Case Report

SARS-CoV-2 Infection-Related Acute Parkinsonism and Encephalitis: Is There a Clinicoradiological Correlation?

Abstract

COVID-19 infection can cause neurological manifestations as early and late complications (chronic COVID syndrome). These include headache, dizziness, confusion, acute cerebrovascular problems, ataxia, and seizures. COVID-19-related encephalopathy, encephalitis, and parkinsonism have been reported earlier; however, the possible links and pathophysiological mechanisms are unclear. In this report, we report a series of patients (n = 5) presenting with acute severe neurological syndromes such as parkinsonism, focal status epilepticus, or acute ataxia as a part of long-hauler COVID-19 infection. We categorized the clinico-radiological and electroencephalographic features in our cases to understand the clinical patterns in SARS-CoV-2 related brain cortex involvement. This might help in future for better clinical categorization for these COVID-19-related neurological manifestations.

Keywords: *COVID-19, encephalopathy, parkinsonism*

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Introduction

COVID-19 infection presents with various symptoms, including nonproductive cough, fever, myalgia, fatigue, dyspnea, diarrhea, and nausea/vomiting, while some patients are known to be asymptomatic.[1] COVID-19 infection can cause neurological manifestations as an early presentation such as confusion, anosmia, and ageusia.[2,3] A systemic review of COVID-19-related publications demonstrated a high likelihood of neurological manifestations in severe COVID-19 infection.[4] Mao *et al*. found central nervous system (CNS) manifestations in 25% of cases mainly presenting as headache (13%), dizziness (17%), impaired consciousness (8%), acute cerebrovascular problems (3%), ataxia (0.5%), and seizures (0.5%).

COVID-19-related encephalopathy and acute parkinsonism have been reported earlier.[5] However, the possible links and pathophysiological mechanisms are unclear. Proposed hypotheses include neurotropism of COVID-19 virus, basal ganglia lesions in a setting of COVID-19-induced thromboembolic encephalopathy, angiotensin-converting enzyme 2 (AEC2) receptor expression, SARS-CoV-2 proteins-related human protein dysfunction causing protein misfolding, and aggregation. COVID-19 pandemic could affect patients suffering from Parkinson's disease with worsening of both motor and nonmotor symptoms.[6] Long-hauler COVID-19 or chronic COVID syndrome can cause various CNS presentations which can be more disabling.[7]

In this report, we detailed a series of patients (n = 5) presenting with acute severe neurological syndromes such as parkinsonism, focal status epilepticus, or acute ataxia as a part of long-hauler COVID-19 infection.

Case Reports

All five patients presented as a cluster within few days of each other in June 2021 following COVID-19 infection as part of the second wave, which affected the city from where the patients belong. Two patients had acute-onset akinetic-bradykinesia syndrome with T2/FLAIR caudate hyperintensity on magnetic resonance imaging (MRI), two others presented with encephalopathy, focal status epilepticus, and periodic lateralized epileptic discharges (PLEDs)

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in electroencephalographic (EEG), and one patient had acute-onset cerebellar ataxia. Raised cerebrospinal fluid (CSF) protein with no or minimal cellular response was found in all the patients except one. The patients and their symptoms have been described here in group-wise categories.

Group 1

Acute-onset akinesia bradykinesia syndrome (Cases 1 and 2)

Case 1

A 71-year-old male, diabetic, systemic hypertensive, presented with dysarthria, left-sided slowing of movements, and confusional state. On examination, he had grade 3/4 rigidity in all four limbs and also neck rigidity of 3/4. The blink rate was reduced with hypomimia. He developed stimulus-sensitive myoclonus, which was more prominent over the right upper limb, especially on arousal. The myoclonus showed habituation on repeated stimulus. Computed tomography (CT) chest COVID severity score was 12/25. MRI brain showed asymmetrical FLAIR hyperintensity with mild diffusion-weighted images (DWIs) restriction in bilateral caudate and lentiform nucleus (right side more affected than left) along with left medial thalamus [Figure 1a and b]. CSF analysis showed proteins 111 mg% and 1 neutrophil without any fungal elements. He received a course of intravenous (IV) immunoglobulin 2 g/kg over 5 days. Over the next several weeks, the patient remained encephalopathic with persistent parkinsonism without any significant clinical improvement.

Case 2

A sixtynine year old male, who is a known case of ischemic heart disease, diabetes and hypertension developed sudden onset of headache and slowness of all activities of daily

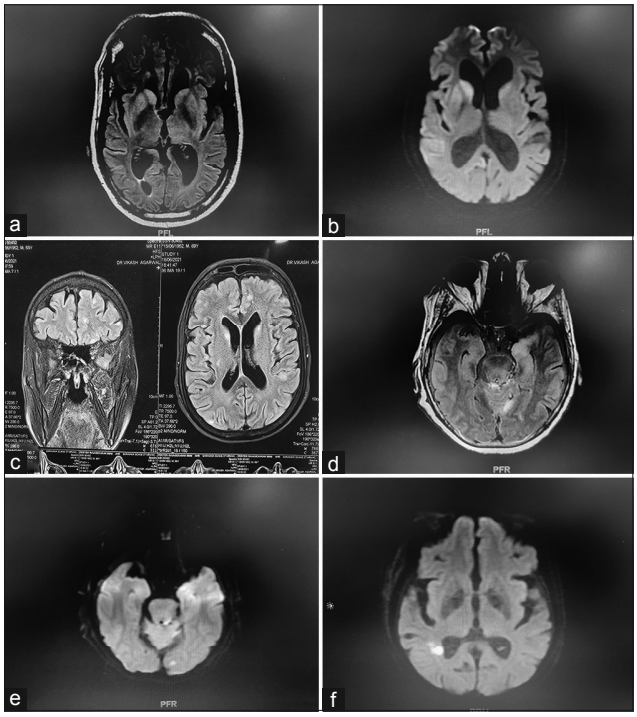

Figure 1: MRI Brain Changes showing specific areas of involvement

Table 1: Clinical, demographic and radiological data with outcomes

Case number	Age	Sex	Syndrome	MRI-DWI changes	CSF proteins (mg %)	CSF cell count	EEG	Comorbidities	Treatment	Outcome
1	71	Male	Parkinsonism with myoclonus	Bilateral caudate, lentiform neucleus	111	1	Diffuse theta-delta	Diabetes, hypertension	Immunoglobulins	No change bed bound
2	69	Male	Parkinsonism	Bilateral caudate, mesial frontal, posterior operculum	61	0	Not done	Diabetes, hypertension, coronary artery disease	Levodopa 400 mg per day	No further deterioration without improvment
3	86	Female	Encephalitis with status epilepticus	Bilateral insula, mesial frontal, hippocampus left >right	240	91	PLEDS left temporal region	Diabetes, coronary artery disease	IV methylprednisolone with antiseizure drugs	Died
4	65	Male	Right focal status epileptics with encephalopathy	Left paramedian frontal and left hippocampus	25	6	PLEDS left temporal region	Diabetes, hypertension, stroke	Antiseizure drugs	Died
5	52	Male	Acute ataxia	Normal	81	1	Not done	Diabetes	Symptomatic treatment	Improved clincally

DWI: Diffusion-weighted imaging, MRI: Magnetic resonance imaging, CSF: Cerebrospinal fluid, EEG: Electroencephalogram, IV: Intravenous, PLEDS: Periodic lateralized epileptiform discharges

living with difficulty in walking. His examination showed bradykinesia on finger tapping, body bradykinesia along with finger–nose test impairment bilaterally [Video 1]. MRI brain showed T2/FLAIR hyperintensity in bilateral caudate and mesial frontal and opercular regions with mild DWI restriction [Figure 1c]. CSF analysis showed proteins 61 mg% with acellularity. He was treated with levodopa 400 mg per day with mild improvement in bradykinesia. However, his overall clinical status remained static. His positron emission tomography scan was done to rule out a paraneoplastic association and showed no evidence of metabolic active tissue in the viscera.

Group 2

Acute encephalitis with focal status epilepticus (Cases 3 and 4)

Case 3

An 86-year-old female, diabetic, hypertensive, and having ischemic heart disease, presented with a fall and comatose state 1 month post-COVID-19 infection. After 3 days of admission, she developed focal right hemiclonic status epilepticus, which needed intubation and IV anesthetic agents. MRI brain showed diffusion restriction in the left insular cortex and mild on the right insular cortex, mesial frontal lobe, and hippocampus along with perimesencephalic subarachonid hemorrhage [Figure 1d and e]. CT angiography of the brain did not reveal any vascular malformation. CSF analysis showed proteins 240 mg%, 91 cells (mononuclear/PMN) with negative HSV DNA polymerase chain reaction (PCR). Both CSF and serum autoimmune encephalitis panels were negative. EEG showed PLEDs over the temporal region [Figure 2a and b]. She was treated with acyclovir and IV methylprednisolone pulse (1 g/day for 5 days). She continued to worsen clinically in the intensive care unit and expired due to secondary sepsis and cardiac arrest.

Case 4

A 65-year-old male, history of recurrent stroke (temporal lobe and right thalamic hemorrhage), hypertension, postdecompression, post-COVID-19 infection status, presented with right-sided hemiclonic seizures and status epilepticus. MRI brain showed diffusion restrictions in the left paramedian frontal and left mesial temporal (hippocampal head and body) [Figure 1f]. CSF analysis showed 25-mg proteins with six neutrophils, HSV DNA PCR test was negative. EEG showed PLEDs over the temporal region [Figure 2c and d]. His C-reactive protein was 204. He continued to be encephalopathic and 4 days after admission, he had sudden bradycardia and desaturation and could not be revived.

Group 3

Acute cerebellar ataxia with headache (Case 5)

Case 5

A fifity two year old diabetic presented with history of acute onset difficulty in walking since one month after a mild COVID-19 infection(which was treated at home based covid care). CT chest showed a CT severity score of 5/25. MRI brain was normal, Vitamin B_{12} >2000

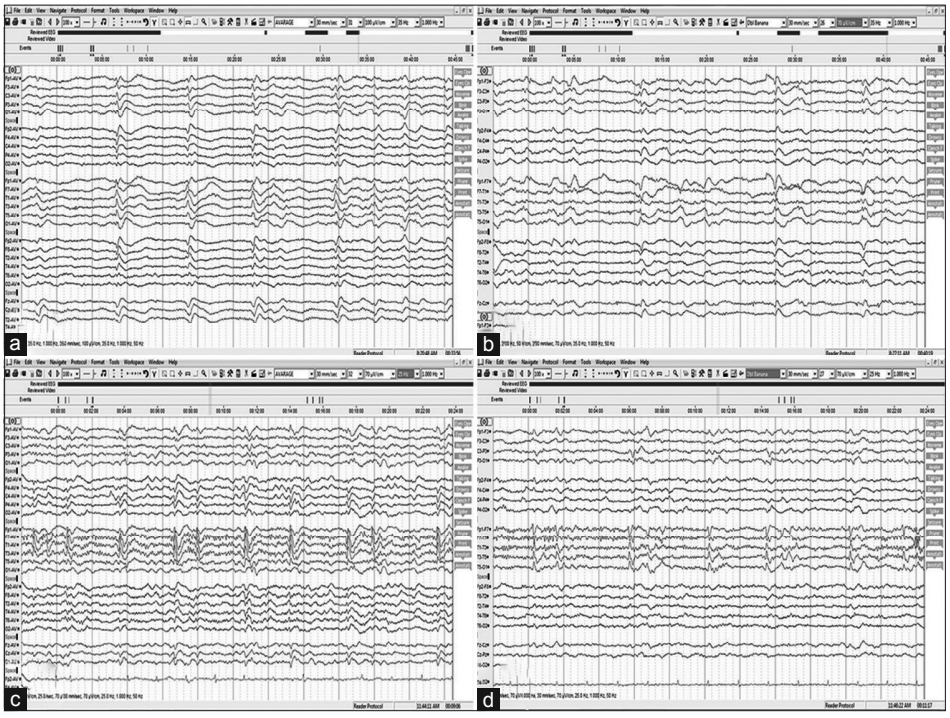

Figure 2: EEG epochs showing PLEDs

units. CSF analysis showed CSF protein was 81 mg% with 1 cell (lympho or PMN). CSF Gene XPERT MTB, culture, and fungal smear were negative. He was treated symptomatically and remains stable on follow-up.

Discussion

We described three groups of acute CNS manifestations of long-hauler COVID-19. All cases had a mild COVID infection 3–6 weeks before the neurological presentation along with multiple comorbidities, namely diabetes, hypertension or prior stroke, and showed MRI changes (except one case), with raised CSF proteins. We correlated the MRI changes with clinical presentation and associated findings.

The cases described in group 1 presented with post-COVID-19 infection acute parkinsonism and myoclonus with bilateral caudate hyperintensity and raised CSF protein. There was no history of prior parkinsonism in these cases or any suggestion of prodromal PD. A previous case described in the literature with akinetic-rigid syndrome, myoclonus, and DaT-single-photon emission computed tomography confirmed bilateral decrease in presynaptic dopamine uptake asymmetrically involving both putamina has drawn attention to post-COVID-19 parkinsonism with much skepticism.[8] Our first patient had similar myoclonus as reported in the previous case; however, the patient did not show any clinical improvement. It has been suggested by Lang *et al*. that the stress of SARS-CoV-2 infection could have unmasked a prodromal Parkinsons's disease and the acute parkinsonism could represent a preexisting nigrostriatal dysfunction.[9] We could not do the nuclear imaging studies in our cases which could have highlighted this viewpoint.

On analyzing the patterns in the MRI findings in correlation with the clinical syndrome, group 1 with acute parkinsonism showed bilateral caudate involvement on initial presentation and only later involvement of the extra basal ganglia regions (like mesial frontal in case number 2). However, group 2 showed a typical insulomesial frontal-hippocampal involvement in both cases. This finding may suggest a likelihood of limbic system involvement when the clinical presentation is encephalitis with focal status epilepticus. However, this observation needs more data with a larger sample size. A case of acute necrotizing encephalopathy has been described in relation to COVID-19 infection.[10] Similar case reports of acute disseminated encephalitis (acute disseminated encephalomyelitis) or ataxia have been reported.[11,12] The CNS injury is presumed to be due to a cytokine storm-mediated tissue damage; however, the degree of the severity of SARS-CoV-2 in our cases was mild. It can be postulated that the presence of comorbidities such as diabetes (which was present in all cases) or hypertension has made the CNS more vulnerable for an immune-mediated or a direct tissue injury subsequently with breach of the blood–brain barrier integrity. Immunotherapy has not altered the clinical course significantly in our cases. This may suggest that the pathophysiological mechanisms of SARS-CoV-2 brain injury are complex and needs further research. There is a need to develop standard treatment protocols in SARS-CoV-2-related CNS manifestations including the degree of intervention by immunotherapy.

Conclusion

Acute severe neurological syndromes such as parkinsonism, focal status epilepticus, or acute ataxia can be a part of long-hauler COVID-19 infection. These presentations have specific MRI findings in brain regions (such as the limbic system, mesial frontal, and basal ganglia) and show EEG changes with raised CSF proteins with variable clinical outcomes. There is a need for further studies in these specific subgroups which will help in better understanding of the role of future treatments including immunotherapy in long-hauler COVID-19 infection.

Patient informed consent

Patient informed consent was obtained.

Ethics committee approval

There is no need for ethics committee approval.

Conflict of interest

There is no conflict of interest to declare.

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Author contribution subject and rate

- Vikash Agarwal (30%): Clinical concept and manuscript write up.
- Dolly Mushahary (10%): Technical support.
- Praveen Chander (10%): Clinical concept.
- Venkatraman.K (10%): Article review.
- Lakshminarayanan.K (10%): Article review.
- Sathish Kumar .V (10%): Article Review.
- S.Dinesh Nayak (20%): Clinical Concept.

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