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Seizures as the main presenting manifestation of acute SARS-CoV-2 infection in children☆

Mohammad Kurd [a,1], Saar Hashavya [b,c,1], Shmuel Benenson [b,d], Tal Gilboa [a,b,*]

[a] Pediatric neurology unit, Hadassah medical center, Jerusalem, Israel
[b] School of medicine, the Hebrew university of Jerusalem, Israel
[c] Pediatric emergency department, Hadassah medical center, Jerusalem, Israel
[d] Unit for Infection Prevention and Control, Hadassah medical center, Jerusalem, Israel

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SUMMARY

Objectives: To explore the rate, characteristics, risk factors, and prognosis of children presenting with seizures as the main symptom of acute COVID-19 (coronavirus disease 2019).
Methods: We conducted a systematic retrospective study to identify all children who presented to the emergency departments of a tertiary academic medical center between March 1st and December 31st 2020 and had a SARS-CoV-2 infection based on RT-PCR (reverse transcription-polymerase chain reaction) from nasopharyngeal swab. Clinical and demographic data were extracted from the electronic medical records and reviewed.
Results: Total of 175 children were diagnosed with acute SARS-CoV-2 infection in the emergency departments during the study period. Of those, 11 presented with seizures. Age ranged from six months to 17 years and 4 were girls. Five presented with status epilepticus and responded to loading doses of anti-seizure medications. Six had fever. Seven had prior history of neurological disorder. Full recovery was the rule.
Significance: Unlike in adults, seizures occur early and may be the main manifestation of acute COVID-19 in children. Seizures, including status epilepticus, may occur without fever even in children with no history of epilepsy and are not associated with severe disease. A high index of suspicion is required for early diagnosis thus infection control measures can be taken.

Introduction

The novel coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 is more likely to cause symptomatic disease in adults than in children. If symptoms do occur, they are often milder compared to those of adults. The main symptoms in children are fever and mild respiratory symptoms [1–5]. Several studies describing the manifestations of acute COVID-19 in children did not report any neurological manifestations, for example, out of 2,306 pediatric patients from China and 81 from Singapore, none reported neurological symptoms [1,2,4]. Non-specific headache, drowsiness, myalgia, and fatigue were reported in 13% of 197 Italian children and 6.6–12% of 1,695 American children and adolescents [3,6,7].

The main central nervous system manifestations described in adults with acute COVID-19 included stroke, transient ischemic attack, alteration in mental status, and seizures. Though the possible link between seizures and acute COVID-19 was suggested previously, in most cases, seizures are not the presenting symptoms and they occur in patients with severe COVID-19 during the course of admission [8–11]. One study reported seizures in 5.5% of children presenting at emergency departments in the United Kingdom, though no cases of status epilepticus are mentioned [12]. Another study reported seizures in 5.4% of children admitted due to COVID-19 and multisystem inflammatory syndrome in the United States, however, the reason for admission, time of seizure occurrence, and disease severity of those with seizures were not reported [7]. There is still a paucity of information regarding the prevalence and characteristics of seizures in children with COVID-19.

This study aimed to describe the clinical, demographic, laboratory, neurophysiological, and imaging characteristics of children who presented at the emergency department (ED) with seizures and acute SARS-

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* **Corresponding author –** Tal Gilboa, Pediatric neurology unit, Hadassah medical center, Jerusalem, Israel 91200
E-mail address: talg@hadassah.org.il (T. Gilboa).
[1] contributed equally

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CoV-2 infection.

Study design, methods and patients

This retrospective observational study was conducted and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE), and Enhancing the QUAlity and Transparency Of health Research (EQUATOR) guidelines. We conducted a systematic search of the computerized medical records of the Hadassah Medical Center (HMC) to identify all children (age 0-18 years) who presented at one of the 2 HMC emergency departments (ED) with seizures and had a confirmed diagnosis of acute SARS-CoV-2 infection based on reverse transcription-polymerase chain reaction (RT-PCR) for SARS-CoV-2 from nasopharyngeal swab between 1/3/2020 and 31/12/2020. HMC policy requires PCR testing for all children who present at the ED and require admission, regardless of their symptoms, as well as those who present with symptoms and signs consistent with acute COVID-19 including altered mental status, seizures and syncope.

We used a computerized search to identify all eligible participants from the medical records' archive, using the terms COVID-19 and SARS-CoV-2. We also searched the infectious diseases database to identify all children 0-18 years who had a positive RT-PCR for SARS-CoV-2 during the study period. We cross-referenced the lists to verify the diagnoses and exclude duplicate records. We then searched the medical records of all identified patients to include children who presented to the ED with seizures. The inclusion criteria were positive PCR for SARS-CoV-2 and a clinical diagnosis if seizures. The exclusion criterion was absence of significant information from the medical records.

Demographic data, clinical presentation, admission laboratory findings, management, in-hospital course, imaging findings, electroencephalography (EEG) results, and discharge recommendations were assessed. We defined fever if the measured temperature was $\geq$38 °C at the ED or within 24 h before or after the admission.

Seizures were diagnosed clinically. According to the ILAE definitions [13], we defined status epilepticus (SE) as generalized convulsions lasting more than 5 min or recurrent seizures without full recovery between them or focal convulsion with impaired awareness lasting more than 10 min. Diagnoses of epilepsy, cerebral palsy, intellectual disability, genetic disorders with impaired cognition, autism, malformations of the central nervous system, brain tumors, and any acquired neurological disease (such as demyelinating disease) were defined as an underlying neurological disorder.

The study protocol was designed by the investigators and received approval from the Institutional Review Board (IRB) of the participating institution, IRB number 0783-20-HMO.

We reported median ± standard deviation (SD) for quantitative variables and frequencies and relative frequencies for qualitative variables. We compared the demographic and clinical characteristics with an independent sample *t*-test, Chi-Square, and Fisher's exact test, as appropriate.

Results

Between March 1st and December 31st, 2020, 175 children (age range 0–18 years) presented to the ED and were diagnosed with acute SARS-CoV-2 infection by RT-PCR from a nasopharyngeal swab. Of those, the reason for ED admission was seizures in 11 children (6%).

Table 1 describes the demographic data of the entire cohort (175 children). There were no differences between those who presented with seizures (11 patients) and those who presented with other complaints (164 children) in regards to age, gender, admission length, and ethnic origin. The only significant difference was the rate of prior neurological disorder which was significantly higher in those who presented with seizures ($p < 0.00001$).

During the study period, total of 22,211 visits in the pediatric ED were recorded, including 592 seizure-related visits. Compared to the corresponding period in 2019, there was 26% decline in all visits and 27% decline in seizure-related visits.

Table 1
– Entire cohort demographic data.

	Seizures (n = 11)	No seizures (n = 164)	
Age – median	11.5y	7.8y	NS*
mean (SD)	10.3 (±5. 94)	7.9 (±6.5)	t-test
range	0-17	0-18	
Male / Female	7 / 4	82 / 82	NS*
PMH# -	7 (63%)	15 (9%)	p<
neurological			0.00001
Admission length	3.2 days	2.7 days	NS*
Ethnic$ (A/J)	9 / 2	91 / 73	NS*

NS* non-significant
PMH# past medical history
ethnic$ (Arab / Jewish)

The clinical, laboratory, and imaging findings of the patients who presented with seizures are presented in Table 2. Age ranged from 5 months to 17 years (median 11.5y ±5.9) and four were girls.

Clinical course

Seven children had a temperature of $\geq$38 °C, however, no other typical signs and symptoms of acute COVID-19 were reported in our cohort. None of the children required ventilatory or hemodynamic support. All patients maintained an oxygen saturation of >92% in room-air and showed no signs of COVID-19 lung involvement. Once the seizure resolved, none of the children received supplemental oxygen support. All children were admitted for observation, had an uneventful course and were discharged within 2–6 days (mean 3.09 ± 1.7, median 2). As per HMO policy, the four patients with SE who responded to the first loading dose medication and regained full consciousness while in the ED, were admitted to the regular pediatric COVID-19 ward. One patient (#7) required loading doses of two anti-seizure medications to control his SE, thus was admitted to the intensive care unit for overnight observation.

Nine of the 11 children (82%) presented with generalized tonic-clonic seizures. One child with prior history of uncontrolled epilepsy with multiple seizure types had a focal tonic seizure. The youngest patient, a 5-month-old infant, presented with bilateral asymmetrical tonic-clonic seizure.

Five children presented with convulsive SE; none had a history of prior SE, and one had no history of seizures at all. All five received an appropriate dose of midazolam. One patient responded and the other four required loading doses of anti-seizure medications (ASMs), with successful control of the seizures. Phenobarbital was used in one (5 months of age), valproic acid (VPA) in two, and levetiracetam (LEV) in two.

Seven children had a prior history of neurological disorder; five had epilepsy, one had a single unprovoked seizure 3 years before his admission and one had intellectual disability. Three had uncontrolled seizures despite appropriate medical treatment with ASMs. Patient number 7 had epilepsy with rare seizures (2 per year) and was not taking medications. Four children were taking ASMs in appropriate dosages prior to admission; one was on valproic acid (20 mg/kg/day) and his drug level upon ED admission was 72 mcg/mL (within therapeutic range). Two children were taking levetiracetam (50–60 mg/kg/d), and one was taking both levetiracetam (30 mg/kg/day) and lamotrigine (6 mg/kg/day). Unfortunately, our lab cannot measure the level of these medications.

Family history of febrile seizures, but not epilepsy, was reported in two children, 2 and 9 years old, who never had seizures before. Both had fever >39°c at the time of admission.

Table 2
– Patients presenting with seizures: clinical and laboratory data.

	Age	Temp	G	Seizure	PMH / FH- Neurological	Laboratory	Imaging / EEG
1	0.4	39	F	SE, bilateral tonic clonic, RT > LT		NA 133 K 4.4 WBC 6.3 CRP 0.38 LP - Normal	EEG - normal
2	2.2	39	M	GTC SZ	FH - father + uncle febrile SZ	NA 132 K 3.9 WBC 22.8 CRP 5.8	
3	5.1	36	F	GTC SE	uncontrolled epilepsy (1/month) on LEV (60 mg/kg/day) Congenital CMV	NA 135 K 3 WBC 5.3 CRP – not tested	EEG - epileptic encephalopathy
4	7	37	M	2 GTC SZ		NA 136 K 3.6 WBC 9.1 CRP – not tested	
5	9	39	M	GTC	FH - febrile SZ	NA 131 K 3.7 WBC 8.3 CRP 3.65 LP - 100 RBC, 0 WBC	CT - Normal
6	11.5	37	M	GTC	Single unprovoked GTC 3 years prior to presentation	NA 135 K 4.1 WBC 15.5 CRP 0.11	EEG - Normal
7	13.1	39	M	GTC SE	epilepsy, rare seizures (2/year) ASD and ID	NA 136 K 3.2 WBC 9.3 CRP 2.2	
8	14.8	36	M	Focal tonic	uncontrolled epilepsy on LEV (30 mg/kg/day) + LMG (6mg/kg/day)	NA 137 K 3.5 WBC 10.1 CRP – not tested	
9	15	38	F	GTC	ID, cataract, prematurity 32weeks	NA 134 K 3.9 WBC 9.5 CRP 0.05	EEG – bifrontal sharp waves
10	17.2	38	M	GTC SE	CP with VPS, prematurity 28weeks uncontrolled epilepsy (few mild SZ /week, no GTC 2 years) on LEV (50/mg/kg/day)	NA 140 K 3.7 WBC 12.8 CRP 0.07	CT – shunt, PVL, no change from past imaging
11	17	38.5	F	GTC SE	IVH with VPS Controlled epilepsy On VPA (30 mg/kg/day)	NA 132 K 3.2 WBC 10 CRP 0.05 VPA - 72	CT – shunt, no change from past imaging

T – temperature, G – gender, PMH – past medical history, FH – family history, SE – status epilepticus, GTC – generalized tonic clonic, RT – right, LT – left, ASD – autism spectrum disorder, ID – intellectual disability, CMV – cytomegalovirus, LEV – levetiracetam, LMG – lamotrigine, VPA – valproic acid, LP – lumbar puncture, VPS – ventriculoperitoneal shunt, IVH – intraventricular haemorrhage, CRP - C-reactive protein, WBC – white blood cells, EEG – electroencephalography, CT – computerized tomography, PVL – periventricular leukomalacia. NA and K in mmol/L, WBC - x10E^9/L, CRP - mg/L, VPA - mcg/mL

Laboratory tests

Laboratory tests (presented in Table 2) were within normal range in the majority of patients. Leukocyte count was within normal range in eight children (range 3.79-10.33 10E^9/L). C-reactive protein (CRP) was measured in 8 and was mildly elevated in three. Mild hyponatremia (Na 131-133 MMOL/L) was recorded in 5 children and non-clinical hypokalemia (K 3-3.4 MMOL/L) was noted in two.

Two patients, a 5-month-old (patient #1) who presented with SE and a 9-year-old (patient #5) with fever and nuchal rigidity, underwent a lumbar puncture (LP) which showed no sign of infection or inflammation. In both cases the cerebrospinal fluid (CSF) bacterial culture and PCR for common encephalitis pathogens (including Herpes 1 and 2 and enteroviruses) were negative. The CSF was not tested for SARS-CoV-2.

Imaging and electroencephalography

Urgent computerized tomography was performed in three patients; one was normal and two showed previously known findings: periventricular leukoencephalopathy, hydrocephaly, and ventriculoperitoneal shunt. No new findings were noted.

Four children underwent an electroencephalography (EEG) test during the course of admission; two had normal EEG, one had non-specific encephalopathy (similar to his previous EEGs) and one patient, without prior history of epilepsy, had bifrontal sharp waves (patient #9).

Follow up

Six children were seen after discharge (mean 8.3 ± 6.2 weeks, range 1–17 weeks) in one of our campuses, either in an outpatient clinic or in the ED. Since their admission due to COVID-19, two of the six had subsequent seizures: one child had prior history of uncontrolled epilepsy (patient #10) and the other (patient #6) had a single unprovoked seizure three years before he presented with SE due to COVID-19.

Discussion

As the COVID-19 pandemic evolves, reports of a spectrum of neurological syndromes among patients, adults and children, infected with SARS-CoV-2 are emerging. To the best of our knowledge, this is the first study describing the clinical and demographic characteristics of a cohort of children presenting with seizures due to acute SARS-CoV-2 infection. Our findings suggests, that seizures may be the initial and primary manifestation of COVID-19 in children, especially, but not exclusively, in those with a history of neurological disorder, and possibly in children older than 5 years of age. While in our cohort a favorable response to treatment was seen in all cases, further follow up is required to determine the long-term prognosis.

We identified 11 children who presented to the ED due to seizures and diagnosed with acute COVID-19, out of 175 children diagnosed in the ED with acute COVID-19 (6%). Our cohort is similar to other cohorts describing the clinical presentation of acute COVID-19 in pediatric

patients in regards to age and comorbidities, however, most studies did not report seizures [1,4,6,14]. The population in these studies is diverse and ranges from asymptomatic children who were tested due to exposure to patients with influenza-like symptoms admitted to the hospital. Seizures were not reported even in 2 meta-analyses, covering over 7,700 children reported in both retrospective studies and case reports worldwide [5,15]. In a study describing the symptoms of children presenting at the ED in the United Kingdom, the rate of seizures was 5.5%, similar to the rate in our cohort [12].

The indication for testing children in the ED for acute COVID-19 varies among different centers and changed during the course of the pandemic [1,4]. In some centers only children with influenza-like symptoms or close contact with confirmed COVID-19 patient were tested [1,4,6,16]. It is possible that the differences in the reported rates of seizures is due to different inclusion criteria for each study. Other possibilities may be differences in viral strains and genetic predisposition in different populations.

Studies in the adult population with COVID-19 reported seizures in 0–2% of the patients. The majority suffered from severe disease and the seizures were usually not the presenting symptom [8,17–20]. Serious neurological manifestations related to COVID-19 infection in children were reported mainly in the setting of multisystem inflammation syndrome (MIS), or severe disease, however, seizures were rarely reported [3,10,21–23]. All of our patients had seizures as the presenting sign of infection and none had severe COVID-19. Moreover, no further seizures occurred during their admission.

Prior neurological disorder was reported in our cohort in 22/175 (12%) children, and in 4–11% in other studies [7,12,24]. Similar correlation was reported previously in adults; history of epilepsy was documented in 46% of adults admitted with acute COVID-19 and had seizures (either at presentation or later in the course) but in only 12% of those who did not have seizures during their admission [8]. We found that those who presented with seizures, had a higher prevalence of prior neurological disorder, especially epilepsy, compared to those who presented with other symptoms (7/11 (64%) versus 15/164 (9%) $p < 0.00001$). LaRovere et al reported prior neurological disorder in 22% of children with neurological involvement (not necessarily seizures), and 8% in those admitted without neurological involvement [7].

Five children in our cohort presented with convulsive SE. This was rarely reported before [10]. In a series of five patients with seizures and severe acute COVID-19, two had SE, one of them was a 2.9-year-old with fever and severe respiratory disease who required multiple medications, ventilatory support and had intracranial mass and hemorrhage and the other was an HIV adult who died due to severe COVID-19 [25]. Three children with prior history of epilepsy, who presented with SE and acute COVID-19 were reported in two separate case reports [11,26]. In a study reporting neurological manifestations of COVID-19 in adults, six had seizures but none had SE [17]. Other studies did not report SE separately from seizures; thus, it is possible that SE happened in other cohorts but data is lacking.

For all five children in our study who presented with SE, including those with known uncontrolled epilepsy, this was their first episode of SE. Moreover, though this did not reach statistical significance, those who presented with seizures tend to be older than those who presented with other complaints. The mean age was 10.3 and 7.8 and the median age was 11.5 and 7.9 of those who presented with seizures and those who presented with other complaints, respectively. Though young age, especially under 12 months, is a known risk factor for SE [27], 4 of our 5 patients with SE were 5–17 years of age. Interestingly, in a cohort of 225 children presenting with febrile seizures and evidence of respiratory viral infection between 2013 and 2017, coronaviruses were associated with seizures in children ages 3–6 years but not 0.5–3 years [28]. In accordance to our findings, Brisca et al reported two girls, five and 11 years old, with prior history of well controlled epilepsy, who presented with fever and prolonged seizures due to SARS-CoV-2 infection [11]. It is possible that unlike other viral illnesses, that tend to cause seizures in infants and toddlers, SARS-CoV-2 and other coronaviruses tend to cause seizures in older children. A larger cohort is needed to test this observation. The pathogenesis of seizures during coronavirus infection is probably not due to direct invasion of the virus into the brain. Even in patients who presented with clinical or laboratory signs of encephalitis the virus is almost never recovered from the CSF [8,29].

The outcome of all SE cases was excellent; All five were treated with appropriate dose of midazolam. One responded to midazolam, three ceased after a loading dose of one ASM, and one required loading doses of two ASMs. Our results are in concordance with the findings of the ESETT study where the success rate of aborting SE refractory to benzodiazepines with a loading dose of VPA or LEV in children was 52% (41–62) [30].

Of the 11 children with seizures, fever (>38°c) was recorded in 54% (6/11). Several studies reported fever in 32 to 100% of children with acute COVID-19, however, the rate of fever in children with seizures, when occurred, was not mentioned [1,12,14,16,17,22]. Though not as common as febrile seizures, non-febrile illness seizures do occur in children, mostly in those under three years of age with rhinorrhea, cough or diarrhea [31]. Unlike the pathophysiology of febrile seizures which is partly understood, the pathophysiology of non-febrile illness seizures is yet to be elucidated. Evidence from animal models supports neuronal hyperexcitability by conformational changes as well as fever and glutamate release by cytokines like IL-1b, produced by the immune system [32]. As seen in our patients, blood markers of inflammation, including WBC and CRP are often normal or mildly elevated in children with COVID-19 [12,22]. Non-febrile illness seizures may be immune mediated in children who are genetically prone to seizures, and it is possible that specific pathogens may stimulate the production of cytokines that do not cause fever but decrease the seizure threshold.

Reports of brain imaging in patients with acute COVID-19 are sparse even in adults. Due to concerns regarding contamination of imaging facilities, such studies were done in many centers, only if necessary [18]. Even when such studies were performed, the findings were not reported [8]. Three of our patients had brain imaging, none showed relevant findings. An infant with a-febrile seizures and no signs of inflammation in the CSF had a normal brain CT and magnetic resonance imaging (MRI) [22]. Splenium signal changes were seen in 4 patients with pediatric MIS on MRI [33]. The pathophysiology leading to such changes is unclear. Currently, neither evidence of viral invasion into the brain, nor existence of autoantibodies such as anti- N-methyl-D-aspartate receptor, anti-myelin oligodendrocyte glycoprotein, and anti-aquaporin-4 were shown [33].

There is still paucity of information in regards to EEG patterns in acute COVID-19. Four of our patients underwent EEG and only one (patient #9) had sharp bi-frontal activity. EEG findings in patients with acute COVID-19 were reported systematically only in adults and the most common pattern was generalized continuous slow-wave activity [34,35]. In a case series of four children with pediatric MIS who presented with new neurological signs (encephalopathy, brainstem signs, cerebellar signs, weakness), three had EEG testing, and the main finding was non-specific background slowing [33]. Thus, there is currently no specific EEG pattern identified associated with COVID-19.

The main limitations of our study are the relatively small number of children with seizures and the retrospective nature of it. Laboratory tests, imaging and EEG were performed based on clinical decisions and thus data is available for only some of the children.

The COVID-19 pandemic continues to affect thousands of patients daily worldwide, including children. The emergence of new mutations of the virus may increase the rate of symptoms in children and it is possible that despite vaccination, SARS-CoV-2 will continue to infect people worldwide. Early diagnosis of COVID-19 is important for infection control. Children who present with symptoms other than influenza-like, might not be tested and thus spread the virus. Moreover, the long-term outcome of children with acute symptomatic seizures associated with COVID-19 is still unknown. We therefore suggest a high index of

suspicion of acute COVID-19 infection in children who present with new onset seizures or exacerbation of prior epilepsy, with or without fever, regardless of other typical signs of acute COVID-19.

Declaration of Competing Interest

None of the authors has any conflict of interest to disclose

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