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Guillain-Barre syndrome in SARS CoV-2: Case series of uncommon neurological complication from tertiary care center, Bengaluru, South India

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ABSTRACT

Coronavirus disease is an infectious disease caused by severe acute respiratory syndrome-coronavirus 2 virus. It predominantly affects respiratory system causing fever, cough, and breathlessness. But it can also affect central nervous system and peripheral nervous system. It is important that physicians keep a high index of suspicion for patients with neurologic symptoms following a recent or during COVID-19 infection. The low rate of initial diagnosis is alarming, as few of the percentage of patients with Guillain-Barre syndrome will develop respiratory muscle weakness requiring invasive ventilation. The ability to recognize the disease process could lead to life saving management. Furthermore, the initiation of therapy such as plasma exchange or intravenous immunoglobulin leads to an accelerated recovery time.

Key words: Guillian-barre syndrome, Coronavirus 2, Demyelination, Immunoglobulins

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a infectious caused by a virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first known case was identified in Wuhan, China, in December 2019.[1] The disease spread worldwide has lead to the COVID-19 pandemic. SARS-CoV-2 membrane is characterized by the presence of the spike (S) glycoprotein, which facilitates entry into cells. It is mainly transmitted by coughing and sneezing through respiratory droplets. It invades the respiratory system through attaching to the respiratory epithelium and it enters the cells through binding to the angiotensin converting enzyme 2 receptors. The mechanisms of SARS-CoV-2 associated neurological manifestations are still not fully understood. Several mechanisms have been proposed to explain SARS-CoV-2-induced neurological disorders. Neurological infections by corona viruses have been previously described in patients with SARS, which is caused by SARS-CoV virus, and Middle East respiratory syndrome (MERS), which is caused by MERS-CoV. According to many studies, the newly emerging SARS-CoV-2 virus that causes COVID-19 is associated with neurological complications involving both the central and peripheral nervous systems.

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Guillain-Barré Syndrome (GBS) is the most frequent cause of acute flaccid paralysis and autoimmune disorder causing demyelination of the peripheral nerves. Its main clinical features are a symmetrical ascending muscle weakness with reduced or absent reflexes and variable sensory involvement with autonomic dysfunction. It most commonly occurs after an viral infection, after immunization with certain vaccines or during the development of specific malignancies. Many patients with severe COVID-19 disease experience a surge of pro inflammatory cytokines, a condition known as a cytokine storm.[2] Cytokine storms can cause damage to the blood-brain- barrier, and their potential role in neurological complications has been documented. The immune-mediated role in COVID-19 pathogenesis is also noted in many cases. The role of immune system hyper activation in GBS is also evidenced by the response to immunoglobulin therapy.[3-5] Acute inflammatory demyelinating polyneuropathy and acute motor axonal neuropathy variants have been reported after SARS-CoV-1 and MERS-CoV infections.[6,7] A possible explanation was also suggested for such immune response is the molecular mimicry.[8] The role of auto antibodies in neurological complications was first suggested by the occurrence of GBS in COVID-19 patients.[9] In Molecular mimicry, a foreign antigen can induce immune cells against self-antigen caused by sequence similarity between foreign and self-peptides.[8]

There have been few reports of GBS in patients of SARS-CoV-2.

Here, we report 5 cases of GBS in COVID-19 patients.

CASE 1

A 55-year-old female presented to our triage with history of fever, cough since 7 days breathlessness since 2 days. She is known case of hypertensive on regular treatment. No other history of co morbidities. On examination pulse was 128 b/m. Blood pressure was 130/90, respiratory rate was 35 b/m, and oxygen saturation was 80%. On auscultation bilateral normal vesicular breath sounds and bilateral crepitations were heard. Cardiovascular examination tachycardia was present. Other systemic examination was normal. Arterial blood gas was suggestive of type I respiratory failure. In view of desaturation, tachycardia and tachypnea was intubated. With Fio_2 40%, PEEP of 8, volume assisted control mode, she maintained saturation of 99%. Reverse transcription polymerase chain reaction (RTPCR) for COVID 19 was positive. Blood investigations showed raised inflammatory markers. After 5 days of intubation, patient showed improvement clinically and tried to wean off. 7th day of intubation, she was extubated and she was put on non-invasive mechanical ventilation. She tolerating non-invasive ventilation. Awake proning was imitated. She started ambulating and chest physiotherapy was given.

15th day of her illness, she started developing lower limb weakness bilaterally. Started from distal muscle weakness progressed to proximal muscle weakness. She was having difficulty in gripping slippers and difficulty in squatting. No h/o upper limb weakness. No h/o sensory involvement. No h/o cranial nerve involvement. No h/o bladder and bowel involvement. On examination, higher mental functions were normal. Cranial nerve was normal. Upper limb tone was normal. Lower limb tone was hypotonia. Power upper limb bilaterally 5/5. Lower limb bilaterally 2/5. Upper limb reflexes were normal. Lower limb reflex was areflexia. Bilateral plantar reflex was mute. Sensory system was normal. No cerebellar involvement. Gait could not asses. Spine was normal.

Acute flaccid paraparesis of bilateral lower limb as working diagnosis was made. Further, LP Cerebrospinal fluid (CSF) was done. CSF analysis revealed 1 lymphocyte cell and albumin was 224 mg/dL, glucose was 48 mg/dL. CSF albumin-cytological disassociation was found. Total white blood cell count was 9900/μL. Blood cultures and urine cultures were negative. Serum procalcitonin level was 0.1 ng/mL. magnetic resonance imaging (MRI) brain and spine was normal. Nerve conduction study of both lower limbs revealed prolonged distal motor latencies and prolonged *F* wave latencies, reduced conduction velocities, suggestive of immune mediated demyelinating polyneuropathy. Patient was diagnosed with GBS.

Patient received 5 days of 1 g/kg/day IV immunoglobulin, steroids, anticoagulants, Vitamin C, and antihypertensive. After 5 days of IV immunoglobulin, patient started noticing improvement in power, was able to walk with support. Limb physiotherapy was started. Patient was discharged on 25th day.

CASE 2

A 64-year-old male presented to our triage with history of fever, cough, and sore throat since 2 days. Weakness of both lower limbs since 2 days. Fever was high grade, intermittent in nature, associated with chills, rigors and sore throat, relieved by medications. Lower limb weakness bilaterally since 2 days, gradual in onset progressed over period of 2 days. He noticed weakness initially in difficulty in gripping slippers and then noticed proximally, difficulty in getting up from bed and floor, climbing down and climbing up stairs. He also noticed difficulty in squatting position. No h/o upper limb weakness. No h/o sensory involvement. No h/o cranial nerve involvement. No h/o bladder and bowel involvement. He is known case of diabetic since 10 years on regular treatment. No other history of comorbidities.

On examination pulse was 128 b/m. Blood pressure was 130/90, respiratory rate was 35 b/m, and oxygen saturation was 90%. On auscultation bilateral normal vesicular breath sounds and bilateral crepitations were heard. On examination, higher mental functions were normal. Cranial nerve was normal. Upper limb tone was normal. Lower limb tone was hypotonia. Power upper limb bilaterally 5/5. Lower limb bilaterally 1/5. Upper limb reflexes were normal. Lower limb reflex was areflexia. Bilateral plantar reflex was mute. Sensory system was normal. No cerebellar involvement. Gait could not asses. Spine was normal. Cardiovascular examination tachycardia was present. Other systemic examination was normal.

ABG was suggestive of type I respiratory failure. In view of desaturation, tachycardia and tachypnea, patient was started on oxygen 4 l/min. He started maintaining 96% saturation. RTPCR for COVID 19 was positive. Blood investigations showed raised inflammatory markers. Random blood sugar (RBS) was 306 mg/dL. HbA1c is 8.5%. Urine ketone bodies negative. Urine analysis showed nil glucose, no pus cells, and albumin +. Renal function test and serum electrolytes within were normal limits. Chest X-ray was showing bilateral lower zone consolidation with predominant peripheral involvement. Working diagnosis of bilateral COVID-19 pneumonia with acute flaccid paraparesis of lower limb of made. LP CSF analysis was done. CSF analysis revealed 2 lymphocyte cell and albumin was 340 mg/dL, glucose was 56 mg/dL. CSF albumin-cytological disassociation was found. MRI brain and spine was normal. Nerve conduction study of both lower limbs revealed prolonged distal motor latencies and reduced conduction velocities, suggestive of immune mediated demyelinating polyneuropathy. Patient was diagnosed with GBS.

Patient received 5 days of 1 g/kg/day IV immunoglobulin, steroids, anticoagulant and Vitamin C and insulin. Limb physiotherapy was started. After 2nd day of IV immunoglobulin, patient started noticing improvement in power, was able to flex leg against gravity. After 1 week, patient started walking with support. Patient was discharged.

CASE 3

A 63-year-old male, previously hospitalized for COVID-19 pneumonia 15 days back got discharged from outside hospital. Patient was on home oxygen therapy with 4 L of oxygen presented to us with 1 week of weakness of both lower limbs and breathlessness since 1 week. Weakness of both lower limb since 1 week. He was not able to roll over on the bed and was not able to flex legs bilaterally. Patient was bound to bed. No history of weakness of both upper limb. No history of sensory symptoms. No h/o cranial nerve involvement. No h/o bladder and bowel involvement. Patient is known case of diabetic, hypertensive and ischemic heart disease on regular treatment. On examination, pulse was 94 beats per minute. Blood pressure was 110/80 mm Hg and respiratory rate was 19 breaths per minute. Saturation was 94% room air. Central nervous system examination higher mental functions normal. Cranial nerve normal. Upper limb tone was normal. Lower limb tone was hypotonia. Power upper limb bilaterally 5/5. Lower limb bilaterally 2/5. Upper limb reflexes were normal. Lower limb reflex was areflexia. Bilateral plantar reflex was mute. Sensory system was normal. No cerebellar involvement. Gait could not asses. Spine was normal. Other systemic examination was normal.

ABG was suggestive of type I respiratory failure. Patient was started on oxygen 4 l/min. He started maintaining 96% saturation. RTPCR for COVID 19 was negative. Blood investigations showed normal inflammatory markers Chest X-ray was showing right lower zone consolidation. Working diagnosis of post COVID acute flaccid paraparesis of lower limb of made. LP CSF analysis was done. CSF analysis revealed 1 lymphocyte cell and albumin was 278 mg/dL, and glucose was 60 mg/dL. CSF albumin-cytological disassociation was found. MRI brain and spine was normal. Nerve conduction study of both lower limbs revealed demyelinating axonal asymmetric sensorimotor neuropathy. Patient was diagnosed with post Covid Guillain-Barre syndrome. He was started on IV Immunoglobulin 1 g/kg/day for 5 days. Patient improved clinically during 3rd day of IV immunoglobulin. Limb physiotherapy was started. Patient fully recovered on 7th day of admission. Patient was discharged on 10th day.

CASE 4

A 50-year-old female came with complaints of fever, breathlessness since 14 days. Fever was intermittent and high grade. It was relieved by taking medications. Breathlessness since 10 days, gradual onset associated with productive sputum, mucoid in consistency. No history comorbidities.

On examination pulse was 110 b/m. Blood pressure was 108/70, respiratory rate 40 b/m, oxygen saturation was 80%. On examination, patient was drowsy. On auscultation respiratory system bilateral normal vesicular breath sounds and bilateral crepitations was heard. Cardiovascular system tachycardia was present. ABG was suggestive of type I respiratory failure. RTPCR COVID 19 was positive. Inflammatory markers were raised. Chest X-ray showed bilateral consolidation. Patient was intubated In view of desaturation, tachycardia, and tachypnea were intubated. With FiO_2 60%, PEEP of 8, volume-assisted control mode, she maintained saturation of 94%. Patient was started on antibiotics, steroids and anticoagulants. After 5 days of

intubation, patients ABG improved and clinically improved, patient was extubated. However, patient was not able to walk. Patient was reassessed. On the central nervous examination, higher mental functions were normal. Cranial nerve was normal. Upper limb tone was normal. Lower limb tone was hypotonia. Power upper limb bilaterally 5/5. Lower limb bilaterally 0/5. Upper limb reflexes were normal. Lower limb reflex was areflexia. Bilateral plantar reflex was mute. Sensory system was normal. No cerebellar involvement. Gait could not asses. Spine was normal. LP CSF analysis was done. CSF analysis revealed 0 lymphocyte cell and albumin was 297 mg/dL, glucose was 70 mg/dL. CSF albumin-cytological disassociation was found. MRI brain and spine was normal. Nerve conduction study of both lower limbs revealed demyelinating axonal asymmetric sensorimotor neuropathy. Patient was diagnosed with post COVID Guillain-Barre syndrome. She was started on IV Immunoglobulin 1 g/kg/day for 5 days. Patient started improving on 4th day of IV immunoglobulin. Her power improved to 3/5. Limb physiotherapy was started. Unfortunately, patient had massive bleeding per rectum 7th during intensive care unit (ICU) stay. Patient was reintubated and was resuscitated but could not survive.

CASE 5

A 43-year-old male presented to us with 1 week of weakness of both lower limbs and fever with breathlessness since 1 week. Cough since 1 week weakness of both lower limb since 1 week. He was not able to roll over on the bed and was not able to flex legs bilaterally. Patient was bound to bed. No history of weakness of both upper limb. No history of sensory symptoms. No h/o cranial nerve involvement. No h/o bladder and bowel involvement. Fever since 1 week. High grade fever associated with chills and rigors. Fever was intermittent and subsided by medications. Breathlessness since 1 week, gradual onset progressive from Grade 1 to Grade 4 relieved by taking medications. Cough since 1 week. Initially dry cough later it became productive, whitish color, scanty in production. Patient is known case of diabetic since 3 years on regular treatment. On examination, pulse was 86 beats per minute. Blood pressure was 140/80 mm Hg, respiratory rate was 22 breaths per minute. Saturation was 94% room air. Central nervous system examination, higher mental functions were normal. Cranial nerve was normal. Upper limb tone was normal. Lower limb tone was hypotonia. Power upper limb bilaterally 5/5. Lower limb bilaterally 0/5. Upper limb reflexes were normal. Lower limb reflex was areflexia. Bilateral plantar reflex was mute. Sensory system was normal. No cerebellar involvement. Gait could not asses. Spine was normal. Other systemic examination was normal.

ABG was suggestive of type I respiratory failure. Patient was started on oxygen 6 l/min. He started maintaining 95% saturation. RTPCR for COVID 19 was positive. Blood investigations showed increased inflammatory markers. RBS was 258 mg/dL. HbA1c is 7.2%. Urine ketone bodies were negative. Urine analysis showed glucose+ and albumin+ Renal function test and serum electrolytes were normal. Chest X-ray was showing left lower zone consolidation. Working diagnosis of acute flaccid paraparesis of lower limb with Covid-19 viral pneumonia was made. LP CSF analysis was done. CSF analysis revealed 1 lymphocyte cell and albumin was 320 mg/dL, glucose was 50 mg/dL. CSF albumin-cytological disassociation was found. MRI brain and spine was normal. Nerve conduction study of both lower limbs revealed demyelinating axonal asymmetric sensorimotor neuropathy. Patient was diagnosed with COVID-19 pneumonia with GBS. He was started on IV Immunoglobulin 1 g/kg/day for 5 days. Patient improved clinically during 4th day of IV immunoglobulin. Limb physiotherapy was started. Patient fully recovered on 8th day of admission. Patient was discharged on 10th day.

DISCUSSION

The first case of GBS and SARS-CoV-2 is reported from China. The patient presented with concomitant neurologic and viral symptoms.[10] Zhao et al., reported a case where there was no latent period. This latent period between the emergence of COVID-19 signs and GBS symptoms provides valuable information regarding the pathogenesis of GBS in COVID-19 infection.[10] For GBS associated with a preceding infection (respiratory or gastrointestinal), the time interval between infection and onset of neurologic symptoms varies, ranging from 3 days to 3 weeks.[11] Case details have been discussed in Table 1. Vaccination details and other metabolic parameters of the patients have been discussed in Table 2. In our cases, patients developed GBS symptoms on the same day of respiratory symptoms in case 2 and case 5, rest of the cases developed symptoms from the interval between 5 and 15 days. For a post infectious process, it is known that the time elapsed between the onset of symptoms of COVID-19 was sufficient enough to leads to the generation of molecular mimicry and triggering an autoimmune process. In contrast, in a para-infectious process, such an interval is not present, and other mechanism must be present. Regarding the latter, it is explained that SARS-Cov 2 can directly lead to the immune dysfunction complication, or that the SARS-Cov-2 virus was capable of inflicting direct damage to radicles and nerves.[12] Alternatively other mechanism is that T-cell activation followed by release of inflammatory mediators by macrophages may be another plausible mechanism, supported by a multisystem inflammatory syndrome leading to para-infectious GBS.[13]

Both the case 2 and case 5 had diabetes as co morbidity. One of the differential diagnoses was diabetic peripheral neuropathy. However, both the patient did not have any symptoms of tingling, numbness or loss of sensation or any previous history of motor weakness of limbs. In both the cases, patient developed sudden onset of symmetrical weakness which involved only lower limbs. Nerve conduction study was suggestive of demyelinating pattern and CSF analysis revealed albumin cytological dissociation.

In our case 1, patient was extubated on day 7 and she developed weakness on 15th day of illness. GBS and critical illness polymyoneuropathy are important causes of weakness in ICU and distinguishing between them is important due to the management and prognostic implications. Critical illness polymyoneuropathy always occurs in association with a critical illness in particular severe sepsis. They may have an association with encephalopathy in early stages. It results in axonal neuropathy leading to decreased compound muscle action potential without a reduction in conduction velocity. Our patient was not in sepsis, had recent respiratory illness, progressive bilateral symmetric paralysis and nerve conduction study suggested demyelinating form associated with reduction in conduction velocity.

CSF analysis in each case demonstrated albumin cytologic dissociation which is commonly seen in GBS.

Table 1: Cases details

Cases	Age/ sex	Days of onset of COVID-19 symptoms and GBS symptoms	Tone	Power	RT-PCR COVID-19 swab	Nerve conduction studies	Treatment	Outcome
1	55 Y/F	15th day	Upper limb normal lower limb hypotonia	Upper limb 5/5 lower limb 2/5	Positive	Lower limbs revealed prolonged distal motor latencies and prolonged *F* wave latencies, reduced conduction velocities	IVI g Immunoglobulin	Discharged on 25th day
2	64 Y/M	Same day	Upper limb normal lower limb hypotonia	Upper limb 5/5 lower limb 1/5	Positive	Lower limbs revealed prolonged distal motor latencies and reduced conduction velocities	IVI g Immunoglobulin	Discharged on 7th day
3	63 Y/M	15 days	Upper limb normal lower limb hypotonia	Upper limb 5/5 lower limb 2/5	Positive	Lower limbs revealed demyelinating axonal asymmetric sensorimotor neuropathy	IVI g Immunoglobulin	Discharged on 10th day
4	50 Y/F	5 days	Upper limb normal lower limb hypotonia	Upper limb 5/5 lower limb 0/5	Positive	Lower limbs revealed demyelinating axonal asymmetric sensorimotor neuropathy	IVI g Immunoglobulin	7th day patient expired
5	43 Y/M	Same day	Upper limb Normal lower limb hypotonia	Upper limb 5/5 lower limb 0/5	Positive	Lower limbs revealed demyelinating axonal asymmetric sensorimotor neuropathy	IVI g Immunoglobulin	Discharged on 10th day

GBS: Guillain-Barre syndrome

Table 2: Vaccination status and metabolic parameters

Cases	Vaccination status	Hb g/dL	Neutrophils%	Lymphocytes %	Neutrophil lymphocyte ratio	Platelets lac	RBS mg/ dL	CRP mg/ dL	LDH IU/ mL	D-dimer
1	Not vaccinated	13.3	79	18	4.3	1,00,000	118	40	525	600
2	Not vaccinated	12.9	73	15	4.8	2,50,000	306	68	384	408
3	Not vaccinated	10.3	84	5	16.8	60,000	94	34	879	1000
4	Not vaccinated	9.6	92	14	6.5	78,000	109	251	1050	2564
5	Not vaccinated	9.7	75	15	5	95,000	258	20	604	885

RBS: Random blood sugar, CRP: C-reactive protein, LDH: Lactate dehydrogenase

A Nasopharyngeal swab of SARS-CoV-2 was done for five patients, and all had positive. Nerve conduction study was done in all our patients. It revealed demyelinating axonal asymmetric sensorimotor neuropathy, prolonged distal motor latencies and prolonged F wave latencies, reduced conduction velocities. All our patients received IV immunoglobulin 1 g/kg/day for 5 days. Out of five patients, four patients got discharged. One patient could not survive because of massive bleeding per rectum, attributed to coagulopathy. Our patients were diagnosed with acute inflammatory demyelinating polyradiculoneuropathy variant.

According to the WHO's, provisional case definition for the association of SARS-CoV-2 with neurological disease is probable when the onset of symptoms is within 6 weeks of suspected acute infection, RNA detected in any sample or antibody evidence of infection, and absence of other probable etiology on evaluation.[14]

Neurological manifestations of COVID-19 occur due to the presence of ACE-2 receptors in the nervous system and skeletal system. Studies revealed SARS-CoV-2 upon infection, the virus attaches to the olfactory epithelium through the ACE-2 receptor, once the virus establishes entry inside the cell, it replicates.[15] There are several possible mechanisms by which COVID-19 affects the nervous system by a secondary effect which is associated with the vascular and prothrombotic effect of the viral infection on the CNS or PNS vasculature, the direct neurotropic or neuro-invasive effect of SARS-CoV-2, a secondary effect of the systemic inflammatory responses triggered by the viral infection and an immune-mediated para-infectious or post-infectious autoimmune effect in response to the viral infection.[16]

As the incidence of SARS-CoV-2 cases increases, it is important that physicians keep a high index of suspicion for patients with neurologic symptoms following a recent COVID-19 infection. The low rate of initial diagnosis is alarming, as 10–15% of GBS patients will develop respiratory muscle weakness requiring ventilatory management. The ability to recognize the disease process could lead to life saving management. Furthermore, the initiation of therapy, plasma exchange, or intravenous immunoglobulin, causes an accelerated recovery time.

CONCLUSION

SARS-Cov-2 virus affects not only respiratory system; it also affects central and peripheral nervous system causing morbidity and mortality. So COVID 19 pneumonia patients should be monitored for weakness of upper and lower limb during the course of illness or during post COVID follow-up, as it can cause acute flaccid paralysis. Patient should be evaluated early for GBS and treatment should be started with IV Immunoglobulin or plasmapheresis along with COVID-19 standard treatment protocol to prevent mortality and morbidity of the patients.

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