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Symmetrical involvement of bilateral midbrain cerebral peduncles in a case of COVID-19 associated encephalopathy

Chun-Hin Cheung*; Hon-Hang Kwan; Yan-Lok Tiffany Lam; Bun Sheng

***Corresponding Author: Chun-Hin Cheung**
Neurology Team, Department of Medicine and Geriatrics, Princess Margaret Hospital, Hong Kong SAR.
Email: ericcheunghin@gmail.com

Abstract

We report a case of COVID-19 associated brainstem encephalopathy, who was a 34-year-old obese man with good past health, noted to have poor conscious level after extubation. Magnetic resonance imaging of the brain showed T2 and FLAIR hyper intense signals at bilateral midbrain cerebral peduncles with restricted diffusion. Clinical and electroencephalographic improvement was seen after intravenous immunoglobulin therapy.

Keywords

Coronavirus disease 2019; Encephalopathy; Brainstem encephalitis; Rhombencephalitis.

Introduction

Three years into the Coronavirus Disease 2019 (COVID-19) pandemic, we now know that it can affect the nervous system in various ways. Among them, COVID-19 associated encephalopathy remains an uncommon but important entity that impairs the sensorium, even if the patient had survived the life-threatening respiratory infection. We present the case of a young man who recovered from COVID-19 but was complicated by COVID-19 associated brainstem encephalopathy, with characteristic radiological findings at the midbrain.

Case Report

A 34-year-old obese man with good past health presented with cough, sore throat, fever and breathlessness for five days. After admission to the isolation ward, he was confirmed Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) positive by polymerase chain reaction (PCR) test of his nasopharyngeal swab. He deteriorated rapidly, required mechanical ventilation on the same day and was transferred to the Intensive Care Unit. The initial cycle threshold (CT) value was 31.3, and the nadir CT

value (highest viral load) was 21.1 on day 2 of admission. He was treated with dexamethasone, Remdesivir, interferon and convalescent plasma. His laboratory tests were remarkable for elevated ferritin at 9341 pmol/L and C-reactive protein at 147 mg/L. His lung condition gradually improved, and on day 13, SARS-CoV-2 IgG was detectable, hence he was extubated.

However, he was noted to have poor conscious level after extubation, with a Glasgow Coma Scale (GCS) of E1V1M1, thus requiring re-intubation and subsequently tracheostomy. Oculomotor dysfunction was evident with vertical gaze palsy. Computed tomography of the head was normal. Electroencephalography (EEG) showed theta-range background with frontal-predominant delta waves, in keeping with encephalopathy. Lumbar puncture showed normal white cell count, protein and glucose, negative bacterial culture, acid-fast bacilli stains and viral encephalitis PCR panel. The autoimmune encephalitis panel in serum and Cerebrospinal Fluid (CSF) was negative, including antibodies against N-methyl-D-aspartate receptor (NMDAR), leucine-rich glioma-inactivated 1 (LGI1), contactin-associated protein-like 2 (CASPR2), a*lpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) A/B receptor,* gamma-aminobutyric acid (GABA) A/B receptor and dipeptidyl-peptidase-like protein 6 (DPPX). Ammonia level was normal. Thyroid function test was normal and anti-thyroid antibodies were negative. Magnetic resonance imaging (MRI) of the brain showed T2 and FLAIR hyperintense signals at bilateral midbrain cerebral peduncles (involving bilateral substantia nigra), with restricted diffusion, and without contrast enhancement (Figure 1).

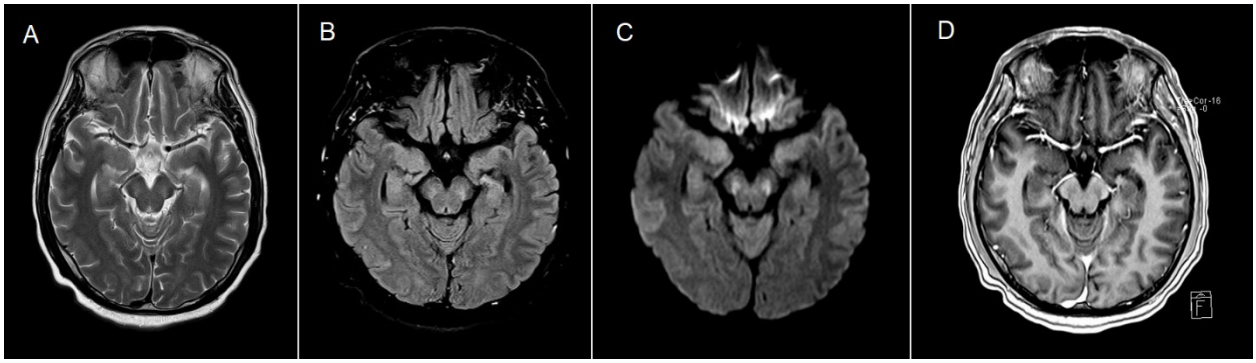

Figure 1: Magnetic resonance images of the patient.
(A) T2-weighted image at the level of midbrain shows rather symmetrically increased signal at bilateral substantia nigra, without significant mass effect.
(B) FLAIR sequence image at the level of midbrain shows rather symmetrically increased signal at bilateral substantia nigra, without significant mass effect.
(C) Diffusion weighted sequence image at the level of midbrain shows restricted diffusion at the lesions.
(D) Post gadolinium T1 weighted sequence image at the level of midbrain shows no significant enhancement at the midbrain lesions.

The impression was COVID-19 associated brainstem encephalopathy, or rhombencephalitis, presumably immune-mediated. He was empirically given intravenous immunoglobulin (IVIg) for five days. His GCS gradually improved to E4VTM6. He became alert, able to nod his head on command and answer questions with gestures. Repeated EEG four days after IVIg also showed interval improvement with less delta waves. He weaned off the ventilator on day 39 of admission. However, he remained tetraplegic due to critical illness polyneuropathy, and was transferred to the convalescence unit for rehabilitation.

Discussion

Our case illustrated how encephalopathy can complicate severe COVID-19 infection even after stabilization of the respiratory status and resolution of its infectivity. In a study that included more than five hundred COVID-19 patients [1], 31.8% had encephalopathy. Very often, they are revealed upon weaning from the ventilator, after sedative drugs are taken off. The pathophysiology of COVID-19 associated encephalopathy is likely multifactorial, but an immune-mediated mechanism may be the best explanation. A dysregulated systemic immune response, or cytokine storm, is common in severe COVID-19; altered mental status can result from high levels of proinflammatory cytokines [2]. Although believed to be an inflammatory entity, COVID-19 associated encephalopathy patients usually have normal white cell count and protein level in the CSF [3]. CSF SARS-CoV-2 PCR test was not ordered for our patient, as the result would unlikely alter the treatment plan. Indeed, CSF SARS-CoV-2 PCR test is more often negative than positive in cases of COVID-19 related neurological symptoms [4]. COVID-19 associated neurological dysfunction is more likely caused by autoimmunity instead of direct cytopathic effect of virus.

A wide spectrum of MRI findings had been reported for COVID-19 associated encephalopathy, including normal imaging, signal change over periventricular regions, cortical or subcortical white matter, as well as specific patterns like acute necrotizing encephalopathy (ANE), acute disseminated encephalomyelitis (ADEM) and posterior reversible encephalopathy syndrome (PRES) [5]. Our patient had T2 and FLAIR signal change with restricted diffusion at bilateral midbrain cerebral peduncles. Latest research has discovered antibodies against novel brainstem neuronal antigens in COVID-19 patients [6], and future studies may improve our understanding on COVID-19 associated encephalopathy targeting the brainstem.

Conclusion

Our case of COVID-19 associated encephalopathy has a special pattern with symmetrical involvement of bilateral midbrain. The patient responded well to immunosuppressive therapy, suggesting probably an immune-mediated mechanism. More studies are needed to further characterize encephalopathy with this radiological pattern.

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Authors Information: Chun-Hin Cheung*; Hon-Hang Kwan; Yan-Lok Tiffany Lam; Bun Sheng
Neurology Team, Department of Medicine and Geriatrics, Princess Margaret Hospital, Hong Kong SAR.

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