Received: 25 January 2022 | Revised: 5 May 2022 | Accepted: 5 May 2022

DOI: 10.1111/epi.17293

Epilepsia®

BRIEF COMMUNICATION

Provoked seizures and status epilepticus in a pediatric population with COVID-19 disease

Apirada Thongsing | **Donya Eizadkhah** | **Cheryl Fields** | **Karen Ballaban-Gil**

Departments of Neurology and Pediatrics, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, New York, USA

Correspondence
Karen Ballaban-Gil, Isabelle Rapin Division of Child Neurology in the Saul R Korey Department of Neurology, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, USA.
Email: kballaba@montefiore.org

Abstract

We are reporting 16 pediatric patients (ages 0–18-years-old) who presented to our urban hospital emergency room with seizures and coronavirus disease 2019 (COVID-19) during the surge of the Omicron variant. There was an increased number of pediatric patients with seizures and COVID-19 during this period as compared to prior COVID-19 surges. The 16 patients ranged in age from 3 months to 12 years of age. Five of the 16 patients (31%) had a prior history of epilepsy. Eight patients (50%) presented in status epilepticus, and in six patients (38%) the seizures appeared to have focal features. Fourteen patients (88%) presented with a complex provoked seizure defined as exhibiting either focality, seizure >5 min in length, or more than one seizure in 24 h. We suggest that in the pediatric population, when compared to prior variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the Omicron variant is more likely to be associated with neurologic symptoms, including complex provoked seizures.

KEYWORDS

COVID-19, febrile seizure, febrile status epilepticus, provoked seizure, status epilepticus

1 | INTRODUCTION

The neurological manifestations of pediatric coronavirus disease 2019 (COVID-19) include headache, altered mental status, encephalopathy, and seizure.[1] In prior reports, seizure has typically been an uncommon event in pediatric COVID-19. For example, in a large 2020 study, only 11 (6%) of 175 children diagnosed with COVID-19 in an emergency department presented with seizures. In contrast, we noted an increase in seizures at presentation during a resurgence of COVID-19 cases[2] in New York City, primarily due to the Omicron severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant. We therefore examined the occurrence of seizures in children with COVID-19 during the recent Omicron variant surge in comparison to that seen in the two prior surges experienced at our urban institution in New York City.

2 | METHODS

This retrospective study was approved by the Montefiore Medical Center Institutional Review Board, which provided a waiver of informed consent. The My Reports tool in the Epic electronic medical record system was used to identify all patients seen at The Children's Hospital at Montefiore (CHAM) with positive polymerase chain reaction (PCR) for COVID-19 during the study time period. All charts of COVID-19-positive patients were reviewed to identify patients who had seizures at the time

of presentation. The 4-week study period during the Omicron COVID-19 surge (December 12, 2021 to January 7, 2022), as well as the comparison 4-week periods during the two prior COVID-19 surges, were chosen based on the peak numbers of COVID-19 patients seen across our hospital system since March 2020. The peak numbers were identified from hospital-distributed data reports of daily incidence of COVID-19 cases throughout the Montefiore Health System. The diagnosis of COVID-19 was confirmed for all patients by a positive reverse-transcriptase PCR (RT-PCR) assay from a nasopharyngeal swab sample. Some patients underwent cerebrospinal fluid (CSF) analysis, electroencephalography (EEG), and/or brain imaging. At the time of this study, COVID-19 vaccinations were available for children age 5 years and above.

3 | RESULTS

During the study period, 872 pediatric patients (ages 0–18 years) with COVID-19 infection were seen in the emergency department or admitted to CHAM. Of these 872 patients with COVID-19, 16 patients (1.8%) presented with clinical seizures. A total of 104 patients with COVID-19 required admission to the children's hospital, 11 (11%) of whom were admitted for seizure management. Demographic information and relevant neurologic history are summarized in Table 1. Clinical course and seizure semiology is summarized in Table 2.

For comparison, during the first surge of COVID-19 in New York City, from April 6, 2020 to May 3, 2020, a total of 38 pediatric patients presented to our children's hospital with COVID-19, two of whom (5%) presented with complex febrile seizures. During the second surge of COVID-19 in New York City, from January 29, 2021, to February 25, 2021, a total of 64 patients presented to our children's hospital with COVID-19; none of these patients had seizures.

The patients ranged in age from 3 months to 12 years of age. Four patients (25%) had a history of epilepsy. Eleven of the 16 patients (69%) were 4 years of age or younger and thus were not eligible for COVID-19 vaccination. Eight patients (50%) were female. All 16 patients tested positive for COVID-19 on viral PCR test and were negative for influenza A, influenza B, and respiratory syncytial virus (RSV), which are included on the same viral assay as the COVID-19 test. Two patients also had broader respiratory viral panels sent; one was positive for adenovirus and one was positive for human metapneumovirus. Eleven patients (69%) had fever defined as a temperature ≥100.5 °F during their intercurrent illness, either prior to presentation or during the hospital stay. Seven patients had a reported maximum temperature of 102 °F or higher. At the time of presentation, five patients were eligible for COVID-19 vaccination; however, none had a documented COVID-19 vaccination.

Three patients were born prematurely (between 31 and 34 weeks of gestation). The remaining 13 patients (81%) were born at term. Four patients (21%) had a prior history of febrile seizures and five patients (31%) had a prior history of focal epilepsy; seven patients (44%) had no prior history of febrile or afebrile seizures. Three of the five patients with epilepsy presented with seizures that were more prolonged than their typical seizures. Only one patient with epilepsy had an EEG completed during the admission; however, because this patient lives outside of the United States, no prior studies were available for comparison.

Eight patients (50%) presented with status epilepticus, defined as seizure activity lasting at least 5 min. Two (13%) of the 16 patients required intubation for status epilepticus. In six patients (38%) the seizures appeared to have focal features, including gaze deviation, head turn, or tonic or clonic movements of one extremity. Fourteen patients (88%) presented with a complex provoked seizure defined as exhibiting either focality, seizure >5 min in length, and/or more than one seizure in 24 h.

Eight patients (50%) required treatment with a benzodiazepine and/or a loading dose of intravenous (IV) antiseizure medications to stop their seizures. Of these eight patients, only two patients' seizures resolved following benzodiazepine administration; the other six required additional treatment with intravenous antiseizure medications, either levetiracetam or fosphenytoin. One patient continued to have clinical seizures despite fosphenytoin and required intubation, ultimately responding to propofol.

The length of hospital admission ranged from 0 to 8 days. Fifteen patients (94%) had other symptoms of COVID-19 either preceding or during their hospital course. Of these 15 patients, 14 had cough, congestion, and/or rhinorrhea, and one patient had emesis and diarrhea. One patient had a papular, blanching rash on his hands and feet in addition to upper respiratory symptoms, and was believed to clinically have coxsackie virus in addition to COVID-19. Eleven patients had laboratory investigations; of these 11 patients, 2 (18%) had an elevated white blood cell count to 19 and 27.8 thousand/μl. Six patients had a C-reactive protein (CRP) test; of these patients, one had an elevation in CRP to 1.3 mg/dl. One patient had both an elevated white blood cell count and elevated CRP; this patient was the youngest in the cohort (3-months-old) and presented with complex febrile seizures with multiple seizures in 24 h. Three patients had CSF samples collected, all with unremarkable white blood cell counts after correction for traumatic samples, normal glucose,

TABLE 1 Demographics and relevant neurologic history

Patient no.	Age	Sex	Prior seizure history	Gestational term	Other relevant neurologic history	Family history of seizures
1	3 months	M		Full term		
2	6 months	F	Febrile seizures	Full term		
3	14 months	F		Full term		
4	14 months	M	Focal epilepsy	Full term		
5	17 months	F		34 weeks, 3 days		
6	21 months	M	Febrile seizures	37 weeks		
7	23 months	F		37 weeks		
8	2 years	M	Febrile seizures	Full term	Global developmental delays, autism, known subcortical white matter signal abnormality on MRI	
9	2 years	M	Febrile seizures	Full term	Global developmental delays, history of HIE	
10	3 years	F		Full term		Yes
11	4 years	F		31 weeks, 5 days	Global developmental delays, known absence of septum pellucidum and small optic nerve on MRI	Yes
12	6 years	F	Focal epilepsy	Full term		
13	6 years	M	Focal epilepsy	Full term		Yes
14	7 years	M		33 weeks	Mild speech delay	Yes
15	10 years	F	Focal epilepsy	Full term	Speech and fine motor delays, history of right hemispheric stroke and venous sinus thrombus	
16	12 years	M	Focal epilepsy	Full term		Yes

Abbreviations: F, female; HIE, hypoxic-ischemic encephalopathy; M, male; MRI, magnetic resonance imaging.

and normal protein. Six patients had imaging studies completed during their hospitalization. Four of the six patients had computed tomography (CT) of the head without contrast, one had a brain magnetic resonance imaging (MRI) study without contrast, and one had a head ultrasound. All of these imaging studies were either normal or consistent with known structural lesions.

4 | DISCUSSION

During the Omicron surge, there was an increased number of COVID-19 infections in the pediatric population and a higher incidence of hospital presentation for seizures compared with prior 4-week period of COVID-19 surges in 2020 and 2021. During the 4 weeks of our study period, there were 872 pediatric COVID-19 cases, of which 16 presented with seizures. Similarly, in South Africa during the Omicron surge, there was an increase in pediatric hospitalizations as compared with previous waves, and ~20% of hospitalized children had convulsions.[3] However, they did not report the high number of complex febrile seizures and status epilepticus that we observed.

The pathophysiology of seizures in patients with COVID-19 is unclear. CSF sampling in two of our patients with status epilepticus was unremarkable and neuroimaging in six patients did not demonstrate new pathology. Reports of brain imaging in patients with acute COVID-19 are sparse, even in the adult literature. Due to concerns regarding the sedation of patients with active COVID-19 infection, as well as concerns about the potential contamination of imaging facilities, most hospitals performed neuroimaging studies in COVID-19 patients only if clinically necessary.

Previous studies reporting the occurrence of febrile seizures or status epilepticus in children with COVID-19 are scarce.[4,5] Notably, the majority of our patients (88%) had complex febrile/provoked seizures, with status epilepticus

TABLE 2 Clinical course and seizure semiology

Patient no.	Age	Days admitted	Fever	T_{max}	Intubation	Seizure type	Clinical Focality	Status Epilepticus	2+ seizures in 24 h	EEG results
1	3 months	4	Yes	105 °F		Complex febrile seizure	-	-	+	Normal
2	6 months	0	Yes	101 °F		Complex febrile seizure	-	+	-	
3	14 months	0	Yes	102.9 °F		Complex febrile seizure	-	-	+	
4	14 months	1				Simple provoked seizure	-	-	-	
5	17 months	6	Yes	104.5 °F	Yes	Complex febrile seizure	+	+	-	Normal
6	21 months	0	Yes	101.1 °F		Simple febrile seizure	-	-	-	
7	23 months	2	Yes	101.6 °F		Complex febrile seizure	+	-	-	
8	2 years	0	Yes	103 °F		Complex febrile seizure	-	-	+	
9	2 years	6				Focal provoked seizure	+	-	-	Electroclinical seizures originating from the right central region lasting <30 s each
10	3 years	2				Focal provoked status epilepticus	+	+	-	
11	4 years	8	Yes	103 °F	Yes	Complex febrile seizure	-	+	-	Background slow, disorganized, no focality
12	6 years	5	Yes	102.9 °F		Complex febrile seizure	+	+	-	Abundant left posterior quadrant spikes and polyspikes
13	6 years	1	Yes	101 °F		Complex febrile seizure	+	+	-	
14	7 years	3				Provoked status epilepticus	-	+	+	
15	10 years	0	Yes	107.1 °F		Provoked status epilepticus	-	+	+	
16	12 years	0				Provoked seizures	-	-	+	

Abbreviations: T_{max}, maximum recorded temperature.

occurring in 50% of our patients. In addition, 38% of our patients presented with focal seizures. Certain strains of viruses have an increased association with seizures. The pathophysiology of febrile seizures/provoked seizure in the pediatric population is unclear.[7] Most commonly, simple febrile seizures are seen in influenza A in Asian populations,[6–8] and human herpesvirus 6 (HHV-6) in American and European populations.[9] It is uncommon for children to present with febrile status epilepticus in the setting of a viral illness,[10] and focal seizures occur in only a small percentage of febrile seizures.[11] However, focal seizures have been reported in 13%–65% of children with benign convulsions with gastroenteritis, most frequently secondary to rotavirus or norovirus infections.[12] The mechanism underlying these focal seizures is unknown, but as our understanding of COVID-19 evolves, we may gain more insight into the mechanisms underlying how these gastrointestinal viral infections cause seizures.

It has been hypothesized that SARS-CoV-2 is not neurotropic but exerts its effects on the CNS via an inflammatory response. Research studies have failed to demonstrate COVID-19 viral PCR in the CSF of affected patients,[13] thus supporting the inflammatory response theory. In addition, biopsy samples of respiratory and nasal mucosa of patients with COVID-19 postmortem have found that the sustentacular cells (which support olfactory cells), rather than the olfactory nerve cells themselves, were infected with SARS-CoV-2, suggesting that the virus does not directly infect nerve cells.[14] Furthermore, there are reports of elevation of cytokines (interleukin 6 [IL-6], IL-10, and tumor necrosis factor α [TNFα]) in patients with intercurrent influenza and seizures as compared with patients with influenza without seizures,[7] suggesting that the inflammatory response is possibly the main driver of these illness-related seizures. The mechanism of provoked seizures in children with COVID-19 may similarly be related to this inflammatory response.

5 | SUMMARY

As the COVID-19 pandemic continues, this case series brings awareness to the risk of seizures associated with COVID-19 in pediatric patients. We observed an increase in seizures in our pediatric patients with COVID-19 related to the Omicron variant, as compared to prior surges. In particular, a concern is the higher rate of complex febrile seizures and status epilepticus in these patients. Given that the long-term outcome in pediatric patients presenting with febrile seizures or status epilepticus in the setting of COVID-19 is unknown, clinicians should be aware of this risk and follow these children closely as the pandemic continues.

ACKNOWLEDGMENT

The authors acknowledge with gratitude the clinical staff of the Pediatrics and Neurology Departments for their excellent technical expertise and dedication to patient care during the COVID-19 pandemic.

AUTHOR CONTRIBUTIONS

All authors participated in study design and conceptualization of the study. Drs. Thongsing, Eizadkhah, and Fields participated in data collection. Drs. Thongsing, Eizadkhah, and Fields participated in the analysis or interpretation of the data. All authors participated in the drafting or revising of the manuscript for intellectual content.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

ORCID

Apirada Thongsing https://orcid.org/0000-0001-6248-7625

REFERENCES

1. Lin JE, Asfour A, Sewell TB, Hooe B, Pryce P, Earley C, et al. Neurological issues in children with COVID-19. Neurosci Lett. 2021;743:135567.
2. Kurd M, Hashavya S, Benenson S, Gilboa T. Seizures as the main presenting manifestation of acute SARS-CoV-2 infection in children. Seizure. 2021;92:89–93.
3. Cloete J, Kruger A, Masha M, du Plessis NM, Mawela D, Tshukudu M, et al. Rapid rise in paediatric COVID-19 hospitalisations during the early stages of the Omicron wave, Tshwane District, South Africa. medRxiv. 2022;5:294–302. https://doi.org/10.1101/2021.12.21.21268108.
4. Chegondi M, Kothari H, Chacham S, Badheka A. Coronavirus disease 2019 (COVID-19) associated with febrile status epilepticus in a child. Cureus. 2020;12(8):e9840.
5. Dewiyanti L, Sumarni N, Lie JD, Hidajati Z, Kahayana HP, Lukmasari A, et al. Children with COVID-19 who manifest febrile seizure. Case Rep Med. 2021;2021:9992073.
6. Shinnar S, Glauser TA. Febrile seizures. J Child Neurol. 2002;17(Suppl 1):S44–52. https://doi.org/10.1177/08830738020170010601. PMID: 11918463.
7. Kawada J-I, Kimura H, Ito Y, Hara S, Iriyama M, Yoshikawa T, et al. Systemic cytokine responses in patients with influenza-associated encephalopathy. J Infect Dis. 2003;188(5):690–8. https://doi.org/10.1086/377101
8. Chiu SS, Tse CY, Lau YL, Peiris M. Influenza A infection is an important cause of febrile seizures. Pediatrics. 2001;108(4):E63. https://doi.org/10.1542/peds.108.4.e63. PMID:11581471.
9. Hall CB, Long CE, Schnabel KC, Caserta MT, McIntyre KM, Costanzo MA, et al. Human herpesvirus-6 infection in children. A prospective study of complications and reactivation. N Engl J Med. 1994;331(7):432–8. https://doi.org/10.1056/NEJM199408183310703. PMID: 8035839.
10. Gupta A. Febrile seizures. Continuum (Minneap Minn). 2016;22(1, Epilepsy):51–9. https://doi.org/10.1212/CON.0000000000000274. PMID: 2684473013.

11. Verity CM, Ross EM, Golding J. Outcome of childhood status epilepticus and lengthy febrile convulsions: findings of national cohort study. BMJ. 1993;307(6898):225–8. https://doi.org/10.1136/bmj.307.6898.225
12. Kang B, Kwon YS. Benign convulsion with mild gastroenteritis. Korean J Pediatr. 2014;57(7):304–9. https://doi.org/10.3345/kjp.2014.57.7.304. Epub 2014 Jul 23. PMID: 25114690; PMCID: PMC4127392.
13. Neumann B, Schmidbauer ML, Dimitriadis K, Otto S, Knier B, Niesen W-D, et al. Cerebrospinal fluid findings in COVID-19 patients with neurological symptoms. J Neurol Sci. 2020;418:117090. https://doi.org/10.1016/j.jns.2020.117090
14. Khan M, Yoo S-J, Clijsters M, Backaert W, Vanstapel A, Speleman K, et al. Visualizing in deceased COVID-19 patients how SARS-CoV-2 attacks the respiratory and olfactory mucosae but spares the olfactory bulb. Cell. 2021;184(24):5932–49.e15. https://doi.org/10.1016/j.cell.2021.10.027. Epub 2021 Nov 3. PMID: 34798069; PMCID: PMC8564600.

How to cite this article: Thongsing A, Eizadkhah D, Fields C, Ballaban-Gil K. Provoked seizures and status epilepticus in a pediatric population with COVID-19 disease. Epilepsia. 2022;00:1–6. https://doi.org/10.1111/epi.17293