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Acute Encephalitis Associated with SARS-CoV-2 Confirmed in Cerebrospinal Fluid: First Case in Malaysia

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Dear Editor,

A 69-year-old male with hypertension and atrial fibrillation presented with a 4-day history of fever, cough, and breathlessness, and subsequently developed disorientation and confusion for 1 day. On arrival, his Glasgow Coma Scale was 12/15 (E4, V3, and M5). His body temperature was 37.5°C, blood pressure was 136/60 mm Hg, pulse rate was 72 beats/min , and SpO2 was 98%, with a nasal prong of 3 L/min. There were no symptoms of meningism or long-tract signs. On the following day he became increasingly restless and breathless, and required a high-flow-rate nasal cannula to maintain adequate oxygenation. A diagnosis of Coronavirus disease-2019 (COVID-19) was established based on positivity when using an antigen rapid testing kit (SD Biosensor, Inc., Suwon, Korea). However, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was not detected when the polymerase chain reaction (PCR) was applied to the nasopharyngeal swab sample. High-resolution CT of his lungs showed subpleural ground-glass opacities with reticulation on the background of chronic lung changes. Noncontrast brain CT only revealed an old right lenticular infarct. The opening pressure in lumbar puncture was 9.5 cmH_2O. His cerebrospinal fluid (CSF) was clear, with a protein level of 1.16 g/L, and the CSF/serum glucose ratio was 0.58. A white blood cell count of 50 cells/mm^3 with 100% lymphocytes was seen in the CSF. SARS-CoV-2 was detected in his CSF using PCR with a cycle threshold value of 36.08 and the ORF1ab gene. The results of other CSF analyses were unremarkable.

He was treated with tablet favipiravir at 1800 mg b.i.d. for 1 day followed by 900 mg b.i.d. for 5 days, antituberculosis agents (in view of a high protein level in the CSF with 100% lymphocytes), and intravenous dexamethasone at 8 mg t.d.s., which was later tapered. After 1 week, upon positivity in PCR testing of CSF for SARS-CoV-2, a diagnosis of COVID-19-associated encephalitis was made, and antituberculosis drugs were discontinued. Intravenous methylprednisolone was applied at 500 mg daily for 3 days followed by a tapering dose of oral prednisolone over 24 days. By the second day of methylprednisolone administration, he regained full consciousness after having been disorientated for 10 days. Electroencephalography (EEG) and brain MRI were not available at our center during his admission. EEG findings were normal at a clinic follow-up performed in the third week of his illness. Brain MRI was unremarkable after 1 month of illness. He subsequently remained well with no neurological sequelae.

Neurological manifestations associated with COVID-19 are reported to range from nonspecific symptoms such as dizziness, headache, and fatigue, to diseases such as Guillain–Barré syndrome, encephalitis, myelitis, and acute necrotizing hemorrhagic encephalopathy.[1] Mao et al.[2] reported that 36.4% of hospitalized COVID-19 patients had neurological manifestations. Moriguchi et al.[3] and our case have demonstrated that encephalitis is most likely due to neurotropism of SARS-CoV-2, since the virus was detected in the CSF. Wang et al.[1] found only 1 case among 41 reviewed articles in which SARS-CoV-2 was detected in the CSF.

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Table 1. Summary of our case and previously reported cases

	Our case	Moriguchi et al.[3]	Kamal et al.[7]	Duong et al.[6]
Age, years	69	24	31	41
Sex	Male	Male	Male	Female
Medical history	Hypertension, atrial fibrillation	-	-	Diabetes mellitus, obesity
Presenting symptoms	Fever, cough, breathlessness	Headache, generalized fatigue, fever	Cough	Headache, fever
Neurological symptoms	Altered behavior	Altered behavior	Altered behavior	Seizure
Onset of neurological symptoms	Day 4 of illness	Day 9 of illness	Day 3 of illness	-
Remission of neurological symptoms	Day 14 of illness	-	Approximately 2 weeks	Mentation began to improve by day 5 of admission
Brain CT	Old right lenticular infarct	No evidence of brain edema	Multiple hypodensities in both the external capsules, insular cortex and deep periventricular white matter of bilateral frontal lobes	Normal
Brain MRI	Performed 1 month later. Normal findings	Performed 20 hours after admission. DWI showed hyperintensity along the wall of the inferior horn of the right lateral ventricle. FLAIR images showed hyperintensities in the right mesial temporal lobe and hippocampus with slight hippocampal atrophy	Performed 2 weeks later. Symmetrical abnormal signal intensity in bilateral temporal lobe cortices, involvement of both parasagittal frontal lobes, displaying hyperintensities on T2-weighted/FLAIR and T2-weighted images with corresponding diffusion restriction	-
LP opening pressure	9.5 cmH_2O	32 cmH_2O	-	-
CSF protein, mg/dL	116	-	45	100
CSF cell counts	WBC 50 cells/mm^3 with 100% lymphocytes	WBC 12 cells/mm^3 with 10 mononuclear and 2 polymorphonuclear cells without RBC	WBC <5 cells/mm^3, RBC 150 cells/mm^3	WBC 70 cells/mm^3 with 100% lymphocytes, RBC 65 cells/mm^3
Thorax CT	Subpleural ground-glass opacities with reticulation	Small ground-glass opacity on the right superior lobe and both sides of the inferior lobe	Normal	Normal
EEG	Performed 3 weeks later. Normal findings	-	Performed during admission. Normal findings	Performed during admission. Generalized slowing with no epileptic discharges
Treatment	IV ceftriaxone, subsequently upgraded to meropenem, dexamethasone, methylprednisolone. Tablet clonazepam, favipiravir, sodium valproate, antituberculosis	IV ceftriaxone, vancomycin, acyclovir, steroids, levetiracetam	Tablet chloroquine, lopinavir/ritonavir. IV acyclovir, levetiracetam, lorazepam. IM haloperidol	IV ceftriaxone, vancomycin, acyclovir, levetiracetam

CSF: cerebrospinal fluid, DWI: diffusion-weighted imaging, EEG: electroencephalography, FLAIR: fluid-attenuated inversion recovery, IM: intramuscular, IV: intravenous, LP: lumbar puncture, RBC: red blood cells, WBC: white blood cells.

However, the low sensitivity of the PCR test in the CSF may lead to negative results.[1] It is posited that the transcribial route is the possible source of infection by infecting the nasal cells, which then spreads to the CSF and brain via the olfactory nerve and olfactory bulb.[4] Viruses may also enter the brain through the increased permeability of the blood–brain barrier via cytokine production causing encephalitis.[4] Despite negative PCR results for the CSF, with pleocytosis and elevated protein in the CSF (like in our case), encephalitis is still possible due to an immune-mediated inflammatory mechanism with the absence of direct virus invasion.[4,5]

Clinicians should have a high index of suspicion of COVID-19-related neurological disorders during the current pandemic, since neurological manifestations can be the initial presentation of this viral disease, and to avoid delaying its management.[6] The outcome is favorable in COVID-19-associated encephalitis, and the possible role of high-dose methylprednisolone in this condition should be investigated. Table 1 summarizes our case and previously reported cases of PCR positivity for SARS-CoV-2 in the CSF.

Author Contributions

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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