



SARS-CoV-2 Neurotropism in a 12-Year-Old Filipino Boy with Focal Encephalitis

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Received: March 24, 2022

Revised: April 20, 2022

Accepted: April 20, 2022

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Since the onset of the coronavirus disease 2019 (COVID-19) pandemic, there have been reports of neurological manifestations of COVID-19, mostly in adults, albeit with a few cases described in children [1-3]. Several mechanisms have been proposed to explain how severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may induce neurological damage. There is emerging evidence supporting neurotropism and neuroinvasion in COVID-19, with polymerase chain reaction (PCR) testing of the cerebrospinal fluid (CSF) for SARS-CoV-2 yielding positive results in 6% to 13% of adult and pediatric patients according to a review of the literature [1,4,5].

This report discusses a case of focal encephalitis presenting with seizure and altered mental status following fever and mild respiratory illness associated with COVID-19. A notable aspect of this case was the detection of SARS-CoV-2 RNA in the CSF, despite its absence in two consecutive nasopharyngeal swab specimens. Written informed consent for publication was obtained from the patient's parents.

A previously well 12-year-old Filipino boy, presenting with a 2-day history of chills and undocumented fever, developed seizures and an altered sensorium on the 3rd day of illness. The seizures were described as focal motor right versive seizures with secondary generalization. He

arrived at a nearby hospital in active seizure and was given two doses of diazepam intravenously. Post-ictus, the patient was drowsy but arousable, able to follow commands, and oriented to place and person. The neurological examination was generally unremarkable, except for manual muscle testing of 3/5 on all extremities. A complete blood count was normal, and COVID-19 nasopharyngeal rapid antigen and dengue immunoglobulin G (IgG) and IgM tests were negative. A chest radiograph showed bilateral pneumonia. An axial helical non-contrast multi-detector computed tomography scan of the brain done on day 3 of symptoms revealed edema of the right hemisphere (Fig. 1).

Upon transfer to our institution, the patient was highly febrile with fine crackles on both lower lung fields. Further probing revealed exposure to his father, who had a recent fever and respiratory symptoms but was untested for COVID-19. The patient was drowsy but arousable and was able to follow commands, albeit with slowed responses. He had intact remote memory, good recall, and fair attention, with left central facial palsy, mild left pronator drift, and a positive Oppenheim test on the left. He did not present with sensory deficits or signs of meningeal irritation. Laboratory tests revealed elevated high-sensitivity C-reactive protein (9.94 mg/L) and procalcitonin.

tonin levels (30.96 µg/L). Ceftriaxone was started for pneumonia and levetiracetam to manage seizures. Two SARS-CoV-2 reverse-transcription polymerase chain reaction (RT-PCR) tests of nasopharyngeal swab specimens performed 48 hours apart were negative.

CSF analysis done on the 4th day of illness revealed increased opening and closing pressures, no pleocytosis, and normal protein and glucose levels. RT-PCR testing of the CSF for SARS-CoV-2 was positive. Aerobic culture, latex agglutination test, and viral studies for herpes simplex virus and Japanese encephalitis were negative. During the succeeding hospital days, the patient was more alert, with no new neurological deficits; however, his fever and respiratory symptoms did not improve. The management of COVID-19 was escalated according to local guidelines.

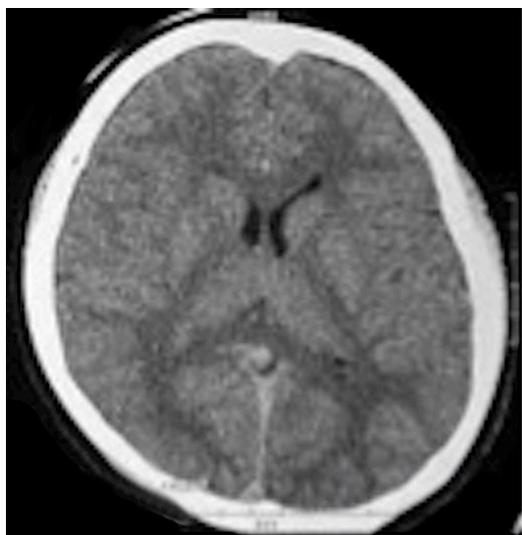


Fig. 1. Axial helical multi-detector computed tomography scan of the brain obtained on day 3 after symptom onset. There is subtle effacement of cortical sulci in the right cerebral hemisphere and mild compression of the right lateral ventricle. There was no hydrocephalus or cerebral herniation.

Electroencephalography showed slower background activity on the right. There was 2 to 3 Hz rhythmic delta activity seen in the right fronto-temporal head region, as well as occasional admixed spike discharges, with the highest electronegativity at right prefrontal electrode (Fp2). Occasional intermittent spikes, spike, and slow-wave discharges were also seen over the left frontal head region, with the highest electronegativity at left prefrontal electrode (Fp1).

Magnetic resonance imaging of the brain (Fig. 2) obtained on day 8 of symptoms showed findings consistent with meningoencephalitis commonly seen in viral diseases. The patient was discharged for home isolation with clinical improvement and afebrile status on the seventh hospital day. A neurological examination revealed more prominent facial asymmetry, spasticity of left-sided extremities, and, aside from left pronator drift, mild weakness of the left lower extremity. Physical rehabilitation was done after completing isolation, 3 weeks after admission. A quantitative COVID-19 antibody test via electrochemiluminescence immunoassay performed during follow-up in the 3rd week after illness onset was reactive for IgG anti-SARS-CoV-2 and non-reactive for IgM anti-SARS-CoV-2. A neurological examination 8 months after discharge showed resolution of motor deficits. The patient has since returned to school.

Although primarily considered a virus impacting the respiratory system, several case studies have highlighted substantial neurological sequelae of SARS-CoV-2 infection [1,2]. The most frequently reported neurological symptoms in pediatric patients were headache, altered mental status, seizures, muscular weakness, and meningism [1]. In a study by LaRovere et al. [3], neurological symptoms were broad and varied by age—seizures/status epilepticus were noted in younger patients, while anosmia, ageusia, headache, fatigue, and weakness were more frequent in older patients. Across all pediatric age groups, approximately one in four patients presented with confusion or altered sensorium. In the

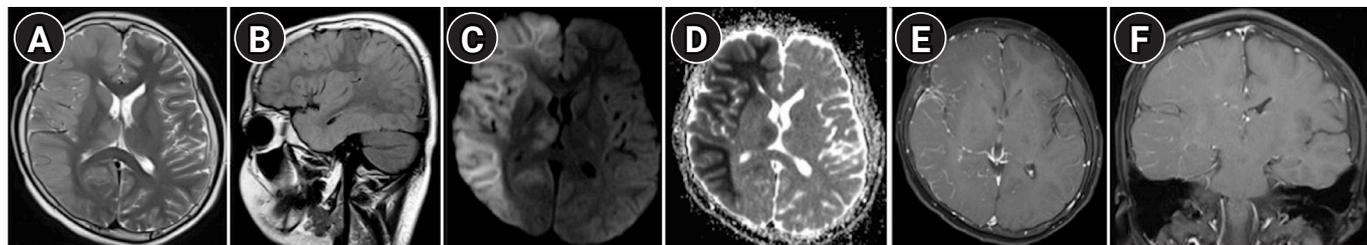


Fig. 2. Magnetic resonance (MR) imaging of the brain obtained on day 8 after symptom onset. (A) Axial T2-weighted and (B) sagittal T2-Fluid-attenuated inversion recovery MR images show abnormal hyperintense signals in the cortex-subcortex of the right cerebral hemisphere, head of the right caudate nucleus, and right thalamus. (C) Axial diffusion-weighted imaging and corresponding (D) apparent diffusion coefficient maps at the same level revealed restricted diffusion in the subcortical white matter of the right cerebral hemisphere. (E) Axial and (F) coronal post-gadolinium fat-suppressed T1-weighted imaging showed diffuse leptomeningeal enhancement in the right cerebral hemisphere.

Philippines, the most frequently reported symptoms are seizures, anosmia, and increased sleeping time. Patients are susceptible to seizures by various mechanisms. New-onset seizures can be triggered by metabolic derangements from systemic complications, while breakthrough seizures can occur in established epilepsy. Ischemic, inflammatory, or direct viral encephalitis can cause a structural insult to the brain, resulting in seizures, as seen in our patient.

Despite numerous reports of neurological manifestations in pediatric COVID-19, few studies have provided evidence to support the neurotropism of COVID-19 by detecting SARS-CoV-2 RNA in CSF. In a literature review by Carroll et al. [4], 13% of patients with COVID-19 and seizures had positive CSF SARS-CoV-2 PCR results, and in a review by Siracusa et al. [1], SARS-CoV-2 RNA in the CSF was only observed in two out of 26 (7.7%) pediatric COVID-19 patients with neurological manifestations, with one case associated with a negative RT-PCR nasopharyngeal swab. In a literature review by Lewis et al. [5] on CSF findings in the setting of COVID-19, CSF SARS-CoV-2 PCR was positive for 17 out of 303 patients (6%), all of whom had symptoms localized to the central nervous system (CNS).

The presence of SARS-CoV-2 RNA in the CSF, despite two negative nasopharyngeal swabs done 48 hours apart, is evidence of acute COVID-19 infection. The first nasopharyngeal swab was done on the 3rd day of symptoms. Kucirka et al. [6] reported that the sensitivity of RT-PCR was highest (80%) 3 days after symptom onset. The patient's second swab was done on the 5th day, with sensitivity still presumed to be high. It is still unclear why both swabs had negative results, despite the patient's respiratory symptoms. In the study by Lewis et al. [5], five out of 16 CSF-positive patients (31%) did not have a positive nasopharyngeal/oropharyngeal SARS-CoV-2 PCR test, but one had positive SARS-CoV-2 serum antibodies. It has been postulated that SARS-CoV-2 may be more persistent in the CNS because it is an immunoprivileged site [7].

In the Philippines, there have been no reports documenting SARS-CoV-2 in the CSF. The notable absence of SARS-CoV-2 in the CSF of most patients with neurological manifestations casts doubt on neurological manifestations resulting from direct invasion of the CNS. However, Lewis et al. [5] emphasized that CSF results change over the course of the patient's illness, as evidenced by patients who had more than one lumbar puncture performed. It has been suggested that the detection of viral neuroinvasion via a positive CSF PCR test is highest when the CSF is obtained 5 days after the onset of neurological symptoms [8]. Additionally, the sensitivity of viral detection via PCR testing is affected by the

virus's genetic variability and technical factors. Rapid CSF clearance, low titers, and the timing of collection also contribute to the challenge of isolating SARS-CoV-2 RNA from the CSF. Regardless, there must be a high index of suspicion for COVID-19 in patients with respiratory symptoms and neurological manifestations.

In our patient, aside from increased pressures, the CSF findings were otherwise normal. The absence of pleocytosis in general, and acellular CSF in particular, is atypical in the setting of viral encephalitis; however, Lewis et al. [5] reported that 10 out of 17 (59%) CSF SARS-CoV-2 positive patients lacked pleocytosis. There is the possibility of false-positive CSF SARS-CoV-2 PCR results in patients with acellular CSF. However, reports have described patients with positive CSF PCR for viruses such as enterovirus, echovirus, adenovirus, and herpes simplex virus in the absence of pleocytosis [9]. How the SARS-CoV-2 virus crosses the blood-brain barrier (BBB) is unclear. In a study by Zubair et al. [10], potential mechanisms of neuroinvasion included transsynaptic transfer across infected neurons, entry via the olfactory nerve, infection of the vascular endothelium, and leukocyte migration across the BBB. It has yet to be determined whether SARS-CoV-2 is transmitted directly to the CNS or carried to the CNS by infected circulating immune cells. It is also unclear whether its neurological manifestations are caused by direct replication in the CNS or neuronal injury promoted by virus-induced inflammation.

Previous reports have shown that positive findings for CSF SARS-CoV-2 PCR are infrequent, leading to the conclusion that neuroinvasion by SARS-CoV-2 may be rare. To the best of our knowledge, this is the first report in the Philippines of COVID-19-associated focal encephalitis in a child, supported by a positive result of SARS-CoV-2 RT-PCR in the CSF. The new-onset focal seizure and acute encephalopathy accompanied by definitive evidence of SARS-CoV-2 in the CSF highlights the neurotropism of SARS-CoV-2. The electroencephalographic and neuroimaging abnormalities found in our patient will necessitate follow-up to understand the impact of COVID-19 encephalitis on the neurodevelopment of affected children. More studies on pediatric COVID-19 patients with neurological symptoms are encouraged to further characterize SARS-CoV-2 as a potential emerging neurotropic virus.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contribution

Conceptualization: ADPC, MAAMV, and JROP. Data curation: ADPC and MAAMV. Formal analysis: MAAMV and JROP. Writing-original draft: ADPC. Writing-review & editing: ADPC, MAAMV, and JROP.

Acknowledgements

We would like to thank Dr. Eugene Lim and Dr. Lara Lim who provided insight and expertise that greatly assisted the research, and Dr. Christa Cuyegkeng for comments that greatly improved the manuscript.

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