked. Intravenous immunoglobulin (0.4 g/kg, for 2 days) was commenced for the patient.

Two days later, he was switched to plasma exchange due to a rise in serum creatinine. The patient developed severe respiratory distress and became intubated 14 days after his admission. We assumed that GBS caused ventilation problems as well as respiratory problems. The patient died on the 20th day of admission due to multi-organ failure.

5. Discussion

Since the outbreak of COVID-19 in China, there have been several case reports of its neurological complications such as acute stroke, encephalopathy and skeletal muscle injury [8]. GBS is a well-known post/para-infectious entity. Recently, Ellul et al. have proposed a probable association of GBS with SARS-CoV-2 infection where onset of weakness was 6 weeks after acute infection [9]. COVID-19-related GBS was first reported in China and was assumed to have a para-infectious profile rather than a post-

Table 1
Nerve conduction study parameters in case 1.

Nerve stimulated	Stimulation site	Recording site	*Amplitude		Latency (ms)		Conduction velocity (m/s)		F wave (ms)	
			Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt
Median (M)	Wrist	APB	3.8	3.6	4.1	4	40	40	32	32
	AF	APB	3.5	3.2						
Ulnar (m)	Wrist	ADM	4	4.1	3.1	3	48	48	32	32
	BE	ADM								
	AE	ADM								
Tibial (m)	Ankle	AHB	NR	NR	NR	NR	NR	NR	NR	NR
	PF	AHB								
Peroneal (m)	Ankle	EDB	NR	NR	NR	NR	NR	NR	NR	NR
	BF	EDB								
	LPF	EDB								
Median (s)	Wrist	Index finger	8	7	3.4	3.5	38	38		
Ulnar (s)	wrist	Little finger	6	6	3	3.1	40	40		
Sural (s)	calf	Post. calf	NR	NR	NR	NR	NR	NR		

*Motor = mV, Sensory = μ V; ms = milli second, Rt = right; Lt = left; AF = anterior fossa; BE = below elbow; AE = above elbow; BF = below fibula; LPF = lateral posterior fossa; APB = abductor pollicis brevis; ADM = abductor digiti minimi; AHB = abductor hallucis brevis; EDB = extensor digitorum brevis; NR = not response.

Table 2

Nerve conduction study parameters in case 2.

Nerve stimulated	Stimulation site	Recording site	*Amplitude		Latency (ms)		Conduction velocity (m/s)		F wave latency (ms)	
			Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt
Median (M)	Wrist	APB	1.8	1.8	4.6	4.5	37	35	NR	NR
Ulnar (m)	AF	APB	1.5	1.5						
	Wrist	ADM	1	1.1	4.1	3.9	34	34	NR	NR
	BE	ADM								
Tibial (m)	AE	ADM								
	Ankle	AHB	NR	NR	NR	NR	NR	NR	NR	NR
	PF	AHB								
Peroneal (m)	Ankle	EDB	NR	NR	NR	NR	NR	NR	NR	NR
	BF	EDB								
	LPF	EDB								
Median (s)	Wrist	Index finger	NR	NR	NR	NR	NR	NR		
Ulnar (s)	wrist	Little finger	NR	NR	NR	NR	NR	NR		
Sural (s)	calf	Post. calf	NR	NR	NR	NR	NR	NR		

*Motor = mV, Sensory = μ V; ms = milli second, Rt = right; Lt = left; AF = anterior fossa; BE = below elbow; AE = above elbow; BF = below fibula; LPF = lateral posterior fossa; APB = abductor pollicis brevis; ADM = abductor digiti minimi; AHB = abductor hallucis brevis; EDB = extensor digitorum brevis; NR = not response.

Table 3

Nerve conduction study parameters in case 3.

Nerve stimulated	Stimulation site	Recording site	*Amplitude		Latency (ms)		Conduction velocity (m/s)		F wave latency (ms)	
			Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt
Median (M)	Wrist	APB	0.8	0.3	4.8	5	37	35	NR	NR
Ulnar (m)	AF	APB	0.8	0.3						
	Wrist	ADM	0.1	0.2	4.1	3.9	33	34	NR	NR
	BE	ADM								
Tibial (m)	AE	ADM								
	Ankle	AHB	NR	NR	NR	NR	NR	NR	NR	NR
	PF	AHB								
Peroneal (m)	Ankle	EDB	NR	NR	NR	NR	NR	NR	NR	NR
	BF	EDB								
	LPF	EDB								
Median (s)	Wrist	Index finger	NR	NR	NR	NR	NR	NR		
Ulnar (s)	wrist	Little finger	NR	NR	NR	NR	NR	NR		
Sural (s)	calf	Post. calf	NR	NR	NR	NR	NR	NR		

* Motor = mV, Sensory = μ V; ms = milli second, Rt = right; Lt = left; AF = anterior fossa; BE = below elbow; AE = above elbow; BF = below fibula; LPF = lateral posterior fossa; APB = abductor pollicis brevis; ADM = abductor digiti minimi; AHB = abductor hallucis brevis; EDB = extensor digitorum brevis; NR = not response.

infectious one [10]. The second case of GBS associated with SARS-CoV-19 was reported from Iran. The case was a 65-year-old man with severe progressive peripheral neuropathy leading to quadriplegia, two weeks after COVID-19 diagnosis based on a positive PCR [11]. Alberti et al. reported the second case of parainfectious SARS-CoV-2-related GBS in a patient presenting simultaneous neurological and respiratory symptoms where the patient died from respiratory failure despite appropriate treatment [12]. De Sanctis et al., by investigating the characteristics of 18 GBS patients associated with SARS-CoV-2 reported around the world, published a systematic review published on the 5th August 2020. Ten patients were male and 8 were female with a mean age of 62 years. Cough and fever were the most frequent observed symptoms of SARS-CoV-2 infection among the patients (72.2%). Concurrent symptoms of GBS and SARS-CoV-2 infection were observed in five patients (27.8%). The frequency of different electrophysiological subtypes was as follows: Acute inflammatory demyelinating polyneuropathy (AIDP) (10 patients), AMSAN (4 patients), acute motor axonal neuropathy (AMAN) (1 patient) and not reported (3 patients). Death and poor prognosis were reported in two (11.1%) and four cases (22.2%), respectively, due to GBS and concurrent complications caused by COVID-19. However, the prognosis was not reported in three cases. All reported patients in this study received intravenous immunoglobulin (IVIg) except for two (88.9%); while one underwent plasma exchange after IVIg therapy.

[13]. Here, we reported three cases of GBS during the active phase of COVID-19 pandemic. Since all of our patients had the symptoms of GBS during the active phase of Corona virus infection, we reiterate the proposed theory of GBS being a *para*-infectious condition in association with COVID-19 infection. (Table 4). As exhibited in these patients, the fast progression and severity of GBS in such cases are significant, as demonstrated in a recent study where 4 out of 5 patients diagnosed with GBS after SARS-CoV-19 infection developed tetraplegia over a period of 36 h to 4 days [5]. While symptoms of GBS were developed after COVID-19 in these patients, one of our cases presented with GBS symptomatology before the onset of COVID-19 symptoms. A similar encounter has been reported in association with Zika virus during its outbreak in 2016 [14,15]. Facial palsy and higher CSF protein levels with severe GBS have been reported in the outbreak of Zika virus [16].

Similarities might be seen in some close viral pathogens; therefore, it is necessary for clinicians to learn from past outbreaks, such as Middle East respiratory syndrome (MERS) and Zika epidemics, where neuromuscular complications were not rare [17]. COVID-19 should be considered in differential diagnoses of rare neuromuscular presentations during the pandemic period. We suggest a full investigation panel to rule out COVID-19 infection in patients presenting with GBS, including rare subtypes. Furthermore, patients presenting with COVID-19 should undergo detailed neurological examinations to specifically seek features of GBS. A severe

Table 4

Characteristics of Three Patients with Guillain-Barré Syndrome after the Onset of Covid-19.

Patient No.	Characteristics	Onset of Neurologic symptoms	Neurologic Signs and Symptoms	CSF analysis	EDX subtype	Treatment	Outcome
1	88-year-old woman	two days prior to admission with severe fatigue and low back pain	Paraparesis developed to quadriparesis, absent DTR in lower limbs and decreased DTR in upper limbs	WBC < 10 cell/ μ l Elevated protein level (88 mg/dl)	AMSAN	Plasma exchange	Favorable, discharged 15 days followed by the admission
2	47-year-old man	About a week prior to admission, coincide with respiratory symptoms	Dysarthria and decreased DTR in lower limbs followed by quadriparesis	WBC < 10 cell/ μ l Elevated protein level (154 mg/dl)	AMSAN	Plasma exchange	Death on the 4th day of admission
3	58-year-old man	7 days followed by admission	muscle weakness, gait disturbance and areflexia	WBC < 10 cell/ μ l Elevated protein level (65 mg/dl)	AMSAN	IVIg & Plasma exchange	Death on the 20th day of admission

CSF, cerebrospinal fluid; EDX, electrodiagnosis; DTR, deep tendon reflex; RBC, red blood cell; WBC, white blood cell; AMSAN, acute motor-sensory axonal neuropathy; IVIg, intravenous immune globulin.

and rapid progressive phenotype of GBS appears to be another neurologic complication of COVID-19 with the possibility of occurrence during the active phase of the disease.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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