

Case Report

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Use of intravenous immunoglobulin to successfully treat COVID-19 associated encephalitis

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Abstract

A 58-year-old male patient presented our emergency department with symptoms of fever and cough of one-week duration. CT scan images of the patient's chest were suggestive of "Coronavirus disease 2019 Reporting and Data System" score of 5, CT severity score of 16 out of 25, and an oxygen saturation of 95% with a positive reverse transcription polymerase chain reaction test for SARS-CoV-2. The patient was administered medications Remdesivir and Methylprednisolone as per the guidelines. He developed altered sensorium during his stay in the hospital and was electively intubated. MRI of the Brain (Plain and Contrast) showed bilateral cerebellar, parieto-occipital hyperintensities on T2/fluid-attenuated inversion recovery mode. Cerebrospinal fluid (CSF) showed five cells (100% lymphocytes), normal protein and glucose. The patient was non-responsive to the standard COVID management guidelines. In suspicion of viral encephalitis/acute disseminated encephalomyelitis, intravenous immunoglobulins (IVIG) were administered for five days. A steady improvement was observed in the patient's sensorium over a period of seven days following IVIG therapy, and the patient was able to walk with support following infusion. This case report suggests the possibility of an immune-mediated encephalitis with COVID-19 and the beneficial role of IVIG in treating the same.

Keywords: Altered sensorium, intravenous immunoglobulins, COVID



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INTRODUCTION

The SARS-CoV-2 novel Coronavirus presents a range of symptoms varying from running nose to upper and lower respiratory tract infections of variable severity^[1]. It is believed that neurological complications can result from SARS-CoV-2 infection based on the knowledge of previous coronavirus epidemics of the severe acute respiratory syndrome and the Middle East respiratory syndrome. Literature on previous coronavirus epidemics of the severe acute respiratory syndrome and the Middle East respiratory syndrome suggests a possible role of SARS-CoV-2 in affecting/involving the neurological system. However, from various literature, it is now evident that COVID-19 can involve multiple organ systems with a specific involvement of the central and peripheral nervous system. Neurological presentations associated with COVID-19 include “anosmia”, “ageusia”, “ataxia”, “seizures”, “hemorrhagic necrotizing encephalopathy” and “Guillain- Barré syndrome”^[2-4]. We present a patient of COVID-19 with altered sensorium who improved following administration of intravenous immunoglobulin (IVIG). This supports the evidence of neurotropism of COVID-19. Studies have shown potential use of IVIG in decreasing the respiratory morbidity and mortality in patients with severe COVID-19 infections^[5,6].

CASE REPORT

A 58-year-old male patient with type 2 diabetes mellitus and hypertension visited our facility with fever, cough and generalized weakness of one-week duration. As per the COVID-19 guidelines, we administered antivirals (Remdesivir 200 mg loading dose on the 1st day, followed by a 100 mg maintenance dose from the 2nd to 10th day), Methylprednisolone (40 mg intravenous injection twice daily but as cytokine storm set in, the patient received as pulse dose of 1 gram single dose per day for 5 days), and other supportive treatments for COVID-19. The patient developed altered sensorium in the form of picking of clothes, irritability, and shouting from day 3. The patient was agitated, and confused, without following verbal commands. Clinical examination revealed no focal neurological deficits and all the vital signs were normal. The patient was in altered sensorium with eye-opening response only to a deep painful stimulus. He was not obeying our commands and was seen to be anxiously moving limbs against gravity. The pupils were bilaterally equal in size, reacting to light with a positive doll’s eye sign. Deep tendon reflexes were absent upon elicitation. A bilateral plantar withdrawal response was observed. There was no neck stiffness, and the kernig sign was negative. Oxygen saturation was about 98% on the 5 L oxygen mask. Blood pressure recorded was 140/80 mmHg.

CT scan of the chest showed “Coronavirus disease 2019 Reporting and Data System” Score 5 with CT severity score of 16/25^[7]. Cerebrospinal fluid (CSF) analysis revealed clear fluid with five cells (100% lymphocytes), normal glucose and protein content. Adenosine deaminase, gram stain and acid fast bacillus were all reported as negative. Steroid dose was increased, and the patient was intubated due to systemic sepsis, hypotension along with a decrease in sensorium. Sepsis could be both due to bacteremia (high serum procalcitonin) and severe viremia. The blood cultures were negative due to early administration of empirical antibiotics.

After his hemodynamics were improved, MRI of the Brain (Plain and Contrast) was performed. It showed T2/fluid-attenuated inversion recovery hyperintensities in the bilateral cerebellum, parieto-occipital areas [Figure 1]. Laboratory investigations reported elevated levels of ferritin (828 ng/mL), lactate dehydrogenase (383 U/L), C reactive protein (73.3 mg/L) and D-Dimer (> 1000) [Table 1].

Review of recent literature on COVID-19 pertaining to acute disseminated encephalomyelitis and the lack of any clinical improvement with regular treatment, propelled us to discuss IVIG option with the patient attendees and a written informed consent was obtained. Treatment with IVIG (0.4 g/kg) was initiated (32

Table 1. Laboratory values of the patient during the stay in the hospital

Parameter	Day 1	Day 2	Day 6	Day 8	Day 10	Day 12	Day 15	At discharge
CRP	93.6	50.1	12.8	22	32.3	73.3	12.8	9.5
Serum Ferritin	348		243		444	489		210
D Dimer	355		306		> 1000		1038	650
LDH	540		437		675			601
IL- 6	17.2				19			

vials of 10 gram IVIG were given over a period of 5 days). Due to the possible delay in the decrease of viral load, a decision was made to discontinue Methylprednisolone. He progressively improved over the next two days, and the patient was well oriented, able to communicate, and was obeying the commands. The patient recovered entirely by the end of the third day post initiation of IVIG treatment.

The patient was sent home on tracheostomy with a 2 L oxygen mask. Decannulation was done two weeks later. At the end of the first 1-month post treatment, the patient was able to walk without support. MRI Brain repeated was reported as being completely normal except for the periventricular ischemic changes. Two months after discharge, patient returned to near normal activity which was confirmed through telephonic conversation.

DISCUSSION

This report discusses the clinical improvement of encephalitis associated with COVID-19 following administration of IVIG. Considerable variation exists within the available literature on neurologic manifestations of COVID-19. Moriguchi *et al.*^[8] reported first COVID-19 associated meningoencephalitis, which was treated with Favipiravir. Poyiadji *et al.*^[3] reported COVID-19- associated necrotizing encephalopathy with many hemorrhagic rim enhancing lesions. IVIG was the primary treatment modality advocated in the case report with an undefined outcome. Paniz-Mondolfi *et al.*^[9] reported COVID-19-associated pneumonia with Parkinson's disease. It was stated in this report that the virus was evident in the capillary endothelium and neuronal cell bodies of the brain. Previously, only one-quarter of the patients with COVID-19 had central nervous system (CNS) manifestations, while Li *et al.*^[2] documented that only about 5% of COVID-19 patients had cerebrovascular events.

As per an earlier report, patients may develop CNS symptoms without associated respiratory symptoms^[10]. The interaction with ACE2 receptors, which are abundant in the vascular and neural cells of the CNS, would have allowed the viral particles to enter the CNS^[11].

A recent study reported that viral particles were replicating in the endothelial cells of the frontal lobe^[9]. This could be attributed to the cytokine storm, which could have altered the blood-brain barrier's permeability. The possible transmission of corona virus through the olfactory tract could explain the associated anosmia^[11]. In our patient, elevated cytokine storm and glial cells' activation could have resulted in an inflammatory injury that can contribute to encephalitis. CSF polymerase chain reaction testing was not done due to the lack of availability of the facility at our center, because of which SARS-CoV-2 encephalitis could not be ruled out.

The presence of anti-cytokine autoantibodies like anti-TNF- α , anti-IL-1 and anti-IL-8 in natural human immunoglobulin, could be the reason for anti-inflammatory action of IVIG^[12]. In addition to this, the natural IgG fraction limits the secretion of proinflammatory cytokines^[12]. Dogan *et al.*^[13] reported the

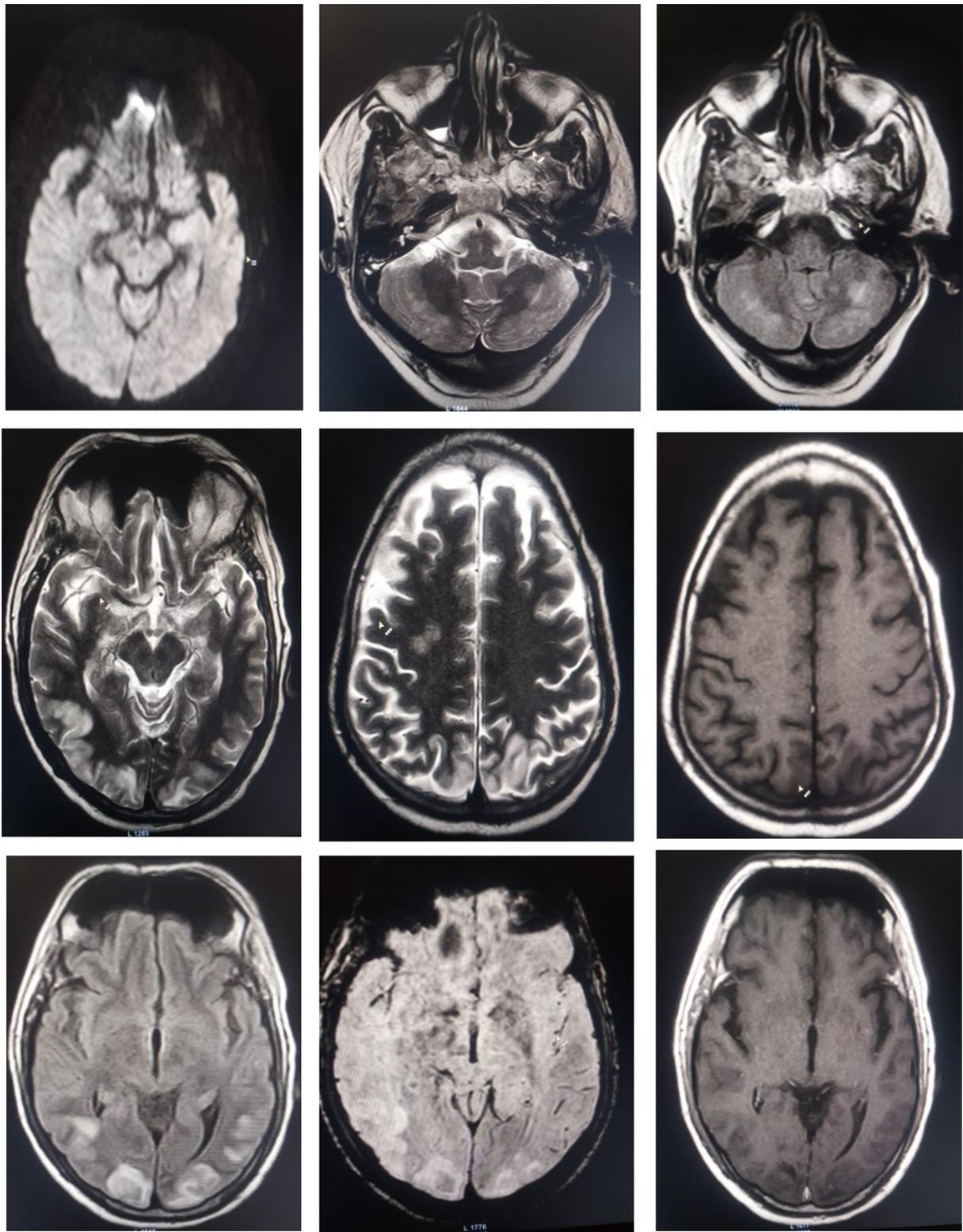


Figure 1. Representative images of the patient showing bilateral cortical/subcortical (temporo-occipital, posterior parietal, right frontoparietal, bilateral cerebellar hemispheres), T2W/FLAIR hyperintensities, with no evidence of diffusion restriction, and no areas of blooming in gradient recalled echo. FLAIR: Fluid-attenuated inversion recovery.

potential benefit of plasmapheresis treatment of COVID-19-related autoimmune meningoencephalitis and highlighted the potential role of autoimmunity.

A similar success of IVIG in the treatment of COVID-19 encephalitis was reported previously. However, guidelines on the usage of IVIG in the management of COVID-19 are lacking. IVIG neutralizes activated complement, modulates B and T cells, and inhibits innate immune cells and the release of cytokines^[14]. Recovery from encephalitis following administration of IVIG could be attributed to the multiple effects it has on the inflammatory mediators. Many randomized controlled trials on evaluation of efficacy of IVIG in the management of severe COVID-19 currently are in process and the results of these trials are awaited.

DECLARATIONS

Authors' contributions

Conceptualization, review of literature, writing, original draft, reviewing and editing: Chenna V
Writing, original draft, reviewing and editing: Jenjeti C
Investigation, writing, original draft, reviewing and editing: Devarapu K

Availability of data and materials

Data are available with corresponding author upon reasonable request.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Informed consent from participant was obtained.

Consent for publication

Consent for publication was obtained from the participant.

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