COVID-19 Post-Infectious Encephalitis Presenting With Delirium as an Initial Manifestation

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Abstract
We report the case of a 65-year-old man with COVID-19 (coronavirus disease-2019) post-infectious encephalitis who presented with delirium as an initial manifestation. He had severe COVID-19 pneumonia and recovered with dexamethasone and tocilizumab. One week after discharge, he developed abnormal behavior and delirium without fever and respiratory symptoms. Brain magnetic resonance imaging showed no abnormalities. Cerebrospinal fluid showed pleocytosis and elevated protein concentrations and was negative for severe acute respiratory syndrome-coronavirus-2 RNA. No anti-neuronal autoantibodies against intracellular and neuronal surface proteins were detected. The cerebrospinal fluid inflammatory changes compatible with post-infectious encephalitis, and the patient recovered with intravenous methylprednisolone and intravenous immunoglobulin therapy. Delirium could be an initial symptom of post-infectious encephalitis in older adults with COVID-19, and these patients may require immunosuppressive therapy.

Keywords
COVID-19, SARS-CoV-2, post-infectious encephalitis, delirium

Introduction
The new coronavirus disease-2019 (COVID-19) caused by the new coronavirus (severe acute respiratory syndrome-coronavirus-2 [SARS-CoV-2]) in Wuhan, China, in 2019 became a global epidemic in 2020. Although SARS-CoV-2 causes acute respiratory infections, it is often accompanied by neurological symptoms such as headache, impaired consciousness, delirium, myopathy, and dysosmia.¹ Also, various neurological complications such as cerebral infarction, encephalitis/encephalopathy, and autoimmune diseases have been reported.²–⁴ As the pathological condition of the neurological complications of COVID-19, (1) direct invasion of virus into the nervous system, (2) neurological symptoms of COVID-19 as a systemic disease, and (3) para-infectious/post-infectious neurological complications, are assumed.⁵ In this article, we present a case of post-infectious encephalitis associated with COVID-19 who presented with delirium as an initial manifestation.

Case Presentation
A 65-year-old man was presented to the emergency department complaining of shortness of breath, fever, cough, and myalgia for 1 week. His history included a 5-year period of diabetes and sleep apnea syndrome, and he had received continuous positive airway pressure therapy. When examined, he was overweight (106 kg body weight, 34.2 kg/m² body mass index), body temperature of 39.9 °C, blood pressure 142/88 mm Hg, heart rate 120 beats per minute, and respiratory rate 20 breaths per minute. His percutaneous oxygen saturation (SpO₂) was 90% and increased to 95% on 2 L/min oxygen supplementation. Both nasopharyngeal rapid antigen test and reverse transcription-polymerase chain reaction (RT-PCR) assay confirmed SARS-CoV-2 infection. Chest radiographs and computed tomography (CT) of the chest showed progressive bilateral patchy interstitial opacities. Laboratory results revealed lymphopenia, elevated C-reactive protein (4.7 mg/dL),
and elevated D-dimers (1.2 g/mL). He received azithromycin and favipiravir. In addition, dexamethasone and prophylactic doses of low-molecular-weight heparin were started. Despite these treatments, hypoxemia deteriorated within several days from admission, and his SpO₂ decreased to 90% regardless of an oxygen supplementation of 12 L/min. His chest CT revealed extensive bilateral airspace consolidations and ground-glass opacities (Figure 1A), and the interleukin-6 inhibitor tocilizumab at 8 mg/kg (800 mg) was administered as a single infusion on day 7. After tocilizumab infusion, the patient’s state significantly improved, and on day 26, he was discharged from hospital after confirming significant improvement in his CT scan (Figure 1B) and 2 negative SARS-CoV-2 RT-PCR from nasopharyngeal swabs. He did not receive a tracheal intubation during the hospitalization.

However, 1 week after the discharge, he developed confusion and verbal communication difficulties, and presented to our department for further evaluation. At presentation, he had no fever, cough, or respiratory symptoms at presentation. Although he showed abnormal behavior and delirious state, his neurologic examination including meningeal irritation sign was normal. Brain magnetic resonance imaging including 3-dimensional volumetric fluid-attenuated inversion recovery and diffusion-weighted imaging revealed no abnormalities in the cerebral cortex/parenchyma, brainstem, and cerebellum. Nasopharyngeal PCR testing was negative for SARS-CoV-2. His SpO₂ was 96%, and laboratory results showed normal C-reactive protein (<0.10 mg/dL) and D-dimers (<1.0 g/mL). His chest CT showed further regression of pulmonary changes (Figure 1C). CSF examination revealed pleocytosis (18/mm³), a high protein level of 115 mg/dL, and no oligoclonal immunoglobulin G bands. SARS-CoV-2 RNA, herpes simplex virus DNA, and varicella-zoster virus DNA were negative in CSF. Concerning autoimmune encephalitis, autoantibodies against intracellular (Hu, Yo, CV2, Ri, Ma2/Ta, GAD65, amphiphysin, recoverin, SOX1, titin, zic4, Tr) and surface antigens (NMDAR, LGI-1, AMPAR, Casper 2, GABAR, DPPX, IgLON5) relevant to central nervous system diseases measured by line blots (EUROLEINE, Euroimmun) and cell-based assays (BIOCHIP, Euroimmun, performed by Labor Berlin) were all negative. Additionally, tissue-based assay revealed no anti-neuronal autoantibodies in the patient’s CSF. Serum aquaporin-4 and myelin oligodendrocyte glycoprotein antibodies were also negative. The patient initiated 1 g/day intravenous methylprednisolone immunosuppressant therapy for 6 days, followed by oral prednisolone (60 mg/day). His delirious state did not improve; however, intravenous immunoglobulin (IVIG) was administered additionally on day 9. His symptoms demonstrated significant improvement after IVIG initiation. Oral prednisolone was tapered, and he was discharged without any symptoms or sequelae on day 24 of the second hospitalization.

Discussion

We have described the case of post-infectious encephalitis associated with COVID-19 who presented with delirium as an initial manifestation. A wide variety of neurological symptoms has been observed among patients with COVID-19. Recent reports indicated that SARS-CoV-2 can present with neurological features and concomitant encephalitis/encephalopathy in serious cases of COVID-19. SARS-CoV-2 has rarely been detected in CSF, and there is accumulating evidence that mechanisms other than direct viral invasion in the CNS contribute to neuropathology. Thus, cytokine storms associated with COVID-19 and the immune reaction may contribute to brain edema and inflammatory changes, including the pathological condition of acute disseminated encephalomyelitis or acute necrotizing encephalopathy. Recent reports indicated that COVID-19 patients presenting with neurological symptoms, including myoclonus, oculomotor disturbance, delirium, dystonia, and epileptic seizures showed anti-neuronal autoantibodies in serum or CSF. In the present patient, no anti-neuronal autoantibodies against intracellular and neuronal surface proteins were detected. However, elevated CSF protein and pleocytosis with negative SARS-CoV-2 RT-PCR revealed inflammatory
changes consistent with post-infectious/autoimmune encephalitis. We were unable to recognize evidence of inflammation on his brain magnetic resonance imaging, this is not uncommon in cases of post-COVID-19 autoimmune encephalitis.\textsuperscript{13,14} Also, this case was remarkable because encephalitis appeared after the regression of COVID-19 pneumonia and the efficacy of immunomodulation with corticosteroid and IVIG supports an immunological mechanism. However, it is unclear whether the combination of steroid and IVIG was effective to his improvement or whether the same outcome could be obtained using steroids alone.

Initially, his delirium was considered to be due to the re-exacerbation of COVID-19 pneumonia, other complications, and metabolic factors by therapeutic agents. However, his laboratory and chest CT results showed no lung injury, and the various examinations results and his clinical course revealed post-infectious encephalitis associated with COVID-19. Among the older adults with COVID-19, delirium was one of the common symptoms at presentation (28%), and was often seen without other typical symptoms.\textsuperscript{15} In addition, delirium was associated with poor outcome and hospital death.\textsuperscript{15} The cause of delirium is assumed to reduce blood oxygen levels, deterioration of circulation dynamics, or complications for sepsis. Our case suggested that some older adults with COVID-19 presenting delirium should be attributable to post-infectious encephalitis and that those patients may require immunosuppressive therapy.

**Conclusion**

We reported the case of post-infectious encephalitis associated with COVID-19 who presented with delirium as an initial manifestation. Since delirium can be the initial symptom of post-infectious encephalitis, especially in older adults with COVID-19, an active examination should be required in consideration of immunosuppressive therapy.

**Declaration of Conflicting Interests**

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**Ethics Approval**

Our institution does not require ethical approval for reporting individual cases or case series.

**Informed Consent**

Verbal informed consent was obtained from the patient for their anonymized information to be published in this case report.

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