**Acute COVID-19 Infection Associated With Necrotizing Disseminated Acute Leukoencephalopathy and Brain Microhemorrhages in a Pediatric Patient**

*Camila De Avila, MD, Luis F. Rauseo Lopez, MD, and Yamini Mandelia, MD*

**Abstract:** We present a case of a 14-year-old, previously healthy female, admitted with acute coronavirus disease 2019 infection and new-onset seizures secondary to virus-associated necrotizing disseminated acute leukoencephalopathy. Her symptoms resolved completely with intravenous immunoglobulin and steroids. Pathophysiology and prognosis of neurologic manifestations of coronavirus disease 2019 remain unclear.

**Key Words:** viral encephalitis, new-onset seizures, acute leukoencephalopathy

(Pediatr Infect Dis J 2021;40:e493–e496)

Acute coronavirus disease 2019 (COVID-19) infection most commonly causes acute respiratory and gastrointestinal disease; however, it has also been associated with a range of disorders of the peripheral and central nervous system (CNS). Literature has described a variety of neurologic and psychiatric clinical presentations associated with COVID-19 infection in adults, including anosmia, ageusia, headaches, dizziness, ataxia, psychosis, dementia, depression, anxiety, mania, acute encephalitis, seizures, meningitis, acute transverse myelitis, Guillain-Barré syndrome, trigeminal neuropathy, optic neuritis, ischemic or hemorrhagic acute cerebrovascular accident and venous sinus thrombosis. Conversely, neurologic repercussions associated with acute COVID-19 infection in children are not well defined.

In pediatric patients, most of the neurologic manifestations have been reported in those diagnosed with multisystem inflammatory syndrome in children, an uncommon but severe illness that develops as a result of a dysregulated inflammatory response after COVID-19 exposure. This report introduces a rare presentation of acute COVID-19 in the pediatric population, associated with new-onset seizures, brain microhemorrhages and virus-associated necrotizing disseminated acute leukoencephalopathy (VANDAL).

**CASE SUMMARY**

A 14-year-old, previously healthy female, presented to the emergency department with fever and status epilepticus. Patient had a fever for 2 days followed by 2 episodes of generalized tonic-clonic seizures 2 hours apart, each lasting 2–3 minutes, with response to seizure medications, but no complete recovery to neurologic baseline between episodes. No prior history of seizures or any neurologic condition was present for the patient. Review of systems was negative except for symptoms of acute presentation. Family history was noncontributory. Physical examination was remarkable for seizure activity and fever on presentation; no focal neurologic deficits were noted. The patient was treated with lorazepam and then loaded with levetiracetam with suppression of seizure activity. She also received vancomycin and ceftriaxone for concerns of bacterial meningitis. Head computed tomography was read as no acute intracranial pathology. Laboratory workup was significant for positive COVID-19 nasopharyngeal swab polymerase chain reaction (PCR) and elevated C-reactive protein. COVID-19 serology testing from cerebrospinal fluid (CSF) was unavailable, hence it could not be done. Other lab results included unremarkable complete blood count, comprehensive metabolic panel, procalcitonin and ferritin levels with a negative urine drug screen. CSF analysis was not consistent with bacterial meningitis. It revealed total nucleated cells of 4/μL with 7% neutrophils, 70% lymphocytes, and 23% monocytes; normal CSF glucose level at 75 mg/dL; and increased level of CSF proteins at 120 mg/dL. CSF culture and meningitis/encephalitis PCR panel which included herpes simplex virus were negative; hence antimicrobials were discontinued. A diagnosis of viral encephalitis was made clinically given the fevers, new-onset seizures and positive COVID PCR testing. Intravenous immunoglobulin (IVIG) and high-dose methylprednisolone were initiated with complete recovery and return to neurologic baseline within 24 hours. A 24-hour electroencephalography was negative for baseline epilepsy or further seizure activity. A brain magnetic resonance imaging with contrast was obtained and showed VANDAL, microhemorrhages and ventriculitis without hydrocephalus (Figures 1 and 2). A second lumbar puncture was not performed as patient recovered to her baseline without neurologic deficits. Following IVIG, patient remained afebrile with stable baseline neurologic examination; inflammatory markers down trended and she was discharged home in good condition on a steroid taper. At pediatric infectious disease follow-up 2 weeks after discharge, she continued to do well with no further seizure activity or neurologic deficits noted. Patient’s magnetic resonance imaging brain with/without contrast repeated 6 weeks after initial presentation showed complete resolution of prior findings (Figures 3 and 4).

**DISCUSSION**

This is a rare case of pediatric COVID-19 associated case of VANDAL and only second documented pediatric case of COVID-19 associated encephalitis. There have been only 22 documented cases of COVID-19 encephalitis in adults. While there is growing evidence to suggest that COVID-19 can have devastating neurologic effects, it remains unclear how COVID-19 invades the CNS.

Numerous theories have been suggested, including neurotropism via angiotensin-converting enzyme 2 or the SARS-CoV-2 spike protein that could target the CNS, employing an immune-mediated cytokine storm.

Furthermore, other factors can substantially increase the risk and
severity of CNS damage. For instance, neurologic complications, including leukoencephalopathy and brain microhemorrhages, have been reported in adults with hypoxemia related to severe respiratory COVID-19 illness. In children, the majority of neurologic manifestations have been documented in patients with multisystem inflammatory syndrome in children or patients with underlying neurologic conditions. Interestingly, our patient had no previous history of neurologic disorders and no respiratory manifestations or...

FIGURE 1. Diffuse relatively symmetric ill-defined T2 fluid-attenuated inversion recovery (FLAIR) hyperintensity around the fourth ventricle.

FIGURE 2. Diffuse relatively symmetric ill-defined T2 fluid-attenuated inversion recovery (FLAIR) hyperintensity along the ependymal surface of the lateral ventricles.
FIGURE 3. Resolution of the hyperintensity around the fourth ventricle on repeat imaging 6 weeks later.

FIGURE 4. Resolution of the hyperintensity along the ependymal surface of lateral ventricles on repeat imaging 6 weeks later.
complications associated with COVID-19, making her presentation even more difficult to explain.

So far, neurologic involvement in most pediatric patients has been reported as transient symptoms with resolution before discharge from hospital. In our case, following IVIG and high-dose methylprednisolone, the patient returned to neurologic baseline within 24 hours of initial presentation. Nonetheless, some patients have developed complex neurologic disorders with unfortunate outcomes, including death or subsequent neurologic deficits. VANDAL is an uncommon diagnosis and emphasizes the complexity and variety of manifestations of acute COVID-19 infection in children. The initial presentation is similar to meningitis, epilepsy, and other CNS disorders, which makes the diagnosis a challenge. Recognition and increased awareness of this condition is important for appropriate clinical management. The effects on long-term neurodevelopmental outcomes are unknown at this time as this is a rare case reported of VANDAL related to COVID-19 in children.

REFERENCES

1. LaRovere KL, Riggs BJ, Poussaint TY, et al; Overcoming COVID-19 Investigators. Neurologic involvement in children and adolescents hospitalized in the United States for COVID-19 or multisystem inflammatory syndrome. JAMA Neurol. 2021;78:536–547.

2. Montalvan V, Lee J, Bueso T, et al. Neurological manifestations of COVID-19 and other coronavirus infections: A systematic review. Clin Neurol Neurosurg. 2020;194:105921.

3. Ellul MA, Benjamin L, Singh B, et al. Neurological associations of COVID-19. Lancet Neurol. 2020;19:767–783.

4. Sharifian-Dorche M, Huot P, Osherov M, et al. Neurological complications of coronavirus infection; a comparative review and lessons learned during the COVID-19 pandemic. J Neurol Sci. 2020;417:117085.

5. Korahnik JJ, Tyler KL. COVID-19: a global threat to the nervous system. Ann Neurol. 2020;88:1–11.

6. Giordano A, Schwarz G, Cacciaguerra L, et al. COVID-19: can we learn from encephalitis lethargica? Lancet Neurol. 2020;19:570.

7. Abu-Rumeileh S, Abdelhak A, Foschi M, et al. Guillain-Barré syndrome spectrum associated with COVID-19: an up-to-date systematic review of 73 cases. J Neurol. 2021;268:1133–1170.

8. McAbee GN, Brosol Y, Pavlakis S, et al. Encephalitis associated with COVID-19 infection in an 11-year-old child. Pediatr Neurol. 2020;109:94.

9. Lin JE, Asfour A, Sewell TB, et al. Neurological issues in children with COVID-19. Neuroloq Lett. 2021;743:135567.

10. Dufort EM, Kounmans EH, Chow EJ, et al; New York State and Centers for Disease Control and Prevention Multisystem Inflammatory Syndrome in Children Investigation Team. Multisystem inflammatory syndrome in children in New York State. N Engl J Med. 2020;383:347–358.

11. Feldstein LR, Rose EB, Horwitz SM, et al; Overcoming COVID-19 Investigators; CDC COVID-19 Response Team. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med. 2020;383:334–346.

12. Lang M, Buch K, Li MD, et al. Leukoencephalopathy associated with severe COVID-19 infection: sequela of hypoxemia? Am J Neuroradiol. 2020;41:1641–1645.

13. Conde Cardona G, Quintana Pajario LD, Quintero Marzola ID, et al. Neurotropism of SARS-CoV-2: mechanisms and manifestations. J Neurol Sci. 2020;412:116824.

14. Baig AM, Khalqee A, Ali U, et al. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci. 2020;11:995–998.

15. Matsche J, Lütgehetmann M, Hagel C, et al. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. Lancet Neurol. 2020;19:919–929.

16. Buzhdygan TP, DeOre BJ, Baldwin-Leclair A, et al. The SARS-CoV-2 spike protein alters barrier function in 2D static and 3D microfluidic in vitro models of the human blood-brain barrier. bioRxiv. Posted June 15, 2020. doi:10.1101/2020.06.15.150912.