Neurological Manifestations of COVID-19: A Series of Seven Cases

Kavya Goel¹, Ajay Kumar², Sahil Diwan³, Santvana Kohli⁴, Harish C Sachdeva⁵, Usha Ganapathy⁶, Saurav M Mustaf⁷, Pravin Kumar⁸

Abstract
Identification of neurological manifestations associated with SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) in patients with no or mild pulmonary infection proves to be a challenge. The incidence of neurological associations of COVID-19 may be small as compared with respiratory disease; however, in the present scenario with an increasing number of cases each day, the overall incidence of patients with neurological manifestations and their health-related socioeconomic impact might be large. Hence it is important to report such cases so that healthcare providers and concerned authorities are aware of and may prepare for the growing burden. The literature on primary neurological manifestations of COVID-19 is limited, and hence our case series is relevant in the current scenario. The most commonly reported neurological complications are cerebrovascular accidents, encephalopathy, encephalitis, meningitis, and Guillain-Barré syndrome (GBS). We present a series of seven cases with various neurological presentations and possible complications from this novel virus infection.

Keywords: Cerebrovascular accident, COVID-19, Encephalitis, Guillain-Barré syndrome, Neurological, SARS-CoV-2.

Introduction
The coronavirus disease (COVID-19) outbreak due to SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) first originated from Wuhan city, China in December 2019 and has rapidly spread as a global health pandemic.¹² This infection has been demonstrated to produce a mild flu-like illness encompassing fever, cough, breathlessness, and other mild symptoms, such as headache, lethargy, and generalized weakness in a majority of patients.³ Originally considered a primarily respiratory disease,⁴ new facts have emerged regarding extra-pulmonary complications of the COVID-19 illness. Neurological manifestations are common in the advanced stages of the disease.⁵ Although the exact mechanism by which SARS-CoV-2 penetrates the central and peripheral nervous system (CNS and PNS) is not yet known, the two most likely theories are (1) hematogenous spread of SARS-CoV-2 from systemic circulation to the cerebral circulation and (2) dissemination through the cribriform plate and olfactory bulb.⁶ Angiotensin-converting enzyme 2 (ACE 2) receptors that are present on endothelial cells of the cerebral vasculature act as the cell entry points of the virus.⁷ It may also induce certain microvascular/macrovacular changes leading to nervous system involvement.⁸ We have compiled a case series of confirmed COVID-19 patients who presented with or developed primary neurological manifestations, to better understand the neurological aspect of this disease. The neurological manifestations of COVID-19 are described in Figure 1.

Case Description
A total of seven RT-PCR (real-time reverse transcriptase-polymerase chain reaction) confirmed COVID-19 patients presented to our institute primarily with neurological manifestations (Tables 1 and 2). Two of these cases presented with altered sensorium and a recent history of fever, whereas another two presented with paraparesis. One case presented with hemiplegia and two cases presented with loss of consciousness. Out of the two unconscious patients, one had a history of generalized weakness and the other had dyspnea one day prior to admission. Apart from dyspnea in this patient, no respiratory symptoms were noted in any of the other cases. None of these patients had a history of travel to a foreign country or contact with a confirmed case of COVID-19. Out of all the seven patients, only two had chest X-ray changes, i.e., homogenous opacities and partial one-sided lung collapse in one and fluffy infiltrates in the other. Five of the patients tested positive in the initial tests while two (case numbers 6 and 7) were initially negative and tested positive.
Table 1: Clinical findings of cases

| No. | Age/sex | Clinical presentation | Classical COVID-19 symptoms | Comorbidities | Final diagnosis | Treatment | Outcome |
|-----|---------|-----------------------|------------------------------|---------------|----------------|-----------|---------|
| 1   | 55 years/M | Left hemiparesis × 1 day | None | Hypertension T2DM | COVID-19 with CVA | Antibiotics, Phenytoin, mannitol, Antithrombosis, Steroids | Expired |
| 2   | 56 years/M | Unconsciousness × 1 day | None | T2DM | COVID-19 with CVA | Antibiotics, Phenytoin, mannitol, Antithrombosis, Steroids | Expired |
| 3   | 59 years/F | Unconsciousness × 1 day | Dyspnea × 1 day | T2DM | COVID-19 with influenza-like illness with CVA | Antibiotics, Phenytoin, mannitol, Antithrombosis, Steroids | Expired |
| 4   | 37 years/F | Altered sensorium × 1 day | Fever × 6 days, Seizure × 1 episode | None | COVID-19 associated CNS infection | Antibiotics, Thromboprophylaxis, Steroids, Levetiracetam | Expired |
| 5   | 19 years/F | Altered sensorium × 10 days | Fever × 10 days | None | COVID-19 associated CNS infection | Antibiotics, Levetiracetam, Thromboprophylaxis, Steroids | Critically ill |
| 6   | 55 years/F | Paraparesis × 6 days, Low backache × 6 days | None | Hypertension | COVID-19 with GBS, complicated by PRES | IVIG, Antibiotics, Thromboprophylaxis, Steroids | Expired |
| 7   | 17 years/M | Progressive ascending quadriparesis × 2 days | Fever at presentation | None | COVID-19 with GBS with septic shock | Antibiotics, IVIG, Thromboprophylaxis, Steroids | Expired |

CVA, cerebrovascular accident; T2DM, type 2 diabetes mellitus; GBS, Guillain-Barré syndrome; IVIG, intravenous immunoglobulins
Table 2: Laboratory and radiological findings of cases

| Case no. | Age/sex | Neuroradiology | CSF study/ neurophysiology | Chest X-ray | RT-PCR | Relevant blood investigations |
|----------|---------|----------------|---------------------------|-------------|--------|-------------------------------|
| 1        | 55 years/M | NCCT: Right MCA territory subacute infarct with no hemorrhagic transformation | Not performed | Bilateral homogeneous opacities with partial right lung collapse | Positive Day 2 | Leukocytosis |
|          |         |                |                           |             |        | Neutrophilia, Lymphopenia, Hyponatremia |
| 2        | 56 years/M | MRI: Left MCA (massive) and Right ACA infarct | Not performed | Unremarkable | Positive Day 2 | Lymphopenia |
|          |         |                |                           |             |        | Neutrophilia, Raised CRP, Deranged liver function, D-dimer: 3250 ng/mL |
| 3        | 59 years/F | NCCT: Multiple subacute cortical infarcts | Not performed | Bilateral infiltrates | Positive Day 2 | Anemia, Thrombocytopenia |
|          |         |                |                           |             |        | D-dimer: 4018 ng/mL, Serum ferritin: 226 ng/mL |
| 4        | 37 years/F | NCCT: Normal | CSF: Normal protein and cell count | Unremarkable | Positive Day 6 | Leukocytosis, Neutrophilia, Lymphopenia |
|          |         |                |                           |             |        | D-dimer: 2994 ng/mL |
| 5        | 19 years/F | NCCT: Diffuse cerebral edema | CSF: Raised proteins and cell count | Unremarkable | Positive Day 10 | Leukocytosis, Lymphopenia, Neutrophilia, Hyponatremia |
|          |         |                |                           |             |        | D-dimer: 2348 ng/mL |
| 6        | 55 years/F | MRI: features of PRES | CSF: Raised proteins, normal cell count NCV: Axonal and demyelinating sensorimotor polyneuropathy | Unremarkable | Positive Day 10 and 21 | Anemia |
|          |         |                |                           |             |        | Lymphopenia, Thrombocytopenia, Hyponatremia |
|          |         |                |                           |             |        | D-dimer: 1804 ng/mL, Serum procalcitonin: 2.02 |
| 7        | 17 years/M | MRI brain: Normal | MRI spine: Normal | CSF: Raised proteins, normal cell count NCV: demyelinating sensorimotor polyneuropathy | Unremarkable | Negative Day 1 and 2, Negative Day 3, Negative Day 8 | Mild leukocytosis |
|          |         |                |                           |             |        | Lymphopenia, Neutrophilia, Hyponatremia |
|          |         |                |                           |             |        | D-dimer: 890 ng/mL |

NCCT, non-contrast computed tomography; MCA, middle cerebral artery; ACA, anterior cerebral artery; MRI, magnetic resonance imaging; CRP, C-reactive protein; NCV, nerve conduction velocity; CSF, cerebrospinal fluid

Discussion

This case series was observed in a single center, catering to COVID as well as non-COVID patients, from June to August 2020. At the onset of the pandemic, the main focus was on patients presenting with respiratory symptoms. So a higher threshold of suspicion of COVID-19 disease was maintained for patients presenting with clear-cut neurological manifestations, without any pulmonary involvement. However, with an increasing number of cases, the focus was shifted towards the possibility of neurological association of COVID-19, and an attempt was made to gather more data in this direction.

It may be remarkable to note that all patients in this case series were less than 60 years of age (mean age 40.1 years), with two of these patients less than 20 years. The patients had a relatively even sex distribution in this case series with three male and four female patients. Four out of seven patients had comorbidities usually associated with a worse outcome, i.e., hypertension and type 2 diabetes mellitus. Table 3 shows the consolidated data from various studies that have contributed to a better understanding of our cases.

USA and UK have also reported multiple cases of COVID patients presenting with CVA, mostly older patients with the majority being ischemic strokes. Oxley et al. reported five such cases which notably consisted of patients younger than 50 years. In our series, all three cases were under 60 years with known risk factors for CVA and diagnosed as ischemic stroke. The first patient in our case series expired within a day of admission and was later found to be COVID positive. This gave us a reason to search for literature on the neurological presentation of COVID infection. Going forward, we have found more cases and evidence of hypercoagulability in COVID patients presenting with stroke. The first patient did not survive long enough to allow D-dimer testing, but the second and third patients showed high values. Beyrouti et al. reported six patients with large cerebral infarcts with elevated D-dimer levels indicating a hypercoagulable state. The third case in our series is different from the first two, as he had associated shortness of breath on presentation, which led to a
quicker diagnosis of COVID-19. This patient had NCCT head changes suggestive of embolism or vasculitis associated infarcts which may be considered a complication rather than a manifestation of COVID-19.

The next two cases in our series had altered sensorium at presentation and encephalitis/meningitis was suspected based on a history of fever with neurological signs. When tested, they were found to be COVID-19 positive. Moriguchi et al.\textsuperscript{13} reported the first confirmed case of COVID-19 associated viral encephalitis from Japan. A 24-year-old man presented with fever followed by seizures and unconsciousness. He had neck stiffness and underwent a CT scan which was normal. There was patchy pneumonia on the CT chest. PCR assay from nasopharyngeal swab was negative but the CSF sample was positive for COVID-19. This presentation may justify the inclusion of the fourth and fifth cases, which had similar initial CNS findings but without any pulmonary involvement. Although it is difficult to diagnose COVID-19 associated CNS infection in such cases, it becomes prudent to keep a high index of suspicion, especially in the middle of a pandemic and absence of any other definitive cause.

There have been several cases reported from China and Italy of GBS associated with COVID-19. The first such case was reported from China of a 61-year-old lady with a history of return from Wuhan but no respiratory symptoms.\textsuperscript{14} She was however infective as two of her relatives caring for her during her hospital stay were found positive for SARS-CoV-2. She later developed fever and cough during her hospital stay. In contrast, the 55-year-old lady, the sixth case in our series, had no history of travel or contact with a confirmed case, or the classical presentation of a febrile illness. She presented to us with paraparesis only and her hospital stay was complicated by PRES. Whether this neurological involvement was causal or coincidental is difficult to say as the patient presented late to the hospital, having gone to a secondary health center previously and there was a further delay in COVID testing due to the complete absence of usual respiratory symptoms. The last case of a 17-year-old boy presented with a relatively faster progression of the disease and developed high-grade fever during his illness, possibly due to sepsis with no response to high-grade antibiotics.

**Conclusion**

As initially perceived, the SARS-CoV-2 virus is not only responsible for respiratory and cardiovascular diseases but also neurological morbidity. This may be secondary to micro/macrovacular changes in the CNS or the PNS or due to a direct invasion of the cerebral endothelium/parenchyma by the virus hematogenously. To make a clear distinction, further studies need to be undertaken with the help of multidisciplinary teams of critical care, neurology, internal medicine, pathology, microbiology, and radiology departments. A low threshold of COVID-19 testing needs to be kept in cases with neurological presentations, particularly in areas with higher COVID-19 infection rates to improve quicker detection, provide early
treatment, and isolate such cases to prevent further transmission in highly susceptible critical patients.

**Justification of Study**

Our case series hopes to highlight the fact that extrapulmonary manifestations of COVID-19 infection are likely to be missed. Hence, a low threshold of testing must be kept in such cases to improve quicker detection, isolation of cases to prevent further transmission, and provision of early treatment.

**Orcid**

Kavya Goel  https://orcid.org/0000-0002-5427-5347
Ajay Kumar  https://orcid.org/0000-0001-5643-7955
Sahil Diwan  https://orcid.org/0000-0002-6489-802X
Santvana Kohli  https://orcid.org/0000-0003-1410-6933
Harish C Sachdeva  https://orcid.org/0000-0003-4476-0506
Usha Ganapathy  https://orcid.org/0000-0001-5472-5769
Saurav M Mustafi  https://orcid.org/0000-0003-0893-2155
Pravin Kumar  https://orcid.org/0000-0002-4827-6650

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