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

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### 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. 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.



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.



- 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. Another study reported seizures in 5.4% of children admitted due to COVID-19 and multisystem inflammatory syndrome in the United States.
- 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-CoV-2 infection.

### Study design, methods and patients

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.



Seizures were diagnosed clinically. According to the ILAE definitions, 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.



### Results

Between March 1<sup>st</sup> and December 31<sup>st</sup>, 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

- Entire cohort demographic data.

	Seizures (n = 11)	No seizures ( <i>n</i> = 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*
РМН# -	7 (63%)	15 (9%)	<b>p</b> <
neurological			0.00001
Admission length	3.2 days	2.7 days	NS*
Ethnic <sup>\$</sup> (A/J)	9/2	91 / 73	NS*

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

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

Table 2

### Laboratory tests

- Laboratory tests were within normal range in the majority of patients. Leukocyte count was within normal range in eight children (range 3.79-10.33 10E<sup>9</sup>/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).



### **Discussion**

- 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.
- 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
- 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.

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. 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.

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)</p> Five children in our cohort presented with convulsive SE. This was rarely reported before. 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 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 Of the 11 children with seizures, fever (>38°c) was recorded in 54% (6/11). 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 . the pathophysiology of non-febrile illness seizures is yet to be elucidated. Evidence from animal models supports neuronal hyper excitability by conformational changes as well as fever and glutamate release by cytokines like IL-1b, produced by the immune system.



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). 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.



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. 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.

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.

## Thank you for your attention