High-dose steroid-responsive COVID-19-related encephalopathy with a sudden onset of dysarthria mimicking stroke: a case report

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ABSTRACT

There has been limited research on encephalitis/encephalopathy, which is a less common coronavirus disease 2019 (COVID-19) neurological complication. The differentiation between stroke and encephalopathy with stroke mimickers is challenging in patients with COVID-19. Here, we describe a case of COVID-19-related encephalopathy mimicking stroke that was successfully treated with high-dose steroid pulse therapy. The patient suddenly experienced language disturbance with a left facial droop and symmetric numbness in his upper limbs. Magnetic resonance imaging (MRI) scans revealed hyperintensities in both the white matter and splenium. No pneumonia was observed. MRI abnormalities and neurological symptoms resolved after steroid pulse therapy and administration of remdesivir. High-dose steroid pulse treatment (for 3 days) might alleviate COVID-19-related encephalopathy.

KEYWORDS: Encephalitis, COVID-19, coronavirus, stroke, steroid

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Introduction

Coronavirus disease 2019 (COVID-19) primarily affects the respiratory system and severely impacts the neurological system. Encephalitis, with two broad categories, autoimmune and infectious encephalitis, is a less common neurological complication of COVID-19 accounting for .215% of cases and remains inadequately explored.[1] Encephalitis/encephalopathy develops in severely ill patients with COVID-19 and results in substantial morbidity and mortality rates. In most patients, encephalitis develops after 14.5 days following the onset of COVID-19 symptoms.[1] Encephalitis/encephalopathy rarely occurs without symptomatic COVID-19.[2,3] Stroke incidence without cerebrovascular risk factors is increasing, with a high incidence of large artery ischemia even in young patients.[4] A postmortem examination of a patient with COVID-19 with encephalopathy during the infectious course showed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral particles in both the cytoplasm of frontal lobe neurons and brain endothelial cells.[5] When a patient with COVID-19 presents with a stroke-like episode, clinicians are often uncertain regarding the appropriate therapeutic method to be adopted. Herein, we describe a case of COVID-19-related encephalopathy that mimicked stroke and was successfully treated with high-dose steroid pulse therapy.

Case report

A 23-year-old man with no significant history of illness presented with a fever, cough, and headache for 5 days and was diagnosed with COVID-19 after positive polymerase chain reaction (PCR) test results for SARS-CoV-2 on a nasopharyngeal swab. The patient did not undergo COVID-19 vaccination. He suddenly experienced language disturbance and a notable left facial droop and symmetric numbness in his upper limbs 213 min prior to arriving at the emergency department of our hospital. Whilst in the ambulance, his percutaneous oxygen saturation level was 98% and the ambulance crew employed written communication since his verbal communication was unintelligible because of the language disturbance. Upon arriving at the hospital, the patient's body temperature was 37.3°C. Neurological examination revealed severe dysarthria, to the extent that he had to be examined twice; however, he did not have aphasia. The patient was alert and responded promptly to the instructions. Skin writing tests using his palms were normal; there was no deficit in higher brain functions such as left and right agnosia, asomatognosia, and apraxia. Other neurological deficits, including facial and limb weaknesses and sensorial impairments, such as numbness, ataxia, and soft palate elevation, were absent. Deep tendon reflexes were normal, without Babinski's sign. The National Institutes of Health (NIH)

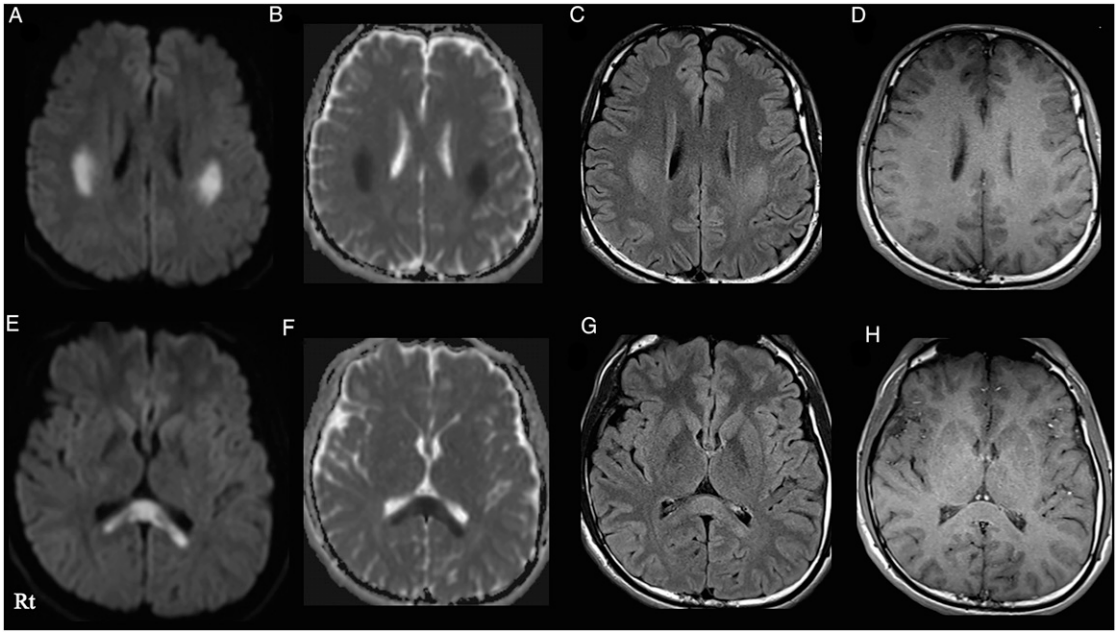

Figure 1. Diffusion-weighted magnetic resonance imaging (MRI) (panel a and e) demonstrated increased signal intensity, and the apparent diffusion coefficient (ADC) map (panel b and f) revealed decreased water diffusivity in both the white matter and splenium. The lesions showed the hyperintensities on fluid attenuated inversion recovery and slightly decreased intensities on T1-weighted MRI.

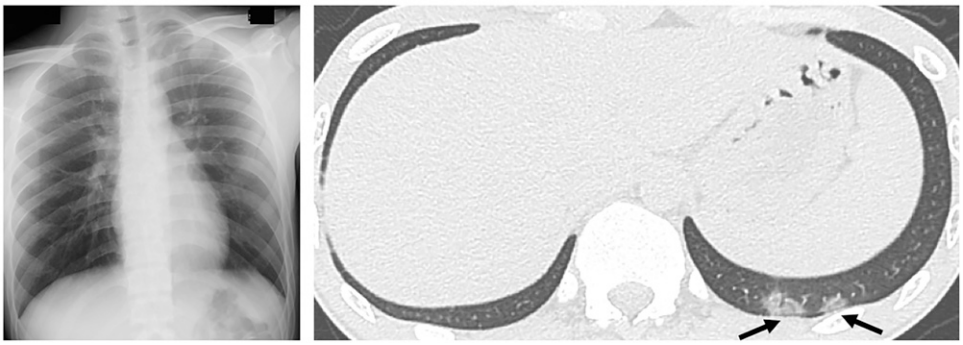

Figure 2. Chest radiography did not showed pneumonia at the admission (left panel). A minor mottled shadow in the lower lung lobe was evident on follow-up chest computed tomography (CT) (right panel).

Stroke Scale score was 2 for severe dysarthria. The patient did not have anosmia. Routine serum laboratory examination results were normal, except for a mild increase in C-reactive protein (.42 mg/dL) levels. The D-dimer level was .6 μg/mL. The following tests were negative: serum anti-nuclear antibody, anti-DNA antibody, anti-neutrophil cytoplasmic antibody, and aquaporin-4 antibody. There was no risk of juvenile cerebral infarction, measured using protein C or S activity and antigen, and anti-cardiolipin antibody. Cerebrospinal fluid (CSF) findings were normal. The IgG results index was .5. PCR for SARS-CoV-2 was positive for the nasopharyngeal swab specimen but not for the CSF specimen. Brain computed tomography (CT) showed no apparent abnormalities, however, cranial magnetic resonance imaging (MRI) scans showed hyperintensities in both the white matter and splenium. Diffusion-weighted MRI revealed an increased signal intensity and the apparent diffusion coefficient (ADC) map revealed decreased water diffusivity in these lesions, with hyperintensities on both T2-weighted MRI and fluid-attenuated inversion recovery (Figure 1). The T1-weighted MRI showed a slightly decreased intensity. Cranial magnetic resonance angiography revealed no intracranial vessel stenosis. Pneumonia was not evident on chest radiography (Figure 2). The patient received intravenous steroid pulse therapy (1 g/kg/day, for 3 days) and intravenous remdesivir (100-200 mg/day, for 5 days). Low-molecular-weight heparin was initiated but discontinued on day 2. Oxygen therapy was not administered during the disease course. On the day after admission, dysarthria resolved without other manifestations. The second MRI (on day 8) showed hyperintensities in the white matter, and those in the splenium were resolved. A minor mottled shadow in the

Table 1. Previous patients with COVID-19 encephalitis/encephalopathy mimicking stroke.

	PATIENT 1 REF[7]	PATIENT 2 REF[2]	PATENT 3 REF[8]	PRESENT CASE
Age/gender	54/M	35/M	57/F	
Risk factor for stroke	Hypertension, dyslipidemia	Migraine	NA	None
COVID-19 symptoms prior to stroke symptoms	1-week sore throat, dysgeusia, hyposmia	No respiratory symptoms	Severe acute respiratory syndrome	Pyrexia
Sudden stroke symptoms	Language disturbance	Dysphagia, mild confusion, right arm incoordination	Language dysfunction	Dysarthria
National institutes of health stroke scale	NA	5	NA	2
Neurological examinations	Aphagia, mild ideomotor slowing	Right arm weakness dysphagia, amnesia, headache (day 3)	Aphagia	Severe dysarthria
Body temperature	37.5	39.7	NA	37.3
Cranial CT	Unremarkable	Unremarkable	NA	Minor mottled shadow
Cranial MRI	No infarction	No infarction	Bilateral hyperintensities in both temporo-mesial lobes	Symmetrical deep white matter and splenium hyperintensities
Electroencephalogram	Unremarkable	Generalized slowing	NA	Unremarkable
Respiratory findings	Bilateral pneumonia on CT	No respiratory infection	NA	No respiratory infection including CT
Serum examinations				
D-dimer (mg/L)	3.32	NA	NA	.6 μg/mL
C-reactive protein (mg/dL)	4.75	NA	NA	.42
White cell count	6.25 (10^9/L)	NA	NA	3100 (/μL)
Blood oxygen saturation	PaO2/FiO2 = 252 (arterial)	NA	NA	None
Cerebrospinal fluid examination				
Cell (mm^3)	2	134	Normal	Normal
Protein (mg/dl)	41	52	Normal	Normal
Treatment				
COVID-19 infection	Oxygen, hydroxychloroquine, intravenous low-dose steroids	NA	NA	Remdesivir
Suspected stroke	Low-molecular weight heparin	Anti-thrombosis	NA	Low-molecular weight heparin
Others	None	None	NA	Steroid pulse therapy
Clinical course	Progressive to agitated delirium, respiratory status worsened, mechanical ventilation	Pyrexia and amnesia persisted	NA	Rapid resolution
Outcome	Mild dysgeusia, language disturbance resolved	Mild dysgeusia	NA	Full recovery
Follow-Up MRI	No infarction	No abnormalities	NA	No infarction, hyperintensities disappeared

NA: not available.

lower lung lobe was evident on the chest CT (Figure 2). The patient was discharged from the hospital after full recovery. Written informed consent was obtained from the patient to publish his medical data and images.

Discussion

Common symptoms of COVID-19-related encephalitis include loss of or decreased consciousness, altered mental status, seizures, headaches, and weaknesses. Aphasia, ataxia, and myoclonus are less common symptoms.[1] Various cerebrovascular diseases associated with COVID-19 have been reported, such as ischemic stroke in the context of stable cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).[6] Our patient showed steroid-responsive COVID-19-related encephalopathy mimicking stroke without respiratory manifestations upon hospital admission. Such encephalitis/encephalopathy has been documented in patients, as shown in Table 1.[2,7,8] Language impairment is a relatively frequent symptom that mimics a stroke. The language impairment in our patient might have been elicited by symmetric subcortical lesions attached to the pyramidal tracts in addition to the left facial droop. Four patients, including our patient, showed pyrexia; however, no respiratory symptoms were noted in two of the patients. Patients without respiratory symptoms have been reported to have cerebral infarction as a complication of COVID-19.[9] Most patients with encephalitis have severe COVID-19 and account for approximately 83.8% of cases.[1] Notably, COVID-19-related encephalitis/encephalopathy may rarely be present in asymptomatic carriers of COVID-19 as in our patient. Five of the 78 patients (23.8%) with encephalitis had no COVID-19 symptoms.[1]

Diffuse white matter hyperintensities and hemorrhagic lesions are common, whereas cerebral edema is less frequent.[1] Symmetric hyperintensities in the subcortical white matter and splenium, where lesions are rich in neuronal fibers but lacking in neuronal cells, were observed in our patient. The MRI splenium images of the present patient were also consistent with the characteristic findings of clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS). Patients with COVID-19 associated with MERS have been reported in a previous study.[10] In splenium lesions on MERS, diffusion-weighted images and ADC maps may reflect intramyelinic edema, which is the diffusion directionality of water trapped between myelin layers;[11,12] this corroborates the MRI results showing that the hyperintensities were resolved after steroid treatment.

The incidence of encephalitis as a complication of COVID-19 is low; however, the estimated risk increases with the severity of COVID-19.[1] SARS-CoV-2 enters the central nervous system via two plausible routes: angiotensin-converting enzyme 2 (ACE2) receptors located on epithelial cells of the blood-cerebrospinal fluid barrier and retrograde axonal transport of peripheral neural pathways such as the olfactory mucosa.[1] The pathophysiology of encephalitis as a complication of COVID-19 involves direct invasion of the nervous system via transsynaptic propagation due to SARS-CoV-2 binding to ACE2 receptors. This molecular mimicry caused by cross-reactivity between immune molecules and SARS-CoV-2 antigens results in systemic inflammation known as a cytokine storm.[1]

Efficacious management protocols for COVID-19-related encephalitis/encephalopathy remain elusive. As in our study, Cao et al. reported that three of five patients showed marked improvement in neurological status within one week of methylprednisolone administration, an intravenous corticosteroid (1 g, for 5-10 days).[13] A different study reported that a patient with COVID-19 encephalitis responded to high-dose methylprednisolone (1 g/day, for 5 days); furthermore, generalized slowing on the electroencephalogram was resolved. However, cranial MRI in the patient was normal during the course of the disease.[14]

Differentiation between stroke and encephalitis/encephalopathy with stroke mimickers is challenging in patients with COVID-19. Encephalitis/encephalopathy should be considered in cases of coexisting persistent pyrexia and a sudden onset of language impairment. High-dose steroid pulse treatment (for 3 days) might alleviate COVID-19-related encephalopathy.

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Author contributions

H Kataoka and N Kikutsuji were responsible for the overall study design, and wrote the manuscript. N Kikutsuji, T Kiriyama and H Kataoka contributed to acquisition of data. N Kikutsuji, and H Kataoka contributed to analysis and interpretation of data. H Kataoka and S Kazuma contributed to drafting and critical revision of part of the submitted materials.

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