Encephalopathy With Akinetic Mutism in a Child With COVID-19 Infection: A Case Report

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ABSTRACT

Introduction: COVID-19 has been associated with neurological complications, including encephalopathy and akinetic mutism.

Case Presentation: A 7-year-old unvaccinated boy presented with visual hallucinations, urinary incontinence, and akinetic mutism 13 days after he was exposed to COVID-19. He had minimal respiratory symptoms, including just 1 day of fever and cough. Evaluations showed slowing on electroencephalogram, normal cerebrospinal fluid, normal brain magnetic resonance imaging, and mild sinus bradycardia. He recovered rapidly to baseline after 5 days of intravenous methylprednisolone.

Discussion: COVID-19-related encephalopathy including akinetic mutism is usually found in older adult patients with more severe COVID-19 illness. Our case demonstrates that akinetic mutism can present in children with mild COVID-19 illness and that it can respond rapidly and completely to intravenous methylprednisolone.

Conclusions: COVID-19-related encephalopathy may be immune mediated. A heightened awareness of its association with COVID-19 illness should lead to earlier diagnosis and consideration of immunomodulatory therapy.

INTRODUCTION

The SARS-CoV-2 virus has led to a pandemic of coronavirus disease 2019 (COVID-19), affecting more than 394 million people worldwide and 75 million in the United States as of February 7, 2022.[1] Children have represented approximately 17.4% of total cases in the United States.[2] In children with COVID-19, the most common presenting symptoms include fever, cough, and rhinorrea.[3]

Encephalopathy also can be seen in patients with COVID-19.[4-6] The hallmark of encephalopathy is an altered mental state, including some combination of a persistent altered level of consciousness, altered behavior, or cognitive dysfunction.[7]

Akinetic mutism is a form of encephalopathy where there is a marked reduction in spontaneous goal-directed motor activity and expressive language, not explainable by deficits in arousal or sensorimotor function and with preserved ability to respond briefly with vigorous and persistent prompting.[8]

Here we describe a boy who presented with akinetic mutism concurrently with COVID-19 infection. He additionally had simple visual hallucinations, sinus bradycardia, and urinary incontinence. He responded rapidly and completely to intravenous (IV) methylprednisolone.

CASE PRESENTATION

A 7-year-old unvaccinated boy was exposed to COVID-19 (hereafter day 1) in December 2021, at which time the Omicron Variant B.1.1.529 was the dominant strain among new cases.[9] He remained asymptomatic until day 13 when he reported to his parents that he saw "fuzzy spots" when looking out the window. Later, while playing with Legos, he was seen to struggle, and he joked, "I need glasses because I can't see just like Daddy." He developed a cough and fever of 102 °F before becoming somnolent. Vision returned to normal that same day. However, by that afternoon, he became less responsive and would answer questions only with much prompting and only by nodding his

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head or with 1- or 2-word responses. The next day (day 14), he was still somnolent but arousable. He was noted to stand listlessly with a blanket draped over him or to wander aimlessly around the house. He experienced urinary incontinence, after which he was unable to undress himself to shower. He had to be carried to the family car on the way to a community emergency department (ED). In the ED parking lot, he wandered off and walked into a parked car.

Past medical history revealed a prior diagnosis of Lyme disease 3 months earlier. Symptoms included fatigue, loss of appetite, and joint pain that resolved after completing a course of doxycycline. He was the twin product of an embryo transfer with donated egg and sperm. Development has been normal. He lives with his father, who is a truck driver, his mother, who is a homemaker, and his twin brother. He is homeschooled and doing well.

At the community ED, he was afebrile with stable vital signs. He remained nonverbal and would not obey commands from medical personnel. His laboratory values are detailed in Table 1. He was positive for SARS-CoV-2 by polymerase chain reaction (PCR). He was admitted overnight at the local hospital and received 1 liter of IV fluids, 2 grams of ampicillin/sulbactam, and 10 milligrams of IV dexamethasone. By the morning, his clinical picture had not improved, and he was transferred to our hospital, arriving on day 15.

Table 1. Laboratory and Imaging Results

Day Obtained	Test or Imaging	Result (Reference Range)
Day 14, outside hospital	ESR	26 mm/hour (0-15)
	C-reactive protein	1.1 mg/dL (0.0-0.9)
	SARS-CoV-2 (PCR)	Positive A
	Complete metabolic profile	Normal including ALT, AST
	Complete blood count	Normal
Day 15, outside hospital	Urinalysis	Normal
Day 16 (2nd day at our hospital)	Cerebrospinal fluid (CSF)	Clear, colorless White cells: 3 (≤ 10/uL) Red cells: 1 (< 1/uL) Protein 18 mg/dL (15-40) Glucose 59 mg/dL (40-80) Gram stain: no organisms seen Culture: no growth at 5 days
	CSF PCR film array	negative for *Escherichia coli* K1, *Haemophilus influenza, Listeria monocytogenes, Neisseria meningitides, Streptococcus agalactiae*, *Streptococcus pneumoniae*, cytomegalovirus, herpes simplex virus 1, herpes simplex virus 2, human herpes virus 6, human parechovirus, varicella zoster virus, *Cryptococcus neoformans*
	Autoimmune encephalopathy panel (CSF and blood)	Negative for informative autoantibodies (AMPA-R, Amphiphysin, AGNA Type 1, ANNA Type 1, ANNA Type 2, ANNA Type 3, CASPR2-IGG CBA, CRMP-5-IGG, DPPX AB IFA, GABA-B Receptor, GAD65 AB Assay, GFAP IFAF, IGLON5 IFA, LGI1-IGG CBA, MGLUR1 AB IFA, NIF IFA, NMDA-R AB, PCA, Type TR, PCA Type 1, PCA, Type 2)
	Oligoclonal band profile	Negative for oligoclonal bands
	Lyme, CSF	0.40 LIV (≤ 0.99)
	Myelin oligodendrocyte glycoprotein FACS assay, serum	Negative
	Fast stroke MRI/MRA with and without contrast	Normal
Day 20 (6th day at our hospital)	TSH	0.85 uIU/mL (0.35-4.94)
	Free T4	0.68 ng/dL (0.70-1.48)

Abbreviations: ESR, erythrocyte sedimentation rate; PCR, polymerase chain reaction; ALT, alanine transaminase ; AST, aspartate aminotransferase; LIV, Lyme index value; FACS, fluorescence-activated cell sorting; MRI, magnetic resonance imaging; MRA, magetic resonance angiogram; TSH, thyroid stimulating hormone.

On arrival, he remained somnolent but was arousable with verbal and gentle tactile stimulation. Respiratory status was normal. He remained nonverbal and would not obey commands from medical personnel but would respond to his father after vigorous prompting with head nods or 1- or 2-word responses. Visual tracking and motor function in all limbs were intact but were difficult to elicit. Square wave jerks were seen with attempted ocular smooth pursuit. He exhibited mild impairment with rapid alternating movements with both hands. He could move his legs and sit up independently, but spontaneous movements were scarce, and he did not obey requests to walk. The left tympanic membrane was perforated but nonerythematous. brain magnetic resonance imaging/magnetic resonance angiogram (MRI/MRA) was significant only for mucosal thickening in the paranasal sinuses, fluid in the left middle ear, petrous air cells, and mastoid air cells, without evidence of bony destruction or purulence. The brain itself was normal, including on perfusion sequences. Electroencephalogram (EEG) showed diffuse slowing in the delta range in the awake and drowsy states. Lumbar puncture performed under propofol sedation showed an elevated opening pressure of 31.5 cm H_2O (normal 10-25).

After the lumbar puncture, he was started on empiric ceftriaxone, vancomycin, and acyclovir. Topiramate 25 milligrams twice daily also was started due to the elevated opening pressure on lumbar puncture. Topiramate was discontinued after ophthalmologic examination revealed no papilledema. He was noted to have periods of bradycardia, with heart rates dropping as low as 48 beats per minute. A 12-lead electrocardiogram showed only sinus bradycardia. A cerebrospinal fluid (CSF) PCR film array for 13 viral, bacterial, and fungal causes of central ner-

vous system infection was negative (Table 1). With otherwise negative evaluations for infectious etiologies, a 5-day course of daily 30 mg/kg IV methylprednisolone was started on day 16. That same night after the first dose of IV methylprednisolone, he stayed up until the early morning hours and recited an entire Bible verse before going to bed. With each additional day during the course of IV methylprednisolone, he became more responsive and interactive with clinicians. By day 19, he was fully cooperative with exam and near normal in terms of language and spontaneous and elicited motor activity. Ocular smooth pursuit and tests of rapid alternating movements normalized, along with gait and tandem walk. He was able to identify the taste of raspberry versus orange sherbet and to identify the fragrance of cotton balls soaked in the essential oils of orange versus peppermint versus water. On day 20 after receiving the fifth dose of IV methylprednisolone, he was discharged home with a 9-day oral prednisone taper.

Table 2. Timeline of Treatments and Clinical Improvements by Day of Hospital Stay

	Day 13	Day 14[a]	Day 15[b]	Day 16	Day 17	Day 18	Day 19	Day 20[c]
Treatments *(dots denote corresponding treatment provided that day)*								
IV methylprednisolone				•	•	•	•	•
Topiramate				•	•	•		
Ceftriaxone			•	•				
Vancomycin			•	•				
Acyclovir			•	•				
Ampicillin/sulbactam		•	•					
Dexamethasone		•						
Clinical signs and symptoms (shaded box indicates it was present that day; gradient represents improvement, with lightest shading representing the closest return to baseline)								
Fever and cough	■							
Akinetic mutism	■	■	■	■	■	■	■	
Visual hallucinations	■							
Urinary incontinence		■	■	■	■			
Subtle cerebellar signs	*	*	x	x	■	■	■	■
Lethargy	■	■	■	■	■	■	■	■
Unable to follow commands	■	■	■	■	■	■	■	■

[a]Patient presents to community emergency department.
[b]Patient arrives at academic hospital.
[c]Day of discharge.
*Denotes that data were not available for that sign or symptom on that day.
x Denotes that it was not assessed that day.

On return visit on day 59, his mother reported that he had completely recovered back to normal in language, motor function, and behaviors by 2 weeks after going home, and that he had remained normal in every way since that time.

DISCUSSION

COVID-19-related encephalopathy has been previously described, typically associated with older age and more severe COVID-19 illness. In a retrospective review of 841 patients hospitalized with COVID-19 in a single province in Spain, Romero-Sanchez et al[6] found altered level of consciousness in 19.6%, which correlated with older age (>50 years) and more severe disease, as evidenced by increased need for intensive care unit-level care and mechanical ventilation. In a review of electronically available COVID-19 cases up to June 8, 2020, Garg et al[4] confirmed the association of COVID-19 encephalopathy with older age and more severe illness.

COVID-19 related encephalopathy in children appears to be less common. In a systematic review of COVID-19 in children, out of 3707 children identified with COVID-19, encephalopathy was a presenting sign in 25 (0.7%).[10] Abdel-Mannan et al described 4 children with severe COVID-19 who presented with fever and cardiovascular shock, who required mechanical ventilation and who, on extubation, were found to be encephalopathic.[11]

In a review of akinetic mutism in COVID-19, akinetic mutism appeared in 3 subgroups: (1) those with severe respiratory illness, (2) those with meningoencephalitis, and (3) those with delirium and preexisting neuropsychiatric illness.[8] Gaughan et al[12] described a 16-year-old female who presented with fever, sore throat, agitation, anorexia, paranoia, and formed visual and auditory hallucinations who evolved over an 8-day period into akinetic mutism. She was treated with intravenous immunoglobulin (IVIG) starting on hospital day 3 and then IV methylprednisolone starting on hospital day 8. Improvement began 4 weeks after admission, and on discharge home on hospital day 98, she still required help with self-cares.

In contrast, Bauer et al[13] described 2 adolescents who were COVID-19 positive by nucleic acid amplification test and who presented with delirium with minimal-to-no respiratory symptoms. Both patients improved after several weeks of treatment using alpha-2 agonists, dopamine antagonists, and melatonin; 1 patient was also treated with IVIG.

Our case is a companion case to the 2 cases described by Bauer et al,[13] in that COVID-19 symptoms were otherwise relatively mild in our case and in those described by Bauer et al.[13] The other described cases of COVID-19 encephalopathy and akinetic mutism were associated with severe COVID-19 disease, typically discovered after patients were extubated and failed to return to normal mental status. We suggest being alert to the possibility of COVID-19 encephalopathy, even with minimal to no other symptoms of COVID-19. While new onset urinary incontinence and EEG slowing are nonspecific indicators of encephalopathy, akinetic mutism, visual hallucinations, and

bradycardia[14] are somewhat unusual and may suggest COVID-19-related encephalopathy.

The timing of this patient's symptoms and the apparently rapid response to steroids suggest an immune-response etiology to COVID-19 encephalopathy. Others have also noted that steroids and IVIG can be helpful.[11,12,15] This report contributes to the growing body of literature describing atypical presentations of COVID-19 infection, particularly regarding neurologic manifestations in children, and the treatment options.

CONCLUSIONS

This report describes an unusual presentation of a child with mild COVID-19 symptoms and akinetic mutism, simple early visual hallucinations, urinary incontinence, and sinus bradycardia who had a rapid response to IV methylprednisolone. Clinicians should maintain an index of suspicion for COVID-19-related encephalopathy, even when COVID-19 symptoms are mild. We suggest consideration of high-dose steroid therapy and/or IVIG when a patient is past the acute infectious phase and, thus, the symptoms and time course are consistent with an immune-mediated etiology.

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REFERENCES

1. World Health Organization. WHO coronavirus (COVID-19) dashboard. Updated August 10, 2022. Accessed February 7, 2022. https://covid19.who.int/

2. American Academy of Pediatrics. Children and COVID-19: state-level data report. Updated August 8, 2022. Accessed January 15, 2022. https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/

3. Yasuhara J, Kuno T, Takagi H, Sumitomo N. Clinical characteristics of COVID-19 in children: a systematic review. *Pediatr Pulmonol.* 2020;55(10):2565-2575. doi:10.1002/ppul.24991

4. Garg RK, Paliwal VK, Gupta A. Encephalopathy in patients with COVID-19: a review. J *Med Virol*. 2021;93(1):206-222. doi:10.1002/jmv.26207

5. Paterson RW, Brown RL, Benjamin L, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain*. 2020;143(10):3104-3120. doi:10.1093/brain/awaa240

6. Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, et al. Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. *Neurology*. 2020;95(8):e1060-e1070. doi:10.1212/WNL.0000000000009937

7. National Institute of Neurological Disorders and Stroke. Encephalopathy information page. Updated July 25, 2022. Accessed January 15, 2022. https://www.ninds.nih.gov/health-information/disorders/encephalopathy

8. Fusunyan M, Praschan N, Fricchione G, Beach S. Akinetic mutism and coronavirus disease 2019: a narrative review. *J Acad Consult Liaison Psychiatry*. 2021;62(6):625-633. doi:10.1016/j.jaclp.2021.08.009

9. Wisconsin Department of Health Services. COVID-19: about variants. Updated July 26, 2022. Accessed April 30, 2022. https://www.dhs.wisconsin.gov/covid-19/variants-info.htm

10. Panda PK, Sharawat IK, Panda P, Natarajan V, Bhakat R, Dawman L. Neurological complications of SARS-CoV-2 infection in children: a systematic review and meta-analysis. *J Trop Pediatr.* 2021;67(3):fmaa070. doi:10.1093/tropej/fmaa070

11. Abdel-Mannan O, Eyre M, Löbel U, et al. Neurologic and radiographic findings associated with COVID-19 infection in children. *JAMA Neurol*. 2020;77(11):1440-1445. doi:10.1001/jamaneurol.2020.2687

12. Gaughan M, Connolly S, O'Riordan S, Tubridy N, McGuigan C, Kinsella JA. Pediatric parainfectious encephalitis associated with COVID-19. *Neurology*. 2021;96(11):541-544. doi:10.1212/WNL.0000000000011476

13. Bauer SC, Moral F, Preloger E, et al. Pediatric COVID-19 delirium: case report of 2 adolescents. *WMJ*. 2021;120:131-136.

14. Capoferri G, Osthoff M, Egli A, Stoeckle M, Bassetti S. Relative bradycardia in patients with COVID-19. *Clin Microbiol and Infect*. 2021;27(2):295. doi:10.1016/j.cmi.2020.08.013

15. Pugin D, Vargas MI, Thieffry C, et al. COVID-19–related encephalopathy responsive to high-dose glucocorticoids. *Neurology*, 2020;95(12):543-546. doi:10.1212/WNL.0000000000010354

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