Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.0371-22
Intern Med 61: 3739-3741, 2022
http://internmed.jp

【 CASE REPORT 】

Possible Autoimmune Encephalitis Associated with the Severe Acute Respiratory Syndrome Coronavirus 2 Omicron Variant Successfully Treated with Steroids

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Abstract:

We encountered a 55-year-old woman with possible autoimmune encephalitis associated with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variant. She was not vaccinated against coronavirus disease 2019 (COVID-19). Consciousness disturbance, myoclonic-like movements and gait disturbance occurred 10 days after the COVID-19 symptom onset. Her neurological symptoms improved two days after methylprednisolone pulse therapy. Cerebrospinal fluid (CSF) was negative for SARS-CoV-2 reverse transcription-polymerase chain reaction, the CSF-to-serum albumin quotient was mildly elevated, and interleukin 6 and 8 levels were normal in serum but mildly elevated in CSF. Omicron variant infection may increase blood-brain barrier permeability and intrathecal inflammation, causing autoimmune encephalitis.

Key words: COVID-19, Omicron, autoimmune encephalitis, gait disturbance, myoclonus, steroid

(Intern Med 61: 3739-3741, 2022)
(DOI: 10.2169/internalmedicine.0371-22)

Introduction

Autoimmune encephalitis is a neurological complication associated with coronavirus disease 2019 (COVID-19) (1). The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variant causes milder symptoms than other variants (2). Thus far, only a single case of neurological complication after such an infection has been reported (3). However, the pathogenesis remains unknown.

We herein report the clinical course and cytokine profile of a patient with possible autoimmune encephalitis associated with the SARS-CoV-2 Omicron variant.

Case Report

A 55-year-old-woman without any medical history was admitted to our hospital in early February 2022 because of an altered mental status. This was during the sixth wave of SARS-CoV-2 infection in Japan predominantly comprising Omicron variant infections. A member of her cohabitating family had been infected with SARS-CoV-2. She was not vaccinated against COVID-19. The patient was well, and then 10 days before admission, she developed a fever. She showed no respiratory or neurological symptoms, and no therapeutic agents were used. Eight days before admission, she tested positive for SARS-CoV-2 using a rapid antigen test and was therefore diagnosed with COVID-19. During the next eight days, she quarantined in a hotel and was well. However, one day before admission, she again developed a fever, and her mental status was altered. When a staff member checked her physical condition, she could not respond appropriately. The patient was then transferred to our hospital.

On admission, the patient's body height was 164 cm, her body weight was 75 kg (body mass index 27.9), her body temperature was 36.5°C, her blood pressure was 141/85 mmHg, her pulse rate was 107 beats/min, and her oxygen saturation was 97% (room air). Her cardiovascular examination findings were normal, lungs were clear on auscultation, an abdominal examination was unremarkable with no hepatosplenomegaly, and no skin lesions were observed. A neurological examination revealed an altered consciousness status (Glasgow Coma Scale; E4V4M6), mild myoclonic-

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Received: May 26, 2022; Accepted: August 21, 2022; Advance Publication by J-STAGE: October 5, 2022
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like movements of the extremities, and mild gait disturbance (Supplementary Material). A blood test showed a normal range of electrolytes, thyroid function, ammonia levels, and glucose levels. Autoantibodies associated with connective tissue diseases, including antibodies against SS-A, SS-B, ds-DNA, RNP, MPO-ANCA, and PR3-ANCA, were negative. Whole-body computed tomography showed no signs of pneumonia or malignancy. Brain magnetic resonance imaging without a contrast agent was normal. A nasopharyngeal swab was positive for SARS-CoV-2 by reverse transcription-polymerase chain reaction (RT-PCR). This test was negative for SARS-CoV-2 variant L452R, and positive for variant G339D, indicating an Omicron variant (4). Electroencephalography showed diffuse, mild, slow waves.

On day 2 of hospitalization, lumbar puncture was performed. The cerebrospinal fluid (CSF) was clear, the opening pressure was 100 mmH_2O, the glucose level was 65 mg/dL, and the protein level was 59 mg/dL. The number of nucleated cells was 27 cells/μL, of which 96% were mononuclear. Gram staining of the CSF did not detect any bacteria. CSF PCR was negative for herpes simplex virus, cytomegalovirus, Epstein-Barr virus, and varicella-zoster virus. RT-PCR for SARS-CoV-2 in CSF yielded negative results. Although the CSF was negative for anti-NMDA receptor antibodies and serum was negative for anti-LGI1 and CASPR2 antibodies, we diagnosed the patient with SARS-CoV-2-related "possible autoimmune encephalitis" based on the criteria of Graus (5).

Two days after receiving high-dose methylprednisolone pulse therapy for three days, the patient's consciousness and electroencephalography findings normalized, and myoclonus-like involuntary movements and gait disturbance disappeared. A second CSF analysis performed on day 10 of hospitalization revealed a glucose level of 58 mg/dL, protein of 25 mg/dL, and cell count of 9 cell/μL, of which all were mononuclear. The patient was discharged on day 16 of hospitalization.

After she was discharged from our hospital, the following CSF test results were obtained: the CSF interleukin (IL)-6 and IL-8 levels, measured by chemiluminescent enzyme immunoassays, were elevated (5.76 pg/mL and 159 pg/mL, respectively), although neither were elevated in serum (2.41 pg/mL and <8 pg/mL, respectively). Both CSF cytokines normalized after steroid pulse therapy (1.98 pg/mL and 34 pg/mlL respectively). The CSF/serum albumin quotient (QALB) was mildly elevated before methylprednisolone pulse therapy (10.3×10^{3}), indicating increased blood-brain barrier permeability; however, the value normalized after therapy (3.63×10^{3}). No IgG index increase or oligoclonal bands were observed.

Discussion

A patient presented with possible autoimmune encephalitis associated with the SARS-CoV-2 Omicron variant. We herein report two novel findings regarding SARS-CoV-2-related neurological complications.

First, we showed that the Omicron variant can cause neurological involvement with consciousness disturbance. The Omicron variant has been reported to be milder than other variants, and it has been suggested that the milder course of infection may be associated with vaccination (2). In the present patient, the lack of vaccination may have contributed to the development of neurological symptoms. In the future, it will be necessary to investigate whether or not vaccination can prevent neurological complications, such as encephalitis and encephalopathy.

Second, we showed that autoimmune encephalitis is a cause of central nervous system complications induced by the Omicron variant. There are three proposed mechanisms of encephalitis pathophysiology as a complication of COVID-19: (i) direct viral invasion of the central nervous system, (ii) systemic inflammation caused by cytokine storm, and (iii) autoimmune reaction through molecular mimicry (6). Among these mechanisms, cytokine-mediated neuroinflammation associated with SARS-CoV-2 infection has been shown to play an important role in the development of autoimmune encephalitis (7). Patients with severe COVID-19 show elevated levels of inflammatory cytokines, such as IL-6 and IL-8 (8), which may affect blood-brain barrier dysfunction (9). Increased CSF IL-6 levels can facilitate intrathecal autoantibody production in anti-NMDA receptor encephalitis (10) and affect blood-brain barrier permeability in neuromyelitis optica spectrum disorder (11). Patients with anti-NMDA receptor encephalitis and anti-aquaporin 4 antibody-positive neuromyelitis optica spectrum disorder after SARS-CoV-2 infection have been reported (12, 13). Based on these reports, hyper-inflammation syndrome accompanying SARS-CoV-2 infection is a trigger of autoimmune encephalitis via increased blood-brain barrier permeability (14).

Patients with encephalopathy and inflammatory neurological syndromes associated with SARS-CoV-2 infection reportedly show distinct cytokine profiles in CSF and serum, and encephalopathy is associated with high serum levels of IL-6, while inflammatory neurological syndromes, such as encephalitis, are associated with high CSF levels of IL-6 (15). In our case, neurological complications developed 10 days after the COVID-19 onset, steroids were effective, a CSF RT-PCR was negative for SARS-CoV-2, the QALB index was mildly elevated, and IL-6 and IL-8 levels were not elevated in the serum but were mildly elevated in the CSF. These findings suggest that SARS-CoV-2 infection may trigger blood-brain barrier dysfunction and intrathecal inflammation to cause autoimmune encephalitis.

In the present case, although the anti-neuronal antibodies described were negative, unknown anti-neuronal antibodies may have been involved in the pathogenesis. Further studies regarding the immunological and genetic backgrounds that predispose patients to develop neurological complications after SARS-CoV-2 infection are needed.

In conclusion, it is important to recognize that autoim-

mune encephalitis may be caused by the Omicron variant of SARS-CoV-2, and the disease should be diagnosed without delay with immunotherapy provided as early as possible.

The authors state that they have no Conflict of Interest (COI).

References

1. Valencia Sanchez C, Theel E, Binnicker M, et al. Autoimmune encephalitis after SARS-CoV-2 infection: case frequency, findings, and outcomes. Neurology **97**: e2262-e2268, 2021.
2. Maslo C, Friedland R, Toubkin M, et al. Characteristics and outcomes of hospitalized patients in South Africa during the COVID-19 Omicron wave compared with previous waves. JAMA **327**: 583-584, 2022.
3. Altmann K, Koziol K, Palaver A, et al. Cytotoxic edema involving the corpus callosum and middle cerebellar peduncles in a young patient with mild COVID-19. Neurology **99**: 115-116, 2022.
4. Wu L, Zhou L, Mo M, et al. SARS-CoV-2 Omicron RBD shows weaker binding affinity than the currently dominant Delta variant to human ACE2. Signal Transduct Target Ther **7**: 8, 2022.
5. Graus F, Titulaer MJ, Balu R, et al. Clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol **15**: 391-404, 2016.
6. Siow I, Lee KS, Zhang JJY, et al. Encephalitis as a neurological complication of COVID-19: a systematic review and meta-analysis of incidence, outcomes, and predictors. Eur J Neurol **28**: 3491-3502, 2021.
7. Dhillon PS, Dineen RA, Morris H, et al. Neurological disorders associated with COVID-19 hospital admissions: experience of a single tertiary healthcare center. Front Neurol **12**: 640017, 2021.
8. Liu J, Li S, Liu J, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine **55**: 102763, 2020.
9. Achar A, Ghosh C. COVID-19-associated neurological disorders: the potential route of CNS invasion and blood-brain relevance. Cells **9**: 2360, 2020.
10. Byun JI, Lee ST, Moon J, et al. Distinct intrathecal interleukin-17/interleukin-6 activation in anti-*N*-methyl-D-aspartate receptor encephalitis. J Neuroimmunol **297**: 141-147, 2016.
11. Fujihara K, Bennett JL, de Seze J, et al. Interleukin-6 in neuromyelitis optica spectrum disorder pathophysiology. Neurol Neuroimmunol Neuroinflamm **7**: 841, 2020.
12. Monti G, Giovannini G, Marudi A, et al. Anti-NMDA receptor encephalitis presenting as new onset refractory status epilepticus in COVID-19. Seizure **81**: 18-20, 2020.
13. Ghosh R, De K, Roy D, et al. A case of area postrema variant of neuromyelitis optica spectrum disorder following SARS-CoV-2 infection. J Neuroimmunol **350**: 577439, 2020.
14. Nabizadeh F, Balabandian M, Sodeifian F, et al. Autoimmune encephalitis associated with COVID-19: a systematic review. Mult Scler Relat Disord **62**: 103795, 2022.
15. Espíndola OM, Gomes YCP, Brandão CO, et al. Inflammatory cytokine patterns associated with neurological diseases in coronavirus disease 2019. Ann Neurol **89**: 1041-1045, 2021.