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Original Article

Treatment related fluctuation and response to intravenous immunoglobulin therapy in post COVID-19 Guillain-Barre syndrome☆

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ABSTRACT

Treatment related fluctuation (TRF) poses a special challenge in the treatment of Guillain-Barre syndrome (GBS). Many cases of GBS following COVID-19 infection have been reported in literature till date, but treatment related fluctuation (TRF) in post COVID-19 GBS has not been reported till date. We report a 35-year-old male patient who developed GBS following COVID-19 infection and had TRF after intravenous immunoglobulin (IV-IG) therapy. He required ventilator support but repeat IV-IG therapy led to complete recovery. Significant proximal muscle involvement, cranial nerve palsy, no antecedent diarrhea and absence of anti-GM1 antibodies are important predictors of TRF in GBS and need to be recognized early in the course of this illness. Early recognition of TRF and differentiating it from other forms of immune mediated neuropathy such as acute onset chronic inflammatory demyelinating polyradiculoneuropathy (A-CIDP) are important for prognostication and management.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has wreaked havoc worldwide and has claimed innumerable lives till date. The clinical spectrum of this disease may range from mild self-limiting flu-like symptoms to the severe form of illness like severe pneumonia and acute respiratory distress syndrome (ARDS) with high morbidity and mortality. With better disease understanding and improved diagnostic techniques, a large number of cases are being detected with florid extrapulmonary manifestations and complications [1,2]. Those extrapulmonary manifestations of *the coronavirus disease 2019 (COVID-19)* range from renal and gastrointestinal to hepatic, cardiac, haematological and neurological dysfunction. A recent study from Wuhan showed that more than one third of admitted patients had some form of neurological symptoms [3]. The neurological features of this infection include anosmia, dysgeusia, dizziness, headache, cerebrovascular accident, acute encephalitis, acute transverse myelitis (ATM) and Guillain-Barre syndrome (GBS) [4,5]. We report a case of GBS secondary to COVID-19, complicated by treatment related fluctuation (TRF). Thorough search of the PubMed and Medline database revealed no such similar cases in English language literature.

2. Case report

A 35-year-old gentleman presented to our institution on 1st January' 2021 with the complaint of diffuse back pain and weakness of both lower limbs which started from the distal legs over last 2 days. Within 1 week he became bedbound with quadriparesis, dysphagia and bilateral lower motor neuron type facial nerve palsy. Neurological examination was significant for bilateral lower motor neuron type facial nerve palsy, reduced tone with symmetrical weakness of 2/5 on the Medical Research Council (MRC) Power Grading Scale in all 4 limbs with involvement of neck and trunk muscles. His deep tendon reflexes were absent. However, he had no sensory or bladder involvement. His Erasmus GBS respiratory insufficiency score was 5 and he was shifted to ICU. His past history was notable for a high grade fever with loss of taste and smell sensation three weeks prior to this presentation. At that time, on 11th December' 2020, his nasopharyngeal swab was positive for SARS-CoV-2 (COVID-19) RNA, done by *RT-PCR (Reverse Transcription*

☆ ***The work will be attributed to the Department of Neuromedicine, Bangur Institute of Neurosciences, IPGMER and SSKM Hospital, Annex 1, 52/1 Shambhunath Pandit Street, Kolkata-700020, India.

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Polymerase Chain Reaction) method. His chest X-ray at that time did not reveal any evidence of consolidation, patchy or lobar infiltrates or ground-glass opacity. His complete blood count, liver and renal function profile, electrolytes, thyroid function test and clotting functions were all within the normal range except raised C-reactive protein (25 mg/L). He was in home isolation during that time, did not develop any respiratory distress throughout his illness and over next 1 week became afebrile.

Antinuclear antibody, extractable nuclear antigen (ENA) panel, antineutrophil cytoplasmic antibodies, syphilis serology and blood-borne virus screen (HIV, hepatitis B and hepatitis C) were negative. Cerebrospinal fluid analysis at this juncture demonstrated cyto-albuminologic dissociation. Nerve conduction studies revealed prolonged distal motor latencies and reduced compound motor action potential and conduction velocity in motor nerves in the upper and lower limbs. Motor action potentials showed marked dispersion in their morphology and conduction block (Figs. 1 and 2). F-waves were not obtained from the median, ulnar, common peroneal and tibial nerves. Sensory nerve conduction studies showed no amplitude in median and ulnar nerves and were within normal limits for both sural nerves. These results fulfill the electrodiagnostic criteria for acute inflammatory demyelinating polyneuropathy/GBS. The details of the nerve conduction study of the patient have been summarized in Table 1.

Treatment with intravenous immunoglobulin at 2 g/kg dose initiated on day 8 of the illness and continued for 5 days and his weakness improved, 4/5 and 3/5 MRC grade in upper and lower limbs respectively with improvement of bulbar and facial palsy and he was planned for discharge.

On 18th January, his limb power started to worsen again. He developed respiratory distress and was put on ventilator as vital capacity went down to 700 ml. Further intravenous immunoglobulin treatment was commenced. His repeat high resolution computed tomography scan of thorax did not reveal any abnormality. He was gradually weaned off ventilator and he became ambulatory after 35 days. The fluctuation of the motor power according to the Medical Research Council (MRC) Power Grading Scale over 5 weeks has been summarized in Table 2.

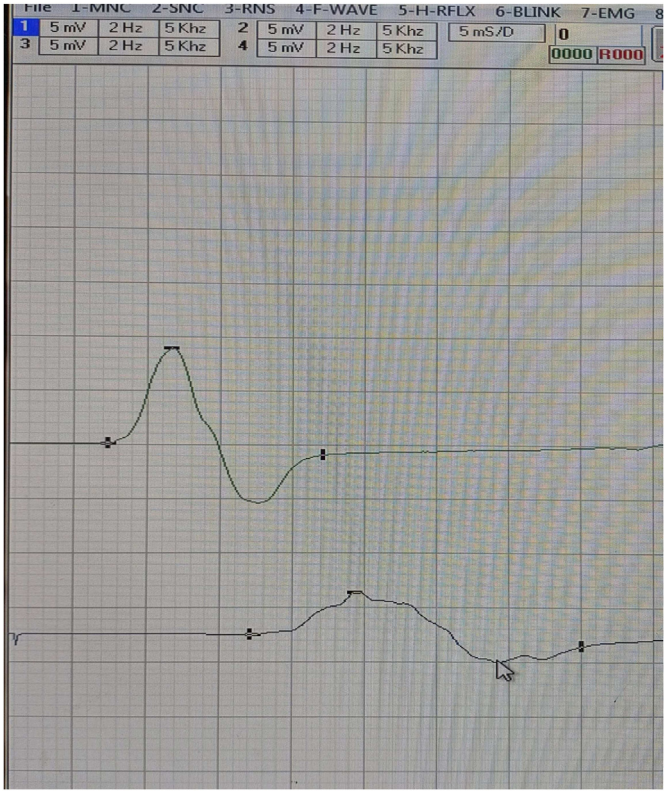

Fig. 1. Motor nerve conduction study of left ulnar nerve showing temporal dispersion.

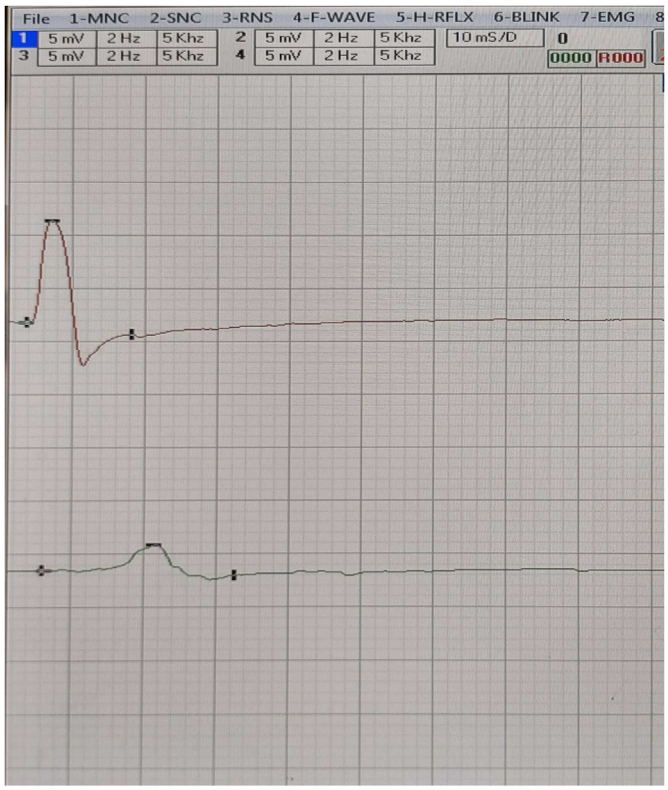

Fig. 2. Motor nerve conduction study of right median nerve showing conduction block.

3. Discussion

In addition to the characteristic respiratory symptoms, reports are emerging of a wide-spectrum of neurological manifestations of COVID-19, which range from milder symptoms such as anosmia to severe complications such as stroke and encephalitis. Guillain-Barre syndrome (GBS) is an immune-mediated neurological disorder, where the peripheral nerves are being affected by the immune system and there is a preceding history of an upper respiratory infection or gastroenteritis in most of the cases [6]. Different mechanisms have been proposed to explain the pathogenesis of GBS following COVID-19. The most accepted mechanism is the formation of antibodies against surface glycoproteins of the pathogen which may damage peripheral nerves due to a similar native protein structures (molecular mimicry) [7]. Other proposed theories include hyperinflammation as a consequence of cytokine storm in patients with COVID-19 [8,9]. Since the outbreak of the pandemic, the incidence of GBS has increased [10]. There have been many reports describing the association between SARS-CoV-2 infection and GBS [11,12].

Treatment related fluctuation (TRF) is defined as at least one grade increment in the GBS disability scale after completion of immunotherapy in the form of immunoglobulin or plasmapheresis followed by at least one grade worsening of the disability scale within the first two months after disease onset [13]. Two important differentials of TRF are recurrent GBS and acute onset chronic

Table 1
Nerve conduction study done on 07.01.2021.

Motor Nerve Conduction Studies:				
Nerve	DML (ms)	CMAP (mv)	Area	CV (m/s)
Right Median	6.56	4.7 (Wrist) 1.7 (Elbow) 1.1 (Erbs)	13.1 (Wrist) 6.2 (Elbow) 4.3 (Erbs)	28.81
Left Median	6.46	2.3 (Wrist) 1.2 (Elbow) 0.7 (Erbs)	7.8 (Wrist) 4.1 (Elbow) 2.7 (Erbs)	30.57
Right Ulnar	5.94	1.1 (Wrist) 1.0 (Elbow) 0.9 (Erbs)	6.5 (Wrist) 5.5 (Elbow) 3.8 (Erbs)	24.01
Left Ulnar	5.42	1.2 (Wrist) 0.3 (Elbow) 0.22 (Erbs)	6.6 (Wrist) 1.4 (Elbow) 1.2 (Erbs)	24.55
Right Tibial	9.06	1.4 (Ankle) 0.3 (Knee)	6.0 (Ankle) 1.2 (Knee)	20.48
Left Tibial	7.50	0.6 (Ankle) 0.5 (Knee)	2.5 (Ankle) 1.3 (Knee)	21.82
Right common peroneal	5.52	1.9 (Ankle) NR (Knee)	7.9 (Ankle) NR (Knee)	Could not be calculated
Left common peroneal	5.94	1.2 (Ankle) NR (Knee)	4.2 (Ankle) NR (Knee)	Could not be calculated
Sensory Nerve Conduction Studies:				
Nerve	DSL (ms)	SNAP (μv)	Area	
Right Median	NR	NR	NR	
Left Median	NR	NR	NR	
Right Ulnar	NR	NR	NR	
Left Ulnar	NR	NR	NR	
Right Sural	2.08	21.8	6.5	
Left Sural	2.29	17.9	7.7	

CMAP – compound motor action potential, CV – conduction velocity, DML – distal motor latency, DSL – distal sensory latency, SNAP – sensory nerve action potential.

Table 2
Fluctuations of motor power over 5 weeks.

	Medical Research Council (MRC) Power Grading Scale			
	Day 7	Day 14	Day 21	Day32
Shoulder abduction	2	4	2	4
Elbow flexion	2	4	2	4
Wrist extension	2	3	2	4
Hip flexion	2	3	2	4
Knee extension	2	3	2	4
Ankle dorsiflexion	2	3	1	4

inflammatory demyelinating polyradiculoneuropathy (A-CIDP), however both possibilities are negated as the disease improved within first 2 weeks, worsened again from 18th day followed by improvement and no further worsening documented over next 8 weeks of onset of initial weakness. A diagnosis of A-CIDP should be thought of when a patient of GBS deteriorates again after 8 weeks from the onset or when deterioration takes place for three times or more. According to a Dutch study, A-CIDP patients rarely develop cranial nerve dysfunction and very rarely need artificial ventilation [13]. TRF in this patient can occur due to prolonged immune response as the disease recurred after the therapeutic effect of immunoglobulin diminished off. The same study also reported almost one out of every ten GBS patients suffer from TRF and the disease almost never show secondary fluctuations beyond 8 weeks.

Many aspects of our patient acted as predictors of TRF. Romano et al. mentioned that comorbidities increase chance of TRF but our patient had none [14]. Significant proximal muscle involvement, cranial nerve palsy, no antecedent diarrhea and absence of anti-GM1 antibodies are important predictors of TRF in GBS, all of them were present in our patient [9]. TRF patients have non-favorable outcome compared to non TRF patients, which is not true in our case [13].

The important mechanisms of action of immunoglobulins are complement inactivation, antibody neutralization, inhibition of cytokines and saturation of Fc receptors on macrophages [15]. Early worsening after treatment followed by improvement on repeat treatment can be due to sustained production of antibodies and rebound immunological response. Many studies contradict this idea as antibody titres do not correlate with clinical worsening [14]. However, clinical scenario of our patient suggests the first explanation.

Worldwide many cases of post COVID-19 GBS are reported, however this is probably the first case reported with TRF and patient was successfully treated with reinstitution of immunoglobulin therapy; came out of ventilation and became ambulatory again.

Contributorship statement

SG and AC contributed to conception, initial drafting of manuscript, critical revision of content and final approval of manuscript. SG, BKR and AP contributed to patient management, conception, critical revision of content and final approval of manuscript. Authors have testified that all persons designated as authors qualify for authorship and have checked the article for plagiarism. All authors had substantial contributions to the conception or design of the work; the acquisition, analysis, or interpretation of the data; drafting the work or revising it critically for important intellectual content, and final approval of the version to be published. All are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Consent

*** An informed written consent was obtained from the patient after full explanation regarding his images being published for academic interest. The patient did not have any objection regarding use of his images and gave due permission to use them.

Declaration of competing interest

We do hereby declare that No author of this paper has a conflict of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included in this manuscript.

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