

# Clinical and laboratory characteristics of children with neurological presentations of COVID-19: a single-center experience

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## ABSTRACT

The study aimed to assess the frequency of neurological presentations of pediatric COVID-19 patients and compare the clinical and laboratory characteristics and the outcomes of those who presented with neurological complaints and those without complaints. A cross-sectional study enrolled 84 children diagnosed with COVID-19 at the emergency department over 12 months. All previously healthy children with a laboratory-confirmed diagnosis of COVID-19 were included in the study. The diagnosis of COVID-19 was made by positive PCR of a nasopharyngeal swab. Patients were divided into 2 groups: group 1 included COVID-19 patients with neurological complaints, and group 2 included COVID-19 patients with non-neurological complaints. Demographical, clinical, and laboratory characteristics were compared among groups. During the study period, 84 children aged 2 months-15 years were diagnosed with COVID-19. Only 17 patients (20.2%) presented with new-onset neurological complaints. Seizure was the most common neurological complaint (58.8%), and febrile convulsion was the most frequent diagnosis of COVID-19 patients with neurological presentation (47.1%). C-reactive protein (CRP) and duration of hospitalization were higher in patients with neurological presentations, with P values of 0.002 and 0.001, respectively. All patients with neurological complaints survived the acute illness. Neurological symptoms were present in 20% of the COVID-19 pediatric patients, having higher CRP than patients with non-neurological presentations. CRP can be used as a reliable indicator for neurological symptoms in COVID-19 pediatric patients.

**KEYWORDS:** COVID-19, neurological, pediatric, SARS-CoV-2.

## INTRODUCTION

Since the beginning of the pandemic, infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has generated a variety of clinical symptoms. Despite the prevalence of respiratory symptoms in the pediatric age group, many children also exhibit neurological symptoms [1]. COVID-19 has been associated with various central and peripheral neurological injuries in adults and children, ranging from mild symptoms such as headache and anosmia to severe presentations such as stroke, seizure, and encephalopathy [2]. In a case series from Saudi Arabia, the neurological manifestations of COVID-19 in juvenile patients exhibited a wide range of clinical problems [3]. Uncertainty surrounds the extent to which the virus induced these neurological issues as opposed to the critical state, underlying degenerative disease, or iatrogenic effects of reusing medicines [4]. The incidence of neurological symptoms in

adult COVID-19 patients varies greatly and approaches 100% [5, 6]. Although COVID-19-associated neurological problems in children are rather common, the published prevalence rates are significantly lower than adult prevalence rates [7, 8]. Due to a lack of adequate research, the frequency of neurological symptoms of COVID-19 in children is uncertain. A multi-center cohort study in the United States indicated that 40% of children with acute SARS-CoV-2 exhibited at least one neurological symptom [9]. Over the course of three months, Line *et al.* looked at the medical records of people with COVID-19 confirmed in the lab and found that 43% of them had neurological symptoms. LaRovere *et al.* reported the lowest rate, with only 22% of neurological involvement in COVID-19 children [10]. The reported prognosis for children with neurological manifestations of COVID-19 is excellent since nearly all have fully recovered [11]. In Iraq and other Arabic countries, there is a paucity of studies examining the neurological presentation of COVID-19

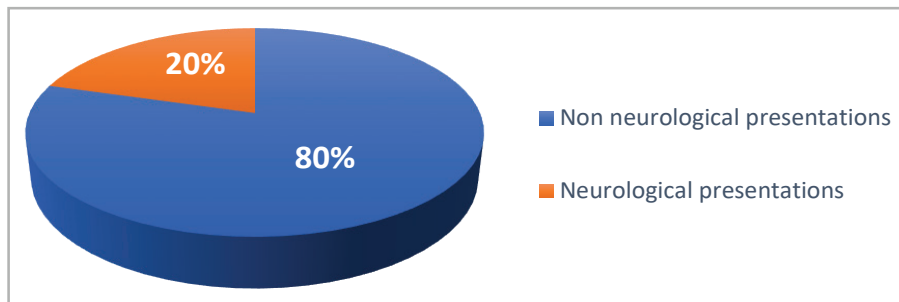


Figure 1. The frequency of neurological presentations in children hospitalized with COVID-19.

in children, with a single published case series from Saudi Arabia [3] and a case report from Iraq describing the neurological manifestation of COVID-19 as part of multisystemic inflammatory disease in childhood (MIS-C) [12]. Although a growing number of review articles and publications describe neurological manifestations of COVID-19 [11–13], its full impact on children under 18 years old is yet unknown [14]. This research intended to determine the prevalence and types of neurological symptoms in COVID-19-infected children. The secondary objective was to discover potential predictors of neurological symptoms.

## MATERIAL AND METHODS

A descriptive, cross-sectional, single-center study was conducted over 12 months from 1<sup>st</sup> April 2020 to 31<sup>st</sup> March at the emergency department of a central child teaching hospital in Baghdad, Iraq.

The inclusion criteria:

- Children with a laboratory-confirmed diagnosis of COVID-19 confirmed by positive polymerase chain reaction (PCR) of a nasopharyngeal swab;
- Previously healthy children (an absence of reported underlying chronic diseases or comorbidities and taking no prescription medications).

We excluded cases with underlying chronic illness or comorbidities and those who refused to give informed consent. All patients had a full neurological assessment by a pediatric neurologist. Accordingly, they were sub-divided into group 1, which included cases with new-onset neurological complaints, and group 2, which included those without neurological complaints.

The demographical, clinical (type of neurological complaints, diagnosis, hospitalization period, and the outcome), and patients laboratory characteristics (C-reactive protein (CRP), total white blood cell, absolute lymphocyte, and absolute neutrophil count, packed cell volume (PCV), and platelets count) were collected and compared for a possible correlation.

Families gave informed consent after briefing about the study's aim. The statistical analysis was carried out using SPSS software version 26. The mean and standard deviation of data with a normal distribution were provided, and the student's T-test was used for comparison. The Mann-Whitney U test was used to assess data with non-normal distributions, which were reported as median and range. The Chi-square test was used to examine categorical variables expressed as numbers and percentages. A statistically significant result was defined as a p-value of less than 0.05.

## RESULTS

During the study period, 84 children (aged 2 months to 15 years) were diagnosed with COVID-19 at the central child teaching hospital and enrolled in the study. Males outnumbered females (54% versus 46%). Only 17(20.2%) patients presented with neurological complaints on admission to the hospital and/or during hospitalization, while 67(79.8%) patients had non-neurological presentations (Figure 1).

In patients with neurological complaints, seizure was the most common neurological complaint seen in 58.8% of patients, followed by headache (47.1%), acute flaccid paralysis, and disturbed level of consciousness (11.8%) (Table 1).

Febrile convulsion was the most frequent neurological diagnosis of COVID-19 patients (47.1%), followed by encephalitis (17.6%) (Table 2). Two cases presented initially with fever and seizure, but during hospitalization, other neurological complaints occurred (one of them developed ataxia and the other hemiparesis), and based on CSF analysis and brain imaging, they were diagnosed with acute demyelinating encephalomyelitis (ADEM).

Duration of hospitalization (p=0.001) and C-reactive protein (CRP) (p=0.002) were higher in patients with neurological presentations. On the other hand, the age and gender of patients, leukocyte counts, absolute neutrophil counts, and absolute lymphocyte counts were not statistically associated with the neurological presentations, as shown in Table 3.

Table 1. Types of neurological presentations in COVID-19 patients (n=17).

Neurological complaints	Frequency (%) *
Seizure	10 (58.8%)
Headache	6 (47.1%)
Acute flaccid paralysis	2 (11.8%)
Disturbed level of consciousness	2 (11.8%)

\* – Patients can have more than one complaint.

Table 2. Diagnoses of COVID-19 pediatric patients who presented with neurological complaints (n=17).

Diagnosis	Frequency (%)
Febrile seizure	8 (47.1%)
Encephalitis	3 (17.6%)
Guillain barre Syndrome (GBS)	2 (11.8%)
Viral meningitis	2 (11.8%)
Acute demyelinating encephalomyelitis (ADEM)	2 (11.8%)

Table 3. Association of patient's characteristics with patient's presentation.

Variables	Neurological presentations of COVID-19		P-value
	Yes (n=17)	No (n=67)	
<b>Age (years)</b>			
Mean±SD	7.6±3.7	5.3±4.6	0.67 <sup>†</sup>
<b>Gender</b>			
Male	13 (76.5%)	52 (77.6%)	0.92 <sup>*</sup>
Female	4 (23.5%)	15 (22.4%)	
<b>Duration of hospital stay (days)</b>			
Mean±SD	5.76±5.5	3.15±1.5	0.001 <sup>†</sup>
<b>Lymphocytes×10<sup>3</sup>/ml</b>			
Median (range)	2.3 (0.2–5.9)	1.6 (0.4–7)	0.72 <sup>†</sup>
<b>Neutrophil×10<sup>3</sup>/ml</b>			
Median (range)	3.4 (2.1–13.1)	4.6 (0.9–15.9)	0.65 <sup>†</sup>
<b>Platelets×10<sup>3</sup>/ml</b>			
Median (range)	259 (169–515)	250 (8–515)	0.94 <sup>†</sup>
<b>Total WBC×10<sup>3</sup>/ml</b>			
Median (range)	7.7 (4.9–21.9)	7.8 (1.07–23.8)	0.59 <sup>†</sup>
<b>CRP mg/dl</b>			
Median (range)	112 (0–168)	30 (0–146)	0.002 <sup>†</sup>
<b>PCV</b>			
Median (range)	33 (17–37)	30.9 (18–37)	0.58 <sup>†</sup>

\* – Chi-square test; † – Student t-test; ‡ – Mann Whitney U test; CRP – C-reactive protein; PCV – packed cell volume; WBC – white blood cell.

In what concerns patients' outcome, only four (4.8%) out of the 84 children enrolled in this study died during hospitalization, and none showed new-onset neurological symptoms.

## DISCUSSION

Since the beginning of the epidemic, physicians have become more aware of neurological symptoms in COVID-19 patients. It has been suggested that neurologists should be involved in the care of COVID-19 patients [15]. It is very important to find out if SARS-CoV2 is linked to neurological symptoms, as this could lead to significant morbidity and mortality [4]. In this study, 20.2% of the children with COVID-19 had new neurological symptoms, which agrees with a USA study reporting that 22% of SARS-CoV-2 hospitalized children had neurological manifestations [10]. However, this frequency is lower than that reported by two previous studies by Lin *et al.* (43%) [2] and Fink *et al.* (40%) [9]. In the current study, the most common neurological symptom in COVID-19 children was a seizure (58.8%). This disagrees with previous studies that reported headache [9] and fatigue [10] as the most common neurological symptom. The difference in the frequency and type of neurological manifestation in this study can be attributed to the lower age of patients compared to previous studies. This could make it hard for patients and their families to describe some neurological symptoms. Under-reporting of headaches in children is common [16, 17]. Even though the rate of neurologic manifestations in pediatric patients with COVID-19 in this study was low, raising clinical awareness regarding neurological complications of COVID-19 to recognize and treat patients early and adequately is vital. For some neurological complications of COVID-19, like GBS and

ADEM, a rapid diagnosis and immediate therapy are vital [18]. Concerning the diagnoses, most (47.1%) cases with a neurological presentation were labeled as having febrile convulsions when sent home. This fits with other studies and reviews that seizures, especially simple febrile seizures, are the most common neurological sign of a coronavirus infection [19].

However, it is worth mentioning that although all these patients underwent cerebral spinal fluid (CSF) testing, which was normal in analysis and negative for bacterial pathogen culture, PCR for SARS-COV2 in CSF was not done in this study due to the unavailability of the test in our center. In this study, the mean duration of hospital stays for neurological cases (5.76±5.5) was significantly higher than those with non-neurological presentation days, and this agrees with the results by Fink *et al.* [9]. Nevertheless, it was contrary to LaRovere *et al.*, who found that the duration of intensive care unit, not hospitalization, was significantly related to the presence of neurological manifestation in COVID-19 [10]. This can be attributed to different clinical diagnoses compared with mild diagnoses in the current study, in which (47.1%) were diagnosed with febrile convulsion, which usually requires a short hospital stay [20]. Although patients with neurological manifestations are older than those with non-neurological complaints, the age of pediatric COVID-19 with neurological presentations did not differ significantly from children with non-neurological ones. This is contrary to results reported in previous studies. Fink *et al.* found that COVID-19 children who present with neurological symptoms tend to be significantly older [9]. The authors believe that this could be the result of many adolescent children, especially those aged ≥16 years, receiving medical care in adult hospitals in Iraq and, as a result missing many cases of neurological presentation of adolescents COVID-19.

In this study, none of the blood indices was significantly related to the presence of neurological manifestations in COVID-19 children, so the above indices do not appear to be reliable indicators of neurological manifestations of pediatric COVID-19, and this agrees with previous studies which document that hospitalized COVID-19 pediatric patients regardless of the type of presentation had no significant changes in laboratory parameters [21, 22]. The cause may be attributed to the non-severe neurological diagnosis carried by about half of the patients. Studies in adults proved that the median CRP value correlates with the severity of COVID-19 and is an independent predictor of mortality [23]. To our best knowledge, no previous study compared blood indices and inflammatory markers in COVID-19 children according to the presence or absence of neurological complaints. Herein CRP was significantly higher in patients who presented with neurological symptoms. CRP is an inexpensive, widely available test used in COVID-19 pediatric patients for early recognition of neurological presentations for early and adequate treatment. All patients with neurological complaints survived the acute illness, which agrees with previous studies [11]. This represents one major difference from the adult population in which the prognosis of COVID-19 cases with neurological presentation had shown a higher risk of mortality regardless of the type of neurological pathology. The risk is aggravated by older age and higher inflammatory markers [24, 25]. The current study had several limitations. First, the small sample size and the fact that it was conducted at a single center in Baghdad-Iraq. Second, after hospital discharge, follow-up was not done, so long-term or delayed neurological complications of COVID-19 were not reported. Third, some neurological complaints, like headaches and fatigue, are subjective, and underreporting is possible. Finally, this study did not conduct PCR for SARS-CoV2 in CSF due to unavailability.

## CONCLUSION

In the pediatric age group, neurological symptoms were present in 20% of COVID-19 patients. Higher CRP levels in COVID-19 pediatric patients are significantly associated with neurological complaints since CRP is an inexpensive, widely available test, so it can be used in COVID-19 pediatric patients for early recognition of neurological presentations to treat patients early and adequately.

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### Conflict of interest

The authors declare no conflict of interest. The abstract was presented at the 1<sup>st</sup> Iraqi Pediatrics-Neurology Conference held in Baghdad, Iraq, on 21<sup>st</sup> January 2022.

### Ethics approval

This study was approved by the bioethical committee of the medical college of Mustansiriyyah University (No. 166, in 2022).

### Consent to participate

All patients consent to participate in the current study.

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## Authorship

NNA contributed to study conception and design. BAI contributed to data analyzing and draft manuscript preparation. SMA contributed to the critical revision of the paper. NNA supervised the research. WN contributed to supervision, funding and acquisition. SMA and NNA gave the final approval of the published version.

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