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Covid-19 associated Guillain-Barre Syndrome: Contrasting tale of four patients from a tertiary care centre in India

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ABSTRACT

Background: Globally, more than 12 million people have been infected with COVID – 19 infection till date with more than 500,000 fatalities. Although, Covid-19 commonly presents with marked respiratory symptoms in the form of cough and dyspnoea, a neurotropic presentation has been described of late as well.

Objective: In this brief communication we report four cases of Covid-19 who presented to our hospital with features suggestive of Guillain-Barre Syndrome (GBS).

Discussion: The mechanisms by which SARS-CoV-2 causes neurologic damage are multifaceted, including direct damage to specific receptors, cytokine-related injury, secondary hypoxia, and retrograde travel along nerve fibres. The pathogenesis of GBS secondary to Covid-19 is not well understood. It is hypothesised that viral illnesses related GBS could be due to autoantibodies or direct neurotoxic effects of viruses.

Conclusion: Nervous system involvement in Covid-19 may have been grossly underestimated. In this era of pandemic, it is very important for the physicians to be aware of association of GBS with Covid-19, as early diagnosis and treatment of this complication could have gratifying results. To the best of our knowledge, this is the first such case series of Guillain-Barre Syndrome associated with Covid-19 to be reported from India.

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1. Introduction

Globally, more than 12 million people have been infected with COVID – 19 infection till date with more than 500,000 fatalities [1]. Although, evolution in COVID-19 research is taking place at a rapid pace, new findings have to be thoroughly checked before any conclusion or treatment protocol is made or modified [2]. Although, Covid-19 commonly presents with marked respiratory symptoms in the form of cough and dyspnoea, a neurotropic presentation has been described of late as well [3]. Guillain Barre Syndrome (GBS) is best described as an acute inflammatory polyradiculoneuropathy clinically characterised by areflexia and progressive weakness of arms and legs. Though, many rare variants of GBS have been described, the commonly observed subtypes such as Acute Motor Axonal Neuropathy (AMAN), Acute Motor Sensory Axonal Neuropathy (AMSAN) and Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP) tend to fulfil the above-mentioned criteria [4]. In this brief communication we report four cases of Covid-19 who presented to our hospital with features suggestive of GBS.

1.1. Case 1

A 55-year-old female with background history of Diabetes Mellitus, Hypertension and Cholelithiasis presented with chief complaints of fever 10 days back lasting for 3 days, pain abdomen for 5 days; acute onset rapidly progressive symmetric weakness of all four limbs for 3 days (lower limbs followed by upper limbs). There was no history suggestive of cranial nerve, bowel or bladder involvement. On examination, patient was hemodynamically stable with 98% oxygen saturation (SpO₂) on room air. Cranial nerve examination was normal. Motor examination revealed generalised hypotonia, Grade 2/5 power in both lower limbs proximally and Grade 3/5 distally, while both upper limbs power was grade 4/5 proximally and grade 3/5 distally as per Medical Research Council (MRC) grading. Deep tendon reflexes were universally absent and plantar response was flexor bilaterally. Sensory examination was normal. Her single breath count (SBC) was 26. Her routine blood investigations including complete blood count, liver and kidney function tests were normal. Viral markers including Human Immunodeficiency Virus, Hepatitis B Surface antigen (HBsAg) and Hepatitis C Virus (HCV) antibody were negative. Serum vitamin B12 levels and Thyroid function tests were normal whereas Glycosylated Hemoglobin (HbA1c) was elevated (9.4%). Covid-19 testing was positive by reverse transcription polymerase chain reaction (RT-PCR). Inflammatory markers were universally elevated (Tables 1 and 2). Chest X ray was

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Table 1
Clinical and laboratory parameters of four cases presenting with Covid-19 associated GBS.

Case	Onset of neurological symptoms	Comorbidities	Cranial nerve involvement	Respiratory involvement	CRP levels (mg/L)	Ferritin levels (ng/ml)	IL-6 levels	D-dimer (FEU/ml)	LDH levels (U/L)
					Normal: <5	Normal: 21.8–274	Normal: 0–7	Normal: 0–0.5	Normal: 135–214
1	10 days after onset of fever	Diabetes mellitus Hypertension Cholelithiasis	No	No	9.4	382	8.21	2.19	278
2	6 days after onset of fever	Hypertension	No	Yes SBC = 12	50	482	10.21	5.19	518
3	One week after the onset of cough and sore throat	Diabetes mellitus Hypertension Chronic kidney disease on maintenance haemodialysis	No	No	34.41	560	44.71	5.49	478
4	10 days after the onset of fever	Hypertension	Yes (Bilateral facial nerve palsy)	No	0.96	322	4.75	0.32	278

normal. Contrast enhanced Magnetic Resonance Imaging (MRI) of the spine was suggestive of degenerative changes in the spine (Table 2). Nerve Conduction Study (NCS) of both upper and lower limbs was suggestive of pure motor axonal polyneuropathy. CSF examination done on fourth day of hospitalisation showed albumino-cytological dissociation (Table 2). After informed consent the patient was started on IV Immunoglobulin (IVIg): 0.4 g/kg body weight per day for five days. In view of a possibility of Covid-19 associated hypercoagulable state (elevated D Dimer) she was also given therapeutic anticoagulation. There was no further progression of her symptoms after starting IVIg and the patient was discharged after 10 days of hospital stay with Grade 4/5 power in both lower limbs and Grade 4+ /5 power in both upper limbs.

1.2. Case 2

A 72-year-old male, known case of hypertension for 5 years on treatment, presented to the emergency department of our hospital with chief complaints of fever 6 days back lasting for 2 days, cough since past 3 days associated with progressive weakness of all four limbs since past 2 days. He had lost the ability to walk independently since 1 day. There was no history suggestive of cranial nerve involvement, diarrhoea, bowel and bladder symptoms, or dog bite. On examination, patient was hemodynamically stable and afebrile. Neurological examination revealed no cranial nerve involvement. Motor examination showed generalised hypotonia, Grade 2/5 power in both lower limbs and grade 3/5 in both upper limbs as per MRC grading. Deep

Table 2
Laboratory parameters, Imaging and clinical outcomes of four cases presenting with Covid-19 associated GBS.

Case	Chest X ray	NCS findings	CSF	MRI spine	Treatment	Outcome
1	Normal	Pure motor axonal polyneuropathy	Protein: 54 mg% Glucose: 114 mg% Cells = 5 cells/cmm; all lymphocytes	Mild degenerative changes. No Cord changes No nerve root enhancement	IVIg: 2 g/kg over 5 days	Good improvement (Able to walk independently at discharge)
2	Ill-defined inhomogeneous infiltrates involving predominantly the upper lobes	Severe demyelinating sensorimotor polyneuropathy affecting all 4 limbs with evidence of conduction block involving both ulnar nerves.	Protein: 74 mg% Glucose: 110 mg% Cells = 0 cells/cmm.	Mild degenerative changes. No Cord changes No nerve root enhancement	IVIg: 2 g/kg over 5 days with supportive treatment	Deteriorated over the course of treatment. Day 2 into IVIg therapy, power in all 4 limbs had reduced to grade 1/5 and patient developed severe respiratory distress requiring intubation and mechanical ventilation. His respiratory involvement due to Covid-19 also continued to worsen and the patient expired after 7 days of hospital admission.
3	Normal	Axonal sensorimotor polyneuropathy affecting all 4 limbs	Protein: 84 mg% Glucose: 94 mg% Cells = 5 cells/cmm; all lymphocytes	Mild degenerative changes. No Cord changes No contrast enhancement	IVIg: 2 g/kg over 5 days	Good improvement (Able to walk independently at discharge)
4	Bilateral lower and midzone infiltrates	Pure motor demyelinating polyneuropathy involving all 4 limb and	Protein: 52 mg% Glucose: 54 mg%	Mild degenerative changes.	IVIg: 2 g/kg over 5 days	Good improvement (Able to walk independently at discharge)

tendon reflexes were universally absent and plantar response was flexor bilaterally. The sensory examination was normal. His SBC was 12. His routine blood investigations including complete blood count, serum sodium and potassium, liver and kidney function tests were normal. Viral markers including Human Immunodeficiency Virus, Hepatitis B Surface antigen (HBsAg) and Hepatitis C Virus (HCV) antibody were negative. Serum B12 levels and Thyroid function tests were normal. Covid-19 testing was positive by RT-PCR technique. Contrast MRI of whole spine was suggestive of degenerative changes in the spine (Table 2). CSF examination showed albumino-cytological dissociation and inflammatory markers were elevated (Tables 1 and 2). Chest X ray showed bilateral ill-defined inhomogeneous infiltrates involving predominantly the upper lobes. IVIG therapy was started at a dose of 0.4 g/kg/day for five days. NCS was suggestive of severe demyelinating sensori-motor polyneuropathy affecting all 4 limbs with evidence of conduction block involving both ulnar nerves. Despite being on IVIG and supportive treatment for Covid-19, the patient had worsening of power in both upper and lower limbs and developed severe respiratory distress requiring intubation and mechanical ventilation. His respiratory involvement (chest infiltrates due to Covid-19) also continued to worsen and the patient expired after 7 days of hospital admission.

1.3. Case 3

A 55-year-old male, known case of Diabetes mellitus, hypertension and chronic kidney disease on maintenance haemodialysis (3/week) presented to OPD with chief complaints of difficulty in walking since 3 days and mild weakness of upper extremities since 1 day. He had history of cough and sore throat 1 week back for 2 days. There was no history suggestive of cranial nerve involvement, diarrhoea, bowel and bladder symptoms, or dog bite. On examination, patient was hemodynamically stable and afebrile. Neurological examination revealed no cranial nerve involvement. Motor examination showed generalised hypotonia, grade 3/5 power in both lower limbs proximally and 4-/5 distally. Upper limb motor examination showed grade 4/5 power bilaterally as per MRC grading. Deep tendon reflexes were absent in both lower limbs and 1+ in both upper limbs. Plantar response was flexor bilaterally. The sensory examination was abnormal with glove and stocking pattern sensory loss (position sense and pain) and positive Romberg's test. His SBC was 22. He underwent routine blood investigations which showed microcytic/hypochromic anaemia, raised blood Urea (61 mg/dL) and Creatinine levels (4.74 mg/dL). Potassium was elevated (5.82 mmol/L) with elevated HbA1c (8.4%). Viral markers including HIV, HBsAg and HCV antibody were negative. Serum vitamin B12 levels and Thyroid function tests were normal. Covid-19 testing was positive by RT-PCR technique. MRI screening of whole spine showed mild degenerative changes with no cord hyperintensity (Table 2). CSF examination showed albumino-cytological dissociation with elevated inflammatory markers (Tables 1 and 2). Chest X ray was normal. NCS was suggestive of axonal sensorimotor polyneuropathy affecting all 4 limbs. IVIG therapy was started on Day 2 of hospital admission and 2 g/kg body weight of same was given over 5 days. Patient had good neurological improvement and was discharged by 9th day with power of grade 4+/5 in both upper limbs and grade 4/5 in both lower limbs.

1.4. Case 4

A 49-year-old male, known case of hypertension on treatment, presented to the neurology outpatient department (OPD) with chief complaints of fever 10 days back which lasted for 2 days followed by 4 days history of progressive lower limb weakness and 2 days history of facial weakness. On examination, patient was hemodynamically stable, afebrile with 98% SpO₂ on room air. Neurological examination revealed bilateral lower motor neuron facial palsy (right > left). Upper limb power was normal across all joints; both lower limb power:

proximal: 3/5; distal: 4/5 as per MRC grading. The Deep tendon reflexes were absent in lower limbs and normal in upper limbs. Sensory examination was normal. Routine blood investigations including complete blood count, serum sodium and potassium, liver and kidney function tests were normal. Viral markers including HIV, HBsAg and HCV antibody were negative. Serum vitamin B12 levels and Thyroid function tests were normal. Covid-19 testing was positive by RT-PCR technique. NCS was suggestive of pure motor demyelinating polyneuropathy involving all 4 limbs. Contrast MRI of whole spine showed mild degenerative changes of the spine (Table 2). CSF examination showed albumino-cytological dissociation with mildly elevated inflammatory markers in the blood (Tables 1 and 2). Chest X-ray showed evidence of bilateral lower and midzone infiltrates. IVIG was given at 0.4 g/kg body weight/day for 5 days with other supportive treatment. Good neurological improvement was observed over the next 5 days and patient was discharged after 7 days. At the time of discharge patient had 4+/5 power in both lower limbs with mild residual facial palsy.

2. Discussion

A member of the beta-coronaviridae family, SARS-CoV-2 is an enveloped, non-segmented, single-stranded, positive-sense RNA virus. The mechanisms by which SARS-CoV-2 causes neurologic damage are multifaceted, including direct damage to specific receptors, cytokine-related injury, secondary hypoxia, and retrograde travel along nerve fibres [5]. Three of the above cases presented with neurological complaints and had no respiratory features secondary to Covid-19, and these were the ones who did quite well with treatment. One patient who presented with respiratory complaints and X-ray changes along with neurological deficits continued to deteriorate even after starting treatment for both GBS and Covid-19, and eventually succumbed to the disease.

In the past GBS has been associated with a number of viral infections, most recently to Zika virus [6]. The pathogenesis of GBS secondary to Covid-19 is not well understood. It is well documented that the cross immunity which plays an important role in GBS secondary to bacterial infections such as *C. jejuni* may not be the main reason behind GBS associated with viral infections namely Dengue and Zika. It is hypothesised that viral illnesses related GBS could be due to autoantibodies or direct neurotoxic effects of viruses [7]. Although, our patients had positive PCR throat swab test, their CSF examination did not show any raised cell count and contrast MRI of the spine did not show any enhancement of caudal nerve roots, thus favouring immune mediated hypothesis. This was further strengthened by an excellent response to IVIG, thus favouring an immune mediated pathogenesis rather than direct viral damage.

Our case series serves to highlight the heterogeneity in clinical presentation and laboratory parameters of patients with Covid-19 associated GBS (Tables 1 and 2). Only one of our patients had cranial nerve involvement (bilateral facial nerve palsy) with no patient developing bulbar symptoms. This was in contrast to typical GBS, wherein cranial nerve involvement is quite common. Less frequent involvement of cranial nerves in GBS secondary to Covid-19 is also in contrast to Zika virus associated GBS, where facial and third nerve involvement was quite common [7]. All the above patients had significantly raised pro-inflammatory markers that might suggest a causal link to pro-inflammatory state secondary to Covid-19. Similar rise in inflammatory markers were noted in other case reports as well, and it was hypothesised that these inflammatory mediators and cytokines may play a role in triggering an immune mediated neuropathy [8].

All our patients developed features of GBS, 5–10 days after the onset of Covid-19 symptoms, which is similar to the interval seen with Guillain-Barré syndrome that occurs secondary to other infections [9]. Most of the previous case reports documented a similar interval duration between the onset of Covid-19 symptoms and GBS [2,9]. Three of our patients had an excellent response to IVIG and were ambulatory

without support within 10 days of starting treatment. Previous case reports show mixed treatment response with some reporting very good recovery, while others reported minimal or delayed response [9,10].

3. Conclusion

Nervous system involvement in Covid-19 may have been grossly underestimated. Over the course of this pandemic, an increasing number of Covid-19 patients are being reported with neurological complications. Some of these neurological presentations, in particular GBS has quite effective treatment options. In this era of pandemic, it is very important for the physicians to be aware of the association of GBS with Covid-19, as early diagnosis and treatment of this complication could have gratifying results. It is also important to differentiate GBS from critical illness neuropathy and respiratory distress secondary to Covid-19 itself, as treatment to the above conditions is quite different and inability to correctly diagnose could lead to significant increase in morbidity and mortality. To the best of our knowledge this case series of Guillain-Barre Syndrome associated with Covid-19 is the first one to be reported from India.

Declaration of Competing Interest

The manuscript, as submitted or its essence in another version, is not under consideration for publication elsewhere, and will not be

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