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Case report of meningoencephalitis associated with SARS-CoV-2 infection showing a decrease in idiopathic focal cerebral blood flow

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Abstract

Some neurological complications are associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A 74-year-old man was diagnosed with infection by SARS-CoV-2. Eighteen days after SARS-CoV-2 infection, he developed disturbed consciousness and aseptic meningoencephalitis. An analysis of cerebrospinal flood revealed an elevated cell count (184/μL) and protein level (260 mg/dL). Cranial magnetic resonance imaging showed no abnormalities. By contrast, ^{123}I-N-isopropyl-p-iodoamphetamine single-photon emission computed tomography showed a significant decrease in cerebral blood flow (CBF) in the left parietal and occipital lobes. He died suddenly 3 months after being transferred to a rehabilitation clinic without any clear cause of death. The SARS-CoV-2 infection can cause aseptic meningoencephalitis with a distinctive decrease in CBF pattern without magnetic resonance image abnormality or intracranial artery stenosis.

Keywords

COVID-19, SARS-CoV-2, infection, cerebral blood flow, meningoencephalitis

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Introduction

The coronavirus disease 2019 (COVID-19) outbreak occurred in December 2019 and rapidly spread throughout the world.[1] COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, can induce an uncontrolled inflammatory response. Although the widespread availability of several types of vaccines showed effectiveness for preventing severe COVID-19 infection,[2] some neurological complications associated with SARS-CoV-2 infection have recently been reported such as stroke, encephalopathy, and long-term cognitive impairment.[3,4]

After the COVID-19 outbreak, some cases of meningitis associated with COVID-19 were reported.[5,6] Based on the pathology of meningitis or meningoencephalitis associated with COVID-19, several hypotheses have been proposed, such as direct infection of the central nervous system by SARS-CoV-2, autoimmune inflammation associated with SARS-CoV-2 infection, and others.[7,8] However, the pathology of meningitis or meningoencephalitis following COVID-19 has still not been confirmed and additional associated case data are needed. In addition, to our knowledge, there are only a few reports that indicate a decrease in focal cerebral blood flow (CBF) with COVID-19-associated meningoencephalitis.

Here, we report a case of COVID-19-associated meningoencephalitis with a distinct decrease in cerebellum blood flow after SARS-CoV-2 infection, but without stroke or intracranial artery stenosis.

Case

A 74-year-old man, who had no medical history including dementia, was diagnosed with SARS-CoV-2 infection, using real-time polymerase chain reaction (RT-PCR). Before SARS-CoV-2 infection, he received a total of three

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injections of the BNT162b2 mRNA COVID-19 vaccine. He displayed a mild fever (38.2°C) but no respiratory symptoms. He gradually began to feel fatigued and his anorexia worsened after the infection, so he was admitted to another hospital 15 days after infection. A laboratory test detected hyponatremia (sodium concentration: 119 mmol/L) as the only abnormality. Due to hyponatremia, both plasma osmolality and vasopressin decreased to 252 mOsm/kg (normal range: 280–290 mOsm/kg) and 2.7 pg/mL (normal range: <2.8 pg/mL), respectively. He was diagnosed with a syndrome (inappropriate secretion of antidiuretic hormone) and was hospitalized in the same hospital. Eighteen days after SARS-CoV-2 infection, despite a gradual improvement in hyponatremia, he developed disturbed consciousness. Electroencephalography showed a generalized theta rhythm (4–5 Hz) without epileptic discharge. Subsequently, a lumbar puncture examination was performed, and analysis of cerebrospinal fluid (CSF) showed that cell count was elevated, at 122/μL (10 polymorphonuclear cells and 112 mononuclear cells), as was protein level (187 mg/mL). He was transferred to our hospital with the diagnosis of COVID-19-associated meningoencephalitis.

Upon arrival at our hospital, he displayed disturbed consciousness, a Glasgow Coma Scale (GCS) of 10 (E3 V3 M5),[9] and a Mini-Mental State Examination score of 20/30, indicating that his short-term memory was impaired. He displayed no meningeal signs or focal deficit. At our hospital, a laboratory test showed that hyponatremia improved, with a sodium concentration of 135 mmol/L. White blood cell count, the level of c-reactive protein, and erythrocyte sedimentation rate were all normal (7100/μL, 0.08 mg/dL, and 9 mm/h, respectively). According to the coagulation test, both the activated partial thromboplastin time and prothrombin time-international normalized ratio were within normal ranges, 26.7 s (normal range: 22.4–37.4 s) and 0.98 (normal range: 0.85–1.15), respectively. Although the level of D-dimer was slightly elevated at 2.9 μg/mL (normal range: <1 μg/mL), thrombosis was not detected in the contrast computed tomography. A new CSF analysis showed that cell count increased further to 184/μL (14 polymorphonuclear cells and 170 mononuclear cells), as did the protein level to 260 mg/dL. The oligoclonal bands were positive and the interleukin 6 level was elevated, at 33.1 pg/mL (normal range of serum: <7.0 pg/mL). The CSF immunoglobulin G index was elevated (0.98), which suggests inflammation of the central nervous system. Tests for herpes simplex virus-deoxyribonucleic acid and bacterial culture were both negative. Other pathogens such as cytomegalovirus, enterovirus, varicella-zoster virus, or Cryptococcus neuroformans/gattii tested negative in CSF.

Cranial magnetic resonance imaging (MRI) showed no abnormalities in the diffusion-weighted image (Figure 1(a)), the fluid-attenuated inversion recovery image (Figure 1(b)), or the gadolinium-enhanced T1 image (Figure 1(c)). No stenosis or occlusion was observed by magnetic resonance angiography (Figure 1(d)). By contrast, ^{123}I-N-isopropyl-p-iodoamphetamine single-photon emission computed tomography (^{123}I-IMP SPECT) showed a remarkable decrease in CBF in the left parietal and occipital lobes (Figure 1(e) and (f)).

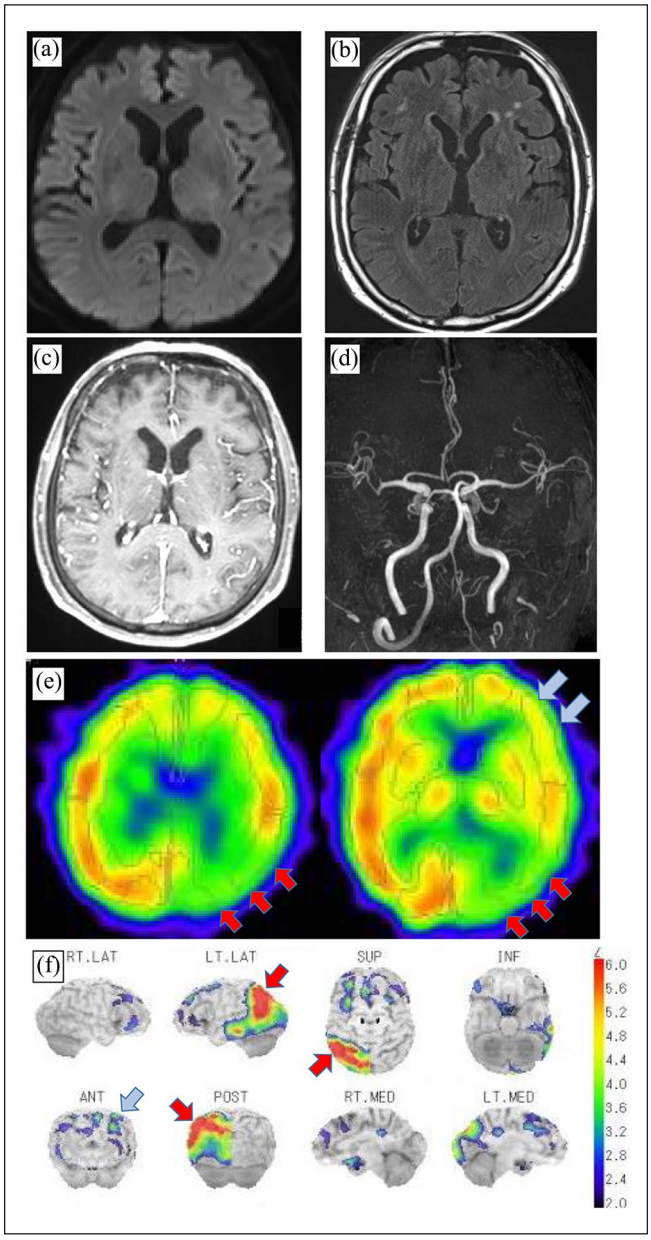

Figure 1. None of the cranial MRI images, namely (a) DWI, (b) FLAIR, and (c) Gd-enhanced T1 weighted, showed any abnormal lesions except for a few chronic ischemic changes. (d) MR angiography showed neither stenosis nor occlusion. By contrast, (e) ^{123}I-IMP SPECT showed a remarkable decrease in cerebral blood flow in the left parietal and occipital lobes (red arrows), and a mild decrease in cerebral blood flow in the left anterior lobe (blue arrows). (f) 3DSSP analysis.
^{123}I-IMP SPECT: ^{123}I-N-isopropyl-p-iodoamphetamine single-photon emission computed tomography; 3DSSP: three-dimensional-stereotactic surface projection; DWI: diffusion-weighted image; FLAIR: fluid-attenuated inversion recovery; MRI: magnetic resonance imaging.

We diagnosed the patient as having aseptic meningoencephalitis associated with SARS-CoV-2 infection and treated him with supportive care but did not provide a specific treatment for meningoencephalitis associated with SARS-CoV-2 infection including immunosuppression therapy. His consciousness gradually improved without any treatments such as corticosteroids or immunoglobulin. Thirty-eight days after infection, the third CSF showed that cell count was still elevated at 165/μL (1 polymorphonuclear cell, 164 mononuclear cells), as was protein level (235 mg/dL). The CSF immunoglobulin G index was still elevated (0.96), but oligoclonal bands became negative. The SARS-CoV-2 RT-PCR was negative, but both of the immunoglobulin G antibodies against SARS-CoV-2 spike protein and nucleoside protein were positive in CSF.

Given that the patient's GCS score improved to 14 (E4V4M6) and the Mini-Mental State Examination score improved to 26/30, our team speculated that this patient's meningoencephalitis would improve without additional treatment, although the CSF inflammation still remained. Thus, he was transferred to a rehabilitation clinic 47 days after infection. Even though his neurological symptoms did not worsen or recur, he died suddenly 3 months after transfer to the rehabilitation clinic. The cause of death was not clear, but because there was no consent, an autopsy was not performed.

Discussion

Here, we report a case of meningoencephalitis associated with SARS-CoV-2 infection. The patient showed disturbed consciousness and aseptic meningoencephalitis after SARS-CoV-2 infection. Although no abnormalities in the cranial MRI or intracranial artery were observed, the left local CBF decreased dramatically, and there were positive antibodies against the SARS-CoV-2 spike protein and nucleoside protein in the CSF, although SARS-CoV-2 RT-PCR was negative.

There are some reports of aseptic meningitis or meningoencephalitis after SARS-CoV-2 infection. Those patients gradually developed neurological symptoms after recovering from SARS-COV-2 infection.[5] Most patients of meningoencephalitis associated with SARS-CoV-2 infection showed hypometabolism of the specific lesion area, but metabolism naturally recovered after a few months.[10] The accurate pathology of meningoencephalitis associated with SARS-CoV-2 infection is still unknown. The level of some cytokines was elevated both in the CSF and in blood in previously reported cases.[10,11] Elevated cytokine can affect the metabolism of the central nervous system.[12] In our case, CSF inflammation markers were high, and antibodies were positive, but RT-PCR was negative against SARS-CoV-2 in the CSF, supporting this immunological hypothesis.

A previous report demonstrated that patients in the early stages of post-COVID-19 (3–4 weeks after SARS-CoV-2 infection) showed hypometabolism, as shown by ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) analysis.[13] Although hypometabolism detected by FDG-PET and hypoperfusion detected by ^{123}I-IMP SPECT share a common pathology in many cases, there is a subtle difference: while the former shows an impact on direct neuron function, the latter shows a dramatic functional change. Our presented case demonstrates that remarkable functional decline can occur in meningoencephalitis associated with COVID-19 although no abnormalities were detected by cranial MRI. This result suggests two pathologies of meningoencephalitis associated with COVID-19. In the first, COVID-19-induced inflammation may disturb the CBF micro-environment. In the second, because meningoencephalitis associated with COVID-19 itself is a unique form of meningoencephalitis, specific brain functions may be considerably disturbed. Infection of the central nervous system with hemodynamic changes may have occurred in patients after SARS-CoV-2 infection, more than was previously considered. Additional analyses of complications to the central nervous system caused by COVID-19 are required.

Finally, we failed to rescue this presented case of meningoencephalitis associated with SARS-CoV-2 infection. We speculate that this aseptic meningoencephalitis would naturally improve because his symptoms improved, although the CSF inflammation markers were still elevated and we did not confirm, using ^{123}I-IMP SPECT, that the left local CBF decreased recovery. His cause of death was unclear because there was no autopsy, although there was the possibility of meningoencephalitis, even though several months had passed since SARS-CoV-2 infection. There is no clear treatment for such a complex and rare condition.[14] However, early intervention has led to favorable outcomes in some cases of thrombosis associated with COVID-19.[4] Although this suggestion remains speculative, initiation of immunosuppression therapy at an early stage might have changed the prognosis in our case. We alert the physicians that a patient's condition can change dramatically and that aggressive treatment may be required for meningoencephalitis with a local decrease in CBF associated with SARS-CoV-2 infection.

Conclusion

Meningoencephalitis with a distinctive decrease in CBF pattern, but without MRI abnormalities or intracranial artery stenosis, was associated with COVID-19.

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Author contributions

K.S. and K.M. were the attending doctors for the present case; K.S. and K.M. drafted the manuscript; T.M. and R.K. helped draft the manuscript; S.F. conceived the study, participated in its coordination, and helped draft the manuscript. All authors read and approved the final manuscript.

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Ethics approval

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

Informed consent

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