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Neurological Manifestations of Pediatric Acute COVID Infections: A Single Center Experience

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) usually leads to a mild infectious disease course in children, while serious complications may occur in conjunction with both acute infection and neurological symptoms, which have been predominantly reported in adults. The neurological complications in these patients vary based on patient age and underlying comorbidities. Data on clinical features, particularly neurological features, and prognostic factors in children and adolescents are limited. This study provides a concise overview of neurological complications in pediatric COVID-19 cases.
Materials and methods: The retrospective study reviewed medical records of all patients who were admitted to our hospital and were diagnosed with COVID-19 by real-time reverse-transcription polymerase-chain-reaction (RT–PCR) assay between 11 March 2020 and 30 January 2021. Patients with a positive PCR result were categorized into two groups: outpatient departments patients and inpatient departments (IPD).
Results: Of the 2530 children who underwent RT–PCR during the study period, 382 (8.6%) were confirmed as COVID-19 positive, comprising 188 (49.2%) girls and 194 (50.8%) boys with a mean

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age of 7.14±5.84 (range, 0–17) years. Neurological complications that required hospitalization were present in 34 (8.9%) patients, including seizure (52.9%), headache (38.2%), dizziness (11.1%) and meningoencephalitis (5.8%).

Conclusion: The results indicated that neurological manifestations are not rare in children suffering from COVID-19. Seizures, headaches, dizziness, anosmia, ageusia and meningoencephalitis are major neurological manifestations during acute COVID-19 disease. Although seizures were the most common cause of hospitalization in IPD patients, the frequency of meningoencephalitis was quite high. Seizures were observed as febrile seizures for children under 6 years of age and afebrile seizures for those over 6 years of age. Febrile seizure accounted for half of all seizure children.

KEYWORDS: COVID-19, neurological manifestations, adolescence, infant, neonates

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a serious infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease spread from a Chinese cluster to almost all other countries within a few weeks in late December 2019. Ever since, the COVID-19 outbreak has drastically changed the world's health concerns and the disease has rapidly spread worldwide, becoming the first pandemic of the 21st century. As of 31 August 2020, more than 25 million patients have been infected with the disease [1].

Neurotropic and neuroinvasive capabilities of coronaviruses have been described in humans. Neurological problems found in patients with coronavirus infection include febrile seizures, convulsions, loss of consciousness, encephalomyelitis and encephalitis. Moreover, neurological manifestations have also been reported in adults with COVID-19 [2]. Despite the high number of people affected, data on clinical features and prognostic factors in children and adolescents are limited [1–3]. The incidence curves of hospitalized patients increase with age, with most severe cases including adults aged over 80 years. Mortality follows this trend and mainly burdens the elderly, but rarely children [4, 5]. Therefore, children comprise a minority of hospitalized patients [6]. Given the limited number of diagnosed pediatric cases and the low associated morbidity rate in children, the literature on pediatric COVID-19 cases is relatively scarce in comparison with the reports on affected adults. Neurological complications in children have only been reported in a few case reports and reviews [4–25]. Mao, *et al.* [23] and Lu, *et al.* [24] also reported that they did not observe neurological complications in pediatric patients during the acute COVID-19 period. A total of 21 studies/case series and 5 case reports include in the study; non-specific neurological manifestations, presenting altogether in 16.7% cases and 1% were found to have been reported with definite neurological complications [13], to our knowledge, there has been no single-center study evaluating children and infants with COVID-19 and neurological complications. In our study, neurological complications requiring hospitalization were seen in 8.9%. This study provides a concise overview of neurological complications in pediatric COVID-19 cases and aimed to investigate neurological complications in pediatric COVID-19 cases admitted to a tertiary care hospital.

MATERIALS AND METHODS

This retrospective, observational single-center study reviewed medical records of all patients who were admitted to our hospital and were diagnosed with COVID-19 between 11 March 2020 and 30 January 2021. Our hospital is the only COVID-19 hospital in our city, a scientific committee was established in our hospital to determine a management algorithm for the detection and treatment of pediatric COVID-19 patients. Based on this algorithm, the patients were classified as outpatients or inpatients.

All the children admitted to our emergency department with fever, cough or breathing difficulties were initially evaluated in our COVID-19 examination rooms and then a detailed examination consisting of contact history, underlying comorbidities, physical examination and laboratory and radiographic workup was performed. A suspected case was defined as an

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individual presenting with the symptoms of COVID-19 and/or a contact history with an individual diagnosed with COVID-19.

All the patients had at least one nasopharyngeal swab specimen positive for SARS-CoV-2 nucleic acid on real-time reverse-transcription polymerase-chain-reaction (RT–PCR) assay, either with a positive result for immunoglobulin G/immunoglobulin M antibodies against SARS-CoV-2. Electronic medical records, serum and biochemical parameters (complete blood count, creatinine kinase, lymphocyte count, C-reactive protein, ferritin and D-dimer), radiological examinations [cranial computed tomography (CT) and magnetic resonance imaging (MRI)] and electroencephalogram (EEG) findings were reviewed for each patient. Demographic and clinical characteristics including age, gender, presenting symptoms and exposure history were retrieved from our hospital database and were recorded.

Patients with a positive PCR result were categorized into two groups: (i) outpatient departments (OPD) patients with neurological manifestations of non-specific symptoms shown that headache, dizziness, anosmia/dysgeusia and vertigo and (ii) inpatient departments (IPD) patients with central nervous system (CNS) disorders shown like that direct viral infection, disorders of consciousness, refracter headache and dizziness and seizures (afebril/febrile seizures and acute symptomatic seizure).

As per our hospital protocol, more than 3-month children; a diagnostic lumbar puncture is performed at the time of admission in all patients presenting with $\geq$2/4 of the classic clinical features of meningitis including headache, fever, meningismus and altered mental status, <3-month children; not sucking, hypoactivity, lethargy, apnea, seizure, fontanel bloating, vomiting, respiratory distress and body temperature changes restlessness, irritability, fever or late sepsis. Patients with focal neurological deficits do not undergo lumbar puncture due to the likelihood of space-occupying lesions and the risk of herniation after lumbar puncture and thus CT is performed in such patients. Cerebrospinal fluid (CSF) is sent to the laboratory for standard investigations including Gram stain, India ink stain, bacterial culture and cryptococcal antigen. Pleocytosis of CSF was defined as a CSF with a white blood cell count (WBC) of over 5 cells/μl or neonatal term patients 20 cells/μl. CSF protein levels of >45 mg/dl and neonatal term patients 100 mg/dl were considered abnormal. CSF glucose levels of <40 mg/dl and neonatal term patients 30 mg/dl were considered low. Suspected cases with no positive RT–PCR results were excluded from the study.

In this retrospective and non-invasive study, no experiments were conducted on the participants. The study was registered in the database of our medical center (identifier: 2021/53) and an approval was obtained from the local ethics committee. A written informed consent was obtained from each patient.

Statistical analysis

Data were evaluated using SPSS for Windows version 23.0 (Armonk, NY: IBM Corp.). Descriptives were expressed as median and minimum–maximum for continuous variables and as frequencies (n) for categorical variables. Categorical variables were compared using Chi-square test or Fisher's exact test. Multiple comparisons were performed using Kruskal–Wallis test. A two-tailed p-value of <0.05 was considered significant.

RESULTS

Of the 2530 children who presented with the symptoms of COVID-19 and/or a contact history with an individual diagnosed with COVID-19 during the study period, 382 (8.6%) were confirmed as COVID-19 positive, comprising 188 (49.2%) girls and 194 (50.8%) boys with a mean age of 7.14 $\pm$ 5.84 (range, 0–17) years. No significant difference was observed between the percentage of boys and girls ($p > 0.05$). Mean age was 8.12 $\pm$ 3.2 months in patients aged <1 year, 3.2 $\pm$ 1.8 years in patients aged 1–5 years, 7.2 $\pm$ 2.8 years in patients aged 6–10 years and 14.2 $\pm$ 3.6 years in patients aged 10–17 years (Table 1). OPD and IPD patients were detected in 259 (67.8%). Additionally, 34 (8.9%) patients had complications that required hospitalization, including seizure (52.9%), headache (38.2%), dizziness (11.1%) and meningoencephalitis (5.8%). Figure 1 presents the flowchart of the study. Among the 54 neonates who were admitted to the neonatal intensive care unit with maternal contact for 0–30 days, 14 patients were diagnosed positive for SARS-CoV-2 infection and only 1

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Table 1. Demographic and clinical characteristics

Parameters	Total	%
Age		
Mean age (years)	7.14±5.84	NA
Age groups		
<1 year	71	18.5
1–5 years	104	27.2
6–10 years	76	19.9
10–17 years	131	34.2
Total (*n*)	382	100
Gender		
Female	188	49.2
Male	194	50.8
OPD patients	225	
IPD patients	34	
Headache	88	23.0
Hospitalized due to headache	13	3.4
Mean age (years)	14.2±3.6 (4–17)	
Anosmia	39	10.2
Ageusia	28	7.3
Dizziness	55	14.3
Vertigo/nausea	15	3.9
Hospitalized due to dizziness	3	0.7
Seizures	18	4.7
Febrile seizure	9	2.3
Acute symptomatic seizure	5	1.3
Afebrile seizure	2	0.5
Meningoencephalitis	2	0.5

neonate was diagnosed with meningoencephalitis. No neurological symptoms were detected in other patients.

OPD patients included headache, dizziness, anosmia/dysgeusia and ageusia/dysgeusia. Neurological complications of OPD patients were detected in 225 (58.9%) patients. Of these, headache was the most common presenting symptom (23%) and the rate of hospitalization due to headache was 38.2%. All the patients with headache were adolescents, who had a mean age of 14.2 ± 3.6 (range, 4–17) years. In severely symptomatic children who received inpatient care, cranial MRI findings were normal and the longest hospitalization period was 5 days. These patients benefited from hydration and antipyretic and analgesic treatment. The second most common non-specific symptom was dizziness (14.3%), followed by anosmia (10.2%), and ageusia/dysgeusia (7.3%). No patient was hospitalized due to anosmia and ageusia/dysgeusia. Dizziness was observed in 14.3% of the patients, and 0.7% of them were hospitalized. The patients hospitalized due to dizziness showed a good response to diphenylhydantoin and hydration therapy.

PD patients were detected in 34 (8.9%). Of the 18 (4.7%) patients who presented with seizure as the first symptom, 9 (2.3%) of them had experienced their first febrile seizure. Of the children who were otherwise healthy and presented to our clinic after their first seizure, 1.8% of them had simple febrile seizures and 0.5% of them had complex febrile seizures. Five (1.3%) patients who were being followed up with a diagnosis of epilepsy presented with an increased frequency of seizures [Lennox–Gastaut syndrome (*n*: 2), Dravet syndrome (*n*: 2) and benign rolandic epilepsy (*n*: 1)]. Two patients who presented with seizure as the first symptom had no fever before or during the follow-up. No seizure activity was detected on EEG. Patients diagnosed as having Todd's paralysis had no seizures throughout the follow-up period.

Two patients who presented with meningoencephalitis (a 4-day old and 3 months old) were also confirmed positive for SARS-CoV-2 on RT–PCR test. Cranial MRI was normal. The CSF examination revealed the following values: WBC 1190 cells/mm^3 (89% segmented neutrophils and 9% lymphocytes), glucose level 35 mg/dl and protein level 352 mg/dl. Streptococcal pneumonia and SARS-CoV-2 were detected in CSF culture. Phenytoin loading and levetiracetam treatment twice daily were continued. Both contrast/non-contrast cranial MRI were normal except for mild meningeal enhancement. The patients were discharged with full recovery after a meningoencephalitis treatment. No sequela occurred in any patient.

DISCUSSION

Children with SARS-CoV-2 infection have different clinical manifestations and outcomes compared to adults. Literature indicates that pediatric cases of SARS-CoV-2 infection are remarkably rare and only a few cases have been reported thus far [1–3]. This study investigated the frequency and characteristics

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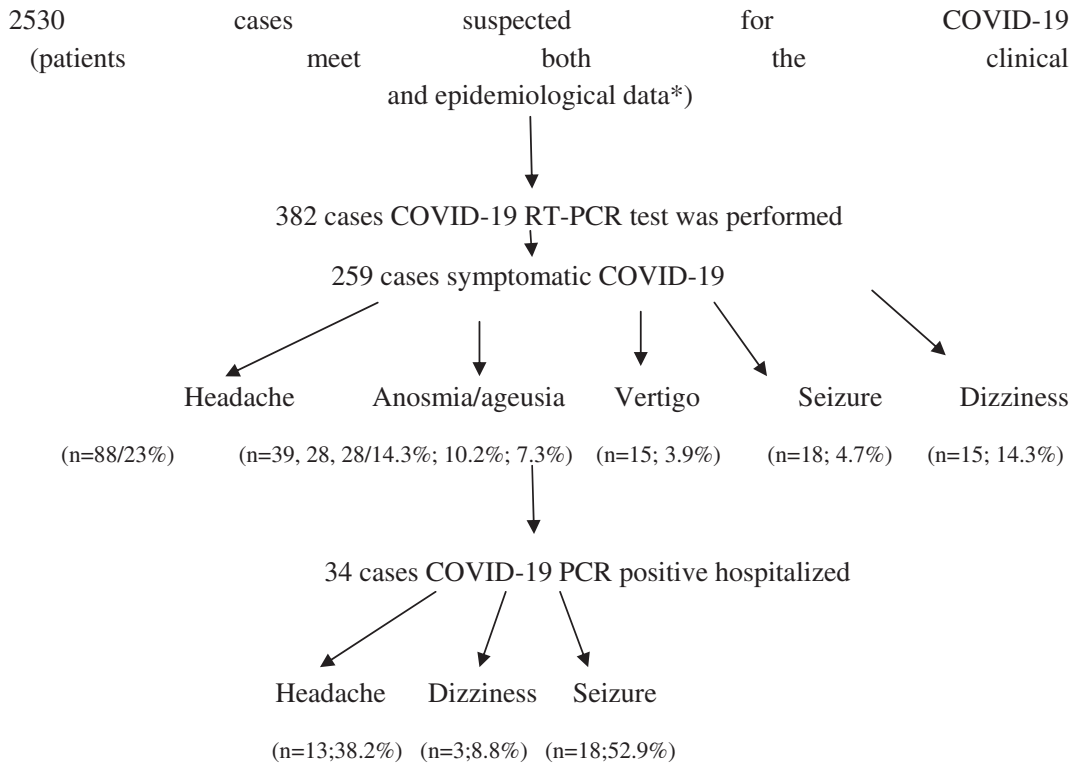


Fig. 1. Flowchart of the study.

*Clinical: acute respiratory infection of any severity, including at least one of shortness of breath, or cough (with or without fever), or fever with no other symptoms. Epidemiological: in the 14-day travel to abroad, or contact with a confirmed COVID-19 case.

of neurological complications in pediatric COVID-19 cases. All the patients, including those with comorbidities, recovered fully and had no sequelae at the time of hospital discharge. Additionally, neurological symptoms were detected in 67.8%, the rate of hospitalization due to neurological complications was 8.9%, and the rate of children that were positive for SARS-CoV-2 infection and had seizures was 4.7%.

Clinical symptoms of COVID-19 show a wide variation across age groups and the rate of test positivity decreases as the age decreases [5–9]. Although, several factors have been proposed regarding the lower effect of COVID-19 in children, there is no substantial evidence to support any of these mechanisms [18–21]. SARS-CoV-2 has a neuroinvasive potential since 36% of adult patients have been reported to have a variety of neurological manifestations including headache, vertigo, acute cerebrovascular events and changes in mental status [22]. A previous study evaluated 171 Chinese children with COVID-19 infection and did not detect neurological involvement in any patient [23]. In recent reports published in Western countries, non-specific headache has been reported as the only neurological symptom in COVID-19-infected children, accounting for 4–28% of all cases [24]. A study by the CDC COVID-19 Response Team evaluated a total of 2572 pediatric patients with a mean age of 11 years, among whom 91% of the patients were infected with COVID-19 through family cluster infection and 57% of them were male. Of the 291 (11%) symptomatic children, 81 (28%) children were followed up due to headache [15]. Parri, *et al.* [14] reported that 4%, Cura, *et al.* [25] detected headache in 9.1%, of the patients. In our study, headache was the most common non-specific presenting symptom and the headache frequency increased with age. Moreover, the frequency of headache in symptomatic COVID-19

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pediatric patients was 23.0% and the rate of hospitalization due to headache was 38.2%. Hypogeusia and hyposmia are frequently reported in COVID-19 cases and have become a cardinal factor in the early diagnosis of the disease [26, 27]. Moreover, anosmia and ageusia have been 30–80% cases and have been rarely reported in children as well. Cura, *et al.* [25] detected anosmia and ageusia in 5% of the patients. Despite these varying rates, in our study, we found a lower frequency of anosmia/ageusia (17.5%) among OPD patients. The frequency of dizziness has been less studied in children. According to the CDC COVID-19 Response Team study, 23% of pediatric patients required follow-up due to dizziness [15]. In our study, dizziness and hospitalization of dizziness were detected in 14.3% and 8.8% of our patients.

Febrile seizure is the most common seizure in childhood and is defined as seizures occurring in children aged older than 6 months associated with a febrile disease not caused by an infection of CNS, without previous neonatal seizures or a previous unprovoked seizure, and not meeting the criteria for other acute symptomatic seizures and its incidence varies between 2% and 5% [28–30]. Even so, these children are at risk of developing seizures and encephalopathy, particularly those suffering from severe disease [13]. A review by Panda, *et al.* [13] evaluated 21 studies and case reports and reported the prevalence of non-specific neurological complications as 16.7% and the prevalence of specific neurological complications (encephalopathy, seizure and meningeal irritation) as 1%. Although there are only a limited number of studies reporting on neurological complications, these complications remain a serious problem. A previous study reported that all the seizures were in the form of acute symptomatic seizures and occurred during febrile episodes while only one seizure was in the form of status epilepticus [13]. To our knowledge, definite demographic variables have not been reported for children with non-specific/specific neurological complications in other case reports and few small case series. In a multicenter Italian study investigating SARS-CoV-2 infection in children and adolescents, Garazzino, *et al.* [12] evaluated 168 pediatric patients and reported the prevalence of afebrile and febrile seizures as 1.8% and 1.2%, respectively. In contrast, the CDC COVID-19 Response Team study reported that no serious neurological complications occurred in their patients, except for non-specific neurological symptoms [15]. In our study, 4.7% of children who were positive for SARS-CoV-2 infection had seizures, among whom 1.8% of them had febrile seizures, 1.3% of them had acute symptomatic seizures, 0.05% of them had afebrile seizures and 0.05% of them had meningoencephalitis. The rate of hospitalization due to seizure was 52.9%. Literature indicates that pediatric COVID-19 patients aged over 6 years who present with afebrile seizures should not be considered epileptic since their seizures may show a wide variety of clinical manifestations as in seizures in pediatric practice [31–35]. In our patients, seizures resolved after the administration of antiepileptic therapy. And a 3-month-old meningoencephalitis with pediatric patient with an incomplete vaccination status was families should be asked.

As recommended by pediatric associations, it is essential to include the SARS-CoV-2 PCR test in the workup of infants aged <3 months [47]. In neonatal children, SARS-CoV-2 test positivity is remarkably low and the most common presenting symptoms include seizure, hypotonicity and encephalopathy [32,36–46,48–52]. Stafstrom, *et al.* [32] reported several cases with neurological symptoms of COVID-19 in the neonatal and infantile period on a case-by-case basis. In our study, a 4-day-old infant with positive maternal contact who had seizures and hypotonia was not detected with SARS-CoV-2 in CSF by RT–PCR, while neuroimaging and lumber puncture findings were suggestive of meningoencephalitis.

In conclusion, the results indicated that neurological manifestations are not rare in children suffering from COVID-19, particularly in those suffering from severe disease are at increased risk of developing non-specific neurological symptoms, febrile/afebrile seizures and meningoencephalitis. We suggest that COVID-19 should be investigated in the etiology of febrile seizures. Pediatric COVID-19 patients aged over 6 years who present with afebrile seizures should not be considered epileptic since their seizures may show a wide variety of clinical manifestations as in the seizure semiology in epileptic patients. We also suggest that acute symptomatic seizures in COVID-19-

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infected children who present with temporal lobe epilepsy can be managed successfully with antiepileptic drugs with favorable short-term outcomes. Care should be taken against COVID-19 meningoencephalitis in infants younger than 3 months, particularly in those with an incomplete vaccination status.

Our study was limited since it was a single-center study and had a relative small sample size for the determination of the frequency of neurological findings in pediatric COVID-19 patients. Further studies evaluating pediatric patients with different neurological clinical symptoms are needed. Available literature about neurological manifestations of COVID-19 is rather limited; therefore, our study will hopefully contribute to increased alertness for both neurologists and non-neurologists about the manifestations of pediatric COVID-19 patients. Further studies involving larger numbers of patients with various neurological complications are needed to provide precise information regarding the treatment and semiology of seizures, EEG, lumbar puncture, and cranial MRI findings and long-term prognosis.

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CONFLICT OF INTEREST

There is no conflict of interest among the authors. We would like to thank all the staff of our hospital for their contributions to patient follow-up and care during the pandemic process.

ETHICAL APPROVAL

The study was approved by the Public Health Agency, Turkey Ministry of Health and by Kanuni Training and Research Hospital Ethics Committee, Trabzon, Turkey (Approval No: 2021/53).

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