Case Series

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COVID-19 Associated Guillain-Barré Syndrome- A Case Series

Internal Medicine Section

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ABSTRACT

The outbreak of Coronavirus Disease-2019 (COVID-19) infection with associated Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) caused modified and compromised immune system that gave rise to various immune mediated disease. Various studies on both central and peripheral nervous system involvement has been reported. The common syndromes reported are meningoencephalitis, myelitis and Guillain-Barré Syndrome (GBS) etc. This case series reports four cases (41-years-old male, 35-years-old female, 50-years-old male and 65-years-old male patients) presenting with the duration from onset of viral illness to neurologic manifestations ranging from 4-60 days. One patient had a typical course of viral symptoms preceding GBS findings and two patient presented with GBS later. A patient was found to be IgG seropositive for SARS-CoV-2 and presented 2 months later of recovery from infection while one case had onset of weakness while having respiratory symptoms. These cases had Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP) who presented with acute flaccid paralysis two to three weeks following COVID-19 infection. All the patients received Intravenous Immunoglobulin (IVIG) as treatment and showed significant improvement. It can be concluded that COVID-19 viral infection is probably related as a causal factor for immune mediated illness like GBS and early identification and treatment has good recovery.

Keywords: Acute inflammatory demyelinating polyradiculoneuropathy, Coronavirus disease-2019, Pandemic

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the causative agent for COVID-19 has manifested from asymptomatic to acute respiratory distress syndrome and severe inflammatory response leading to multiple organ dysfunction and death. According to the currently available resources, SARS-CoV-2 can affect every organ in the body, leading to acute organ damage and long-term effects, the latter effects recently being observed [1]. The upper and lower respiratory tracts are the main sites of involvement of SARS-CoV-2 infection. Pneumonia, with typical ground glass opacities in High-Resolution Computed Tomography (HRCT) thorax, has been noticed as the typical presentation. Recently increasing reports have shown that SARS-CoV-2 infection is associated with involvement of the Central Nervous System (CNS) and the Peripheral Nervous System (PNS) [2-5]. It is either due to direct invasion from virus or indirectly from modified immune response [2]. In this case series, the Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) proven SARS-COV2 cases were diagnosed with GBS based on clinical findings, Cerebrospinal Fluid (CSF) and electrophysiological findings according to the case definitions described by World Health Organisation (WHO) [3].

CASE SERIES

Case 1

A 41-year-old male patient, without co-morbidity, presented with complaints of fever, cough and mild breathlessness on exertion for three days. His RT-PCR from nasopharyngeal swab for SARS-COV2 was positive. HRCT severity score was 7/25. The patient was isolated and symptomatic treatment was started. These symptoms recovered in seven days.

After next 10 days, he noticed paresthesia in both feet and both hands. The symptoms progressed and he found difficulty in getting up from squatting position, climbing upstairs and noticed slippage of footwear. In the next three to four days, he noticed difficulty in doing overhead activities, buttoning, unbuttoning, and facial weakness and was hospitalised in non-ambulatory state.

On examination, his vitals were normal and oxygen saturation was 95% by pulse oximetry. His single breath count was 30. Cranial nerve examination showed bilateral lower motor neuron facial palsy. The tone was reduced in all four limbs. The Medical Research Council scale (MRC scale) power grading system showed grade 4/5 power in both upper limbs at all joints and reduced handgrip. In both lower limbs, powergrade was 4/5 at hip and knee joints and 3/5 at both ankle joints. All deep tendon reflexes were absent. The plantar response was flexor bilaterally. On sensory examination, joint position sense was impaired upto both ankles in lower limbs and upto both wrists in upper limbs; rest sensations were normal. In the setting of rapidly progressive ascending weakness, generalised areflexia and preceding viral illness, provisional diagnosis of GBS was kept.

On further investigations, Complete Blood Count (CBC), sugar, renal function test and serum electrolytes were normal. Serum bilirubin was 1.4 mg%, Aspartate Aminotransferase (AST) (57 U/L), Alanine Transaminase (ALT) 104 (U/L), triglyceride (337 mg%) and C-reactive Protein (CRP) (12 mg/L). CSF showed 5 cells/mm^3 (100% lymphocytes), protein 300 mg/dL (reference range 15-45 mg/dL), sugar 70 mg/dL (blood sugar 96 mg/dL). The serological tests for Human Immunodeficiency Virus (HIV), syphilis, Cytomegalovirus (CMV), Epstein-Barr virus (EBV) were negative. The nerve conduction study showed reduced or absent compound muscle action potentials and sensory nerve action potentials in the lower limbs and upper limbs, absent F wave response in the lower limbs, and prolonged F wave response in the upper limbs. This was suggestive of sensory-motordemyelinating polyradiculoneuropathy (AIDP). MRI lumbosacral spine was normal.

He was treated with Intravenous Immunoglobulin (IVIG) with a total dose of 2 g/kg in divided doses for five days along with physiotherapy. On fifth day his power improved more than 4/5 in all four limbs and he started walking with minimal support of a person. He was discharged on seventh day with symptomatic treatment and over a month he had near complete recovery except having some paresthesia in both feet.

Case 2

A 35-year-old female patient, without co-morbidity, presented with three day history of low grade fever, cough, sore throat and shortness of breath. RT-PCR for COVID-19 from nasopharyngeal swab was advised and found positive. Her HRCT thorax showed severity score of 13/25. The patient was advised home isolation for 14 days, but she started experiencing tingling and numbness in her legs from two days of starting isolation. Overnext two to three days, she developed significant weakness of both lower limbs, both upper limbs and face on both sides. Later her condition worsened, and she became bedbound over next two to three days, for which she was taken to hospital.

On examination, her vitals were normal. Single breath count was 20 and oxygen saturation dropped to 92% by pulse oximetry without oxygen support (initial day one reading was 95%). She was conscious and cranial nerve examination showed bilateral Lower Motor Neuron (LMN) facial palsy. The tone was reduced in all four limbs. Power grading by MRC scale was 3/5 in both upper limbs at all joints with reduced handgrip [4]. In lower limbs, power was 1/5 at both hip joint, 1/5 at the right knee joint, 2/5 at the left knee joint, and 2/5 at both ankle joints. All deep tendon reflexes were absent. The plantar response was flexor bilaterally. On sensory examination, joint position sense was impaired upto both knee ankles in lower limbs and up to both wrists in upper limbs. Provisional diagnosis of GBS was kept based on clinical examination and preceding viral infection.

On further investigations, CBC, sugar, renal function test and serum electrolytes were normal. CSF showed 5 cells/mm^3 (100% lymphocytes), protein 190 mg/dL (reference range 15-45 mg/dL), sugar 68 mg/dL (blood sugar 84 mg/dL). The serological tests for HIV, syphilis, CMV, Epstein-Barr virus (EBV) were negative. The nerve conduction study showed reduced or absent compound muscle action potentials in all four limbs with normal distal latency, normal sensory nerve action potentials in all four limbs and prolonged F wave response in the lower limbs and upper limbs. The nerve conduction study was suggestive of sensory-motor axonal polyradiculoneuropathy.

The patient was given IVIG (2 g/kg) in divided doses for five days, along with other symptomatic treatment and physiotherapy. On day seventh, her power improved to 4/5 in upper limbs and 3/5 in lower limbs. She was discharged on 10^{th} day but she needed support to walk. At three months, she had significant improvement with residual foot drop in both her feet.

Case 3

A 50-year-old male patient, without any co-morbid illness, was suffering with low-grade fever, cough and sore throat for fourth days. He presented to emergency room with progressive weakness of all four limbs and pins and needle sensation in both lower limbs. Weakness started symmetrically in both lower limbs and progressed to involve upper limbs over four days to an extent that he could not walk even with support. The weakness was accompanied by bilateral facial weakness, difficulty in swallowing and slurring of speech, which developed one day after hospitalisation.

On examination, his single breath count was 20. Bilateral asymmetric Lower Motor Neuron (LMN) type facial palsy was present (left >right). On motor examination, the tone was reduced in all four limbs; power was 3/5 in the upper extremities (both proximal and distal groups) with reduced handgrip. In lower limbs, it was 1/5 in both hip and knee joint and 2/5 at both ankle joints. There was generalised areflexia with bilateral flexor. Vibration was impaired upto both knee and elbow. Provisional diagnosis of GBS was kept looking his rapidly progressive ascending illness and generalised areflexia-hyporeflexia. His COVID-19 RT-PCR was positive suggesting COVID-19 infection in recent past.

On investigations, CBC, sugar, renal function test and serum electrolytes were normal. AST was 76 units/l, ALT122 units/l, CRP 45 mg/lL. CSF showed 5 cells/mm^3 (100% lymphocytes), protein 195 mg/dL (reference range 15-45 mg/dL), sugar 71 mg/dL. The serological tests for HIV, syphilis, cytomegalovirus (CMV), Epstein–Barr virus (EBV) were negative. The nerve conduction study showed reduced or absent compound muscle action potentials, prolonged distal latency; normal sensory nerve action potentials in the lower limbs and upper limbs and absent F wave response in the lower limbs, and prolonged F wave response in the upper limbs. The nerve conduction study was suggestive of sensorimotor primary axonal and secondary demyelinating polyradiculoneuropathy. Magnetic Resonance Imaging (MRI) lumbosacral spine was normal.

The patient was started on Intravenous Immunoglobulin (IVIG) (2 g/kg) in divided doses for five days with regular physiotherapy and other symptomatic treatment. He got discharged on 10^{th} day with improvement of muscle power to grade 3. After three months of illness, he was ambulatory but had residual weakness.

Case 4

A 65-year-old male patient, presented with chief complaint of generalised body weakness (all 4 limbs), low back pain radiating to both legs (right >left) and numbness of all four limbs for five days. He was unable to stand up without support during admission. He was a known case of long standing diabetes mellitus and hypertension. In the past, he had history of fever, cough, and sore throat two months back for which he was hospitalised at local hospital and underwent RT-PCR for COVID-19 (nasopharyngeal swab examination), which was positive for SARS-CoV-2. Isolation along with symptomatic treatment was carried out, and later, he was discharged with improvement.

On admission, his vitals were normal. His single breath count was 22 and oxygen saturation was 98% by pulse oximetry. On motor system examination, the tone was reduced in all four limbs, power of 4/5 in the upper extremities (proximal and distal groups), reduced handgrip bilaterally and power 1/5 in both lower extremities (hip, knee and ankle joint). The deep tendon reflexes were absent in all four limbs. In sensory examination, joint position was impaired upto both ankles.

Investigations showed normal CBC, renal function test and serum electrolytes. Blood sugar was 156 mg/dL. SARS-CoV-2 (COVID-19) IgG antibody was positive (400 AU/mL). CSF showed 5 cells/mm^3 (90% lymphocytes), protein 207 mg/dL (reference range 15-45 mg/dL), sugar 83 mg/dL protein. The serological tests for HIV, syphilis, CMV, Epstein–Barr virus (EBV) were negative. The nerve conduction study showed reduced or absent compound muscle action potentials and sensory nerve action potentials in the lower limbs and upper limbs, absent F wave response in the lower limbs and upper limbs. The nerve conduction study was suggestive of sensorimotor Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP). MRI lumbosacral spine was normal.

The patient was started on Intravenous Immunoglobulin (IVIG) 2 g/kg in divided doses for five days with regular physiotherapy. The power of the lower limbs increased 2/5 and remained same in upper limbs during discharge on 10^{th} day from admission.

The [Table/Fig-1] summarises clinical manifestations, lab findings, treatment given and outcome of all four COVID-19 associated GBS cases.

DISCUSSION

The SARS-CoV-2 is a novel coronavirus detected in Wuhan, China, in December 2019 and is the causative pathogen for COVID-19. It targets the respiratory system via fusion with Angiotensin-Converting Enzyme 2 (ACE2) receptor [4]. Earlier in the pandemic

Case no.	Age and gender	Interval between COVID-19 symptoms and GBS	NCS	CSF	Treatment	Outcome
1	41 years, Male	20 days	AIDP	Cells 5 Protein 300	IVIG	Complete improvement in one month
2	35 years, Female	6 days	AMAN	Cells 5 Protein 190	IVIG	Significant improvement with bilateral foot drop at 3 months
3	50 years, Male	4 days	Primary Axonal with secondary demyelination	Cells 5 Protein 195	IVIG	Improvement with residual weakness at 3 months
4	65 years, Male	2 months	AIDP	Cells 5 Protein 207	IVIG	Improvement with residual weakness at 1 month

[Table/Fig-1]: Summary of COVID-19-associated Guillain-Barre syndrome cases.
AIDP: Acute inflammatory demyelinating polyneuropathy; AMAN: Acute motor axonal neuropathy; CSF: Cerebrospinal fluid; F: Female; IVIG: Intravenous venous immunoglobulin; M: Male; NCS: Nerve conduction study

a case series was published by Mao L et al., in Wuhan, China, that showed neurologic manifestations in patients with COVID-19; they concluded that patients with severe COVID-19 illness were more likely to have neurologic symptoms [5]. Thereafter, many cases studies reported neurological involvement in COVID-19 infection that worsens the clinical outcome [6,7]. Both CNS (including headache, epileptic seizure, impaired consciousness and dizziness) and PNS (such as Guillain-Barré syndrome, anosmia and neuralgia) involvement have been described divided as para infectious and post infectious [8]. The mechanism described is either direct invasion affecting cerebrovascular endothelium or brain parenchyma or indirectly through overproduction of cytokines and modulation of immune system [9].

The first case of GBS following SARS-CoV-2 was reported by Zhao H et al., in a 61-year-old female patient, who developed demyelinating polyneuropathy during her visit to Wuhan, China [10]. Following this, many of studies have shown GBS association with COVID-19 and there has been rise in incidence of GBS after the COVID-19 pandemic [6,11-14]. In India also, COVID-19 associated GBS has been reported [13]. According to the WHO, GBS is a polyradiculoneuropathy that occurs when the body immune system attacks part of the peripheral nervous system and it is usually preceded mostly by respiratory or gastrointestinal infection [15]. Viruses have been found associated with GBS, include Campylobacter jejuni, CMV, Epstein-Barr, Zika virus; GBS was also reported following Middle East Respiratory Syndrome and Severe Acute Respiratory Syndrome caused by coronavirus [16,17]. The possible mechanism with this virus is same as described with previous infection associated GBS. An auto-reactive immune response that triggers molecular mimicry between microbial and neural antigens is a major driving force in this disorder. The interaction between microbial agents and the host that dictates the immune response to the unwanted auto reactivity is not well understood yet [18,19].

In the indexfour cases the duration from onset of viral illness to neurologic manifestations have ranged from 4-60 days. One had a typical course of viral symptoms preceding GBS findings (case 3) and two patient presented with GBS later (case 1, 4). Case 4 found to have IgG seropositivefor SARS CoV 2 and presented two months later of recovery from infection. One case (Case 2) had onset of weakness while having respiratory symptoms. Few cases have been reported with concurrent respiratory and neurologic symptoms [14]. Two patients were of AIDP variant while two were of axonal. Toscano G et al., reported five patients from Italy; three with an axonal variant of GBS and two with demyelinating neuropathy [12]. The initial symptoms in all cases were lower limb paresthesia and all followed typical ascending pattern of progression of weakness. The duration from symptoms onset to nadir was four to five days. No patient required assisted ventilation. In all cases, CSF albumino-cytological dissociation were seen. CSF cell count was less than 10 cells/mm^3 in all four cases and CSF protein ranged from 190-300 mg/dL (reference range 15-45 mg/dL). All 4 cases received 2 gram/kg dose of IVIG in five days divided dose and noticed improvement. One patient had complete improvement while three had residual weakness till there last follow-up (from 1-3 months).

These four cases draw attention to GBS occurrence in patients with COVID-19 who experience mild respiratory and general symptoms preceding the onset of GBS. It emphasises that SARS-CoV-2 induces immunological reaction as a post infectious or para infectious process. The recovery varied from a mild change in extremity function to full neurologic recovery. Early identification and management with immune therapy (IVIG or plasma exchange) not only prevents respiratory failure but also ensures good and rapid recovery.

CONCLUSION(S)

There has been rise in neurological manifestations in proportion to number of COVID-19 patients in this pandemic and GBS is one alike. Therefore physicians and health care professionals should be aware of GBS association with COVID-19 and more clinical and epidemiological studies needed to reach expertise and define its pattern in comparison to previous reported post or para infectious GBS.

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