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Case report

# A case of possible atypical demyelinating event of the central nervous system following COVID-19

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ABSTRACT

After the novel coronavirus disease outbreak first began in Wuhan, China, in December 2019, the viral epidemic has quickly spread across the world, and it is now a major public health concern. Here we present a 21-year-old male with encephalomyelitis following intermittent vomiting and malaise for 4 days. He reported upper respiratory signs and symptoms 2 weeks before this presentation. Two cerebrospinal fluid (CSF) analyses were notable for mononuclear pleocytosis, elevated protein (more than 100 mg/dl), and hypoglycorrhachia. Brain Magnetic Resonance Imaging (MRI) showed bilateral posterior internal capsule lesions extending to the ventral portion of the pons and a marbled splenium hyperintensity pattern. Cervical and thoracic MRI showed longitudinally extensive transverse myelitis (LETM), none of which were enhanced with gadolinium. Both the AQP4 and MOG antibodies were negative. Spiral chest computed tomography (CT) scan confirmed to COVID-19 as did the high IgG level against coronavirus, but the oropharyngeal swabs were negative. Neurological manifestations of COVID-19 have not been adequately studied. Some COVID-19 patients, especially those suffering from a severe disease, are highly likely to have central nervous system (CNS) manifestations. Our case is a post-COVID-19 demyelinating event in the CNS.

## 1. Introduction

Coronavirus neuro-invasive characteristics have been identified in humans. It has been shown that severe infection with SARS-CoV-2 is associated with neurological manifestations such as headache, epilepsy, cerebrovascular events, and encephalitis (Bohmwald et al., 2018; Asadi-Pooya et al. 2020). Coronavirus probably enters the CNS through the olfactory bulb, which could cause inflammation and subsequent axonal damage or demyelination (Desforges et al., 2020). We present a young man with COVID-19 and acute encephalomyelitis with newly diagnosed possible demyelinating lesions in the CNS.

## 2. Case report

A previously healthy 21-year-old male with a Bachelor of Science was referred to the emergency room of our hospital on March 20th, 2020. His-family reported that he had a fever with chills, nonproductive cough, and a sore throat 2 weeks before admission, but no hyposmia or hypogeusia. All symptoms decreased in severity within 10 days, after which he developed significant loss of appetite, recurrent vomiting with food intolerance, and generalized malaise. Following 3 days of repeated vomiting, he experienced weakness and paresthesia of the lower limbs, which continued throughout the day. The next day, family members found that he had urinary retention, increased paraparesis severity and weakness in the upper limbs; he also became drowsy. The patient had no headache, vertigo, diplopia, dysphagia, neck pain, or blurred vision.

On examination, his blood pressure was 110/85 mmHg, and his pulse was 98 beats per minute. His-temperature was 37.9 °C, his respiratory rate 20 per minute, and his oxygen saturation 94% while he was breathing ambient air. The patient was lethargic but obeyed simple verbal commands, and there were no evidences of nuchal rigidity, Kernig's or Brudzinski's signs. His-pupils were equally reactive to light. The muscular strength was 4+/5 in the upper limbs and 2/5 in the lower limbs. He had normal deep tendon reflexes in all four limbs and

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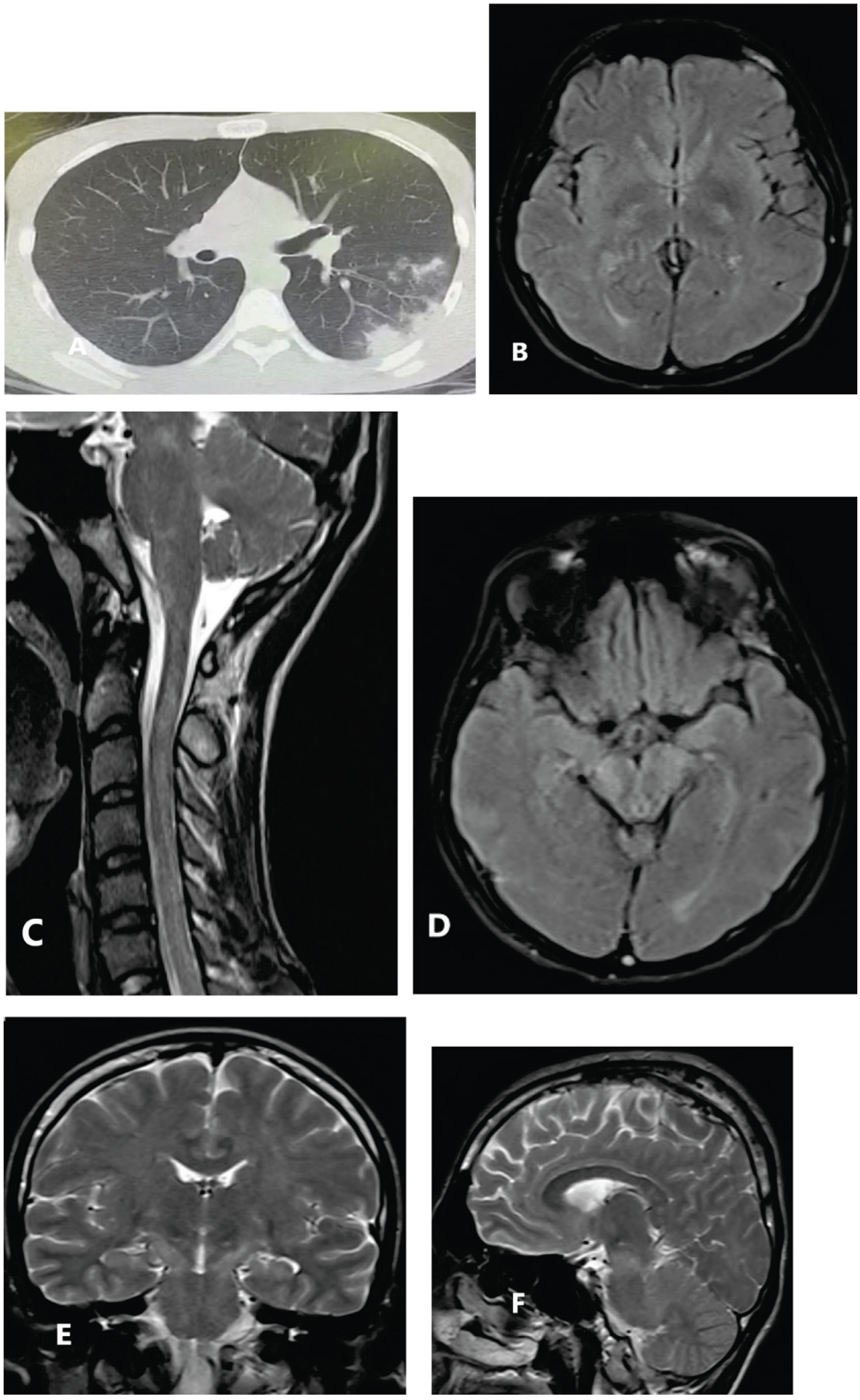


**Fig. 1.** (A) Spiral chest CT scan without contrast shows left lung ground-glass opacity. (B) Axial FLAIR sequence of brain MRI demonstrates bilateral internal capsule hyperintensity. (C) Axial T2-weighted image of the cervical spine shows longitudinally extensive transverse myelitis and hyperintensity at dorsal of upper pons. (D) Axial FLAIR sequence shows bilateral cerebral peduncle hyperintense lesions. (E) Coronal T2 weighted image demonstrates bilateral corticospinal tract involvement. (F) Sagittal T2 weighted image reveals corpus callosum hyperintensity signal abnormalities.

Babinski's sign was absent. The position and light touch sensation were impaired in both lower limbs; additionally, he had a T8 sensory level. The abdominal cutaneous reflex was absent in all directions. A spiral chest CT scan revealed the left lung peripheral ground-glass opacities (Fig. 1A). The patient was transferred to the specialized intensive care unit designated for patients with SARS-CoV-2, and a nasopharyngeal swab was obtained for detection of the COVID-19 genome by a real-time polymerase chain reaction. Initial laboratory tests, as well as

erythrocyte sedimentation rate and c-reactive protein, were normal. Screening tests for human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2) antibodies and also tests for hepatitis B virus (HBV) antigen and antibodies and hepatitis C virus (HCV) antibody were negative. With clinical suspicion of acute disseminated encephalomyelitis (ADEM) along with suspected COVID-19, 250 mL plasma exchange was started daily for 5 days. MRI of the cervical and thoracic spine revealed LETM with an intramedullary lesion extending > 3 segments in the spinal cord. Sagittal T2-weighted fluid-attenuated inversion recovery (FLAIR) brain MRI showed bilateral long corticospinal tract lesions in internal capsules extending to the cerebral peduncles and pons. Moreover, there was a heterogeneous, marbled pattern hyperintensity in the splenium of the corpus callosum (Fig. 1B,C,D, and E) without diffusion-weighted restrictions nor contrast enhancements. The spinal tap showed cloudy and pale-yellow CSF. In the analysis, there were 150 total nucleated cells per microliter, of which 60% were lymphocytes. The CSF protein level was 281 mg/dL, and the glucose level was 34 mg/dL, with a serum glucose level of 110 mg/dL concomitantly. No organism was detected in Gram's staining. Empirical treatment with intravenous vancomycin, meropenem, and acyclovir was initiated. A Polymerase Chain Reaction (PCR) panel of CSF for all viruses, including Herpes Simplex 1 and 2 (HSV1 and HSV2), Hemophilus influenza, etc. and all bacterial/fungal agents including Mycobacterium tuberculosis complex, Listeria monocytogenes, etc. were negative. Serological testing for the antinuclear antibody, antiphospholipid antibodies, human leukocyte antigen (HLA) B5, B51, and Angiotensin-converting enzyme (ACE) were unremarkable. The CSF and serum autoimmune panel investigations, such as Anti-N-methyl-D-aspartate (NMDA) receptor, were negative as were blood cultures for organisms. Two COVID-19 nasopharyngeal swab tests were negative, as was the CSF assay for the genome of the virus. An electroencephalogram revealed a normal background rhythm (8 Hz), with no epileptiform discharges. On day 4, the patient became afebrile, and his mental status improved. Aquaporin-4 receptor (AQP4) and myelin oligodendrocyte glycoprotein (MOG) antibodies in the serum and CSF were assessed, which were both negative and Oligoclonal band (OCB) in CSF was unobtainable. The second CSF analysis findings, 72 h after the first tap, showed 250 total nucleated cells per microliter, with 60% lymphocytes. The CSF protein level was 111 mg/dL, and the glucose level was 65 mg/dL. Serologic tests for COVID-19 were requested, which revealed a negative result for IgM, but the IgG level was 1.6 (positive >1.1). At the end of the second week, the upper limb weakness improved, but the force of the lower limbs was 3+/5.

## 3. Discussion

The main clinical manifestation of human coronaviruses is respiratory involvement, and the leading cause of death is acute respiratory failure. However, there have been reports of extra respiratory manifestations, such as neurological findings (Ashrafi et al., 2020). Recent studies suggest possible mechanisms leading to COVID-19 neuroinvasive and neurotropic characteristics. The first is a direct viral injury to the CNS via blood circulation or nasal epithelium (Wu et al., 2020). Although there are some suggestive case reports of encephalitis (Wu et al., 2020. Ye et al., 2020); there is no definite proof that the SARS-CoV-2 virus directly affects the CNS. The second cause of nervous tissue damage results from the unpredictable effects of the host immune response after an acute infection. Guillain-Barré syndrome (GBS), as peripheral demyelination, is an example of this mechanism. Some cases of COVID-19-related GBS have been reported (Toscano et al., 2020), but the evidence of causality or effect is weak (Toscano et al., 2020. Zhao et al., 2020). The third mechanism is an indirect injury of the CNS due to systemic disease, particularly in patients who are critically ill. The last mechanism is overactivation of the immune response, which results in cytokine release (Yin et al., 2004). According to the literature, neurotropic coronaviruses could induce a “cytokine storm” by releasing a large number of inflammatory markers (Bohmwald et al., 2018), which could activate molecular changes and also reactivate immune-mediated processes (Kim et al., 2017). Together, these mechanisms could induce delayed nervous system damage and neurological complications (Klein et al., 2017).

Studies on SARS-CoV-1 revealed a delayed self-reactive T-cell suppression due to viral replication, which leads to neuroinflammation, demyelination or axonal damage of the CNS (Savarin et al., 2017. Cheng et al., 2019). Moreover, experimental models of coronavirus-induced neurological disease have shown that sustained CNS inflammation of infected animals correlates with increased demyelination (Savarin et al., 2017). Recent studies have shown that the novel coronavirus appears to cross the blood-brain barrier and cause acute or delayed CNS demyelination or axonal damage (Desforges et al., 2020). Acute necrotizing encephalomyelitis following COVID-19 is reported as a case of an acute CNS injury (Poyiadji et al., 2020). Moreover, a recent report revealed that CNS delayed demyelinating events following COVID-19 (Zanin et al., 2020). In our case, the absence of symmetric deep-gray matter involving, hemorrhage and cavitation, and also contrast-enhancing lesions (Poyiadji et al., 2020) are more suggestive of demyelination than necrotizing encephalomyelitis. According to our patient's examination, imaging, and laboratory findings, there are two differential diagnoses, including ADEM or Neuromyelitis-Optica spectrum disorder (NMOSD). In the absence of histopathological evidence, we could not settle on an exact diagnosis for the patient. The presenting symptoms, including new-onset fever and drowsiness along with neurological deficit after regressing respiratory illness, suggested a post-viral ADEM; however, in the absence of lesions’ enhancement as well as callosal involvement, ADEM is less likely. On the other hand, the history of sudden onset of recurrent vomiting, which could indicate the area of postrema syndrome, along with LETM, and corticospinal tract and corpus callosum hyperintensities are more indicative of NMOSD (Wingerchuk et al., 2015). Encephalopathy, however, as a presenting symptom and hypoglycorrhachia are uncommon in NMOSD. In the present study, COVID-19 was not detected in CSF or the nasopharynx presumably due to delayed immune-mediated CNS damage that occurred after the virus was cleared. Moreover, this could be explained by the low sensitivity of the system or delayed sampling (Panciani et al., 2020. Ye et al., 2020. Zanin et al., 2020).

## 4. Conclusion

Severe COVID-19 may affect the CNS and have various acute or delayed neurological complications. During the COVID-19 pandemic, it is important to consider SARS-CoV-2 infection when seeing patients with neurological manifestations, especially those needing immune-modulator therapy, since the established recommendations are insufficient at this time.

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## Declaration of Competing Interest

None.

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## Supplementary materials

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