Original Article

# Neurologic Manifestations of COVID 19 in Children: Prospective Study in a Single Center

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## Abstract

**Background:** The data related to the neurologic manifestations of coronavirus disease 2019 (COVID-19) in children are limited. The frequency of the neurologic manifestations and the risk factors in the development of these symptoms are not clear. **Objectives:** We aimed to determine the exact frequency of the neurological symptoms in pediatric patients with confirmed COVID-19 and to identify the risk factors for the development of neurological manifestations. **Materials and Methods:** We included pediatric Covid-19 patients admitted to the Children's Hospital of Ankara City Hospital between March 22 and June 1, 2020. Neurological findings were questioned by interviewing the patients and their families and detailed neurologic examinations were performed within protection measures. **Results:** A total of 312 pediatric patients with the diagnosis of COVID-19 were enrolled in the study. Sixty-six participants (21.15%) showed neurologic symptoms during COVID-19. Headache was the most common neurologic symptom and present in 14% (*n*: 44) of the cases. The other neurologic symptoms were myalgia (*n*: 30, 9.6%), anosmia/hyposmia (*n*: 6, 1.9%), ageusia (*n*: 2, 0.6%), and vertigo (*n*: 1, 0.3%). Neutrophil-to-lymphocyte ratio (NLR) ($P = 0.002$) and platelet-to-lymphocyte ratio (PLR) ($P = 0.001$) were significantly elevated in patients with neurological symptoms when compared to the patients without the symptoms. **Conclusions:** Physicians should be alert to the neurologic involvement of COVID-19 disease in children. NLR and PLR ratios could have a predictive value for the development of neurological manifestations.

**Keywords:** Children, COVID-19, neurological manifestations

## Introduction

The coronavirus disease 2019 (COVID-19) is a severe acute respiratory syndrome (SARS) caused by a novel coronavirus, SARS-CoV- 2.[1] The disease was first reported in December 2019 in the Wuhan province of China and has spread across the world evolving into a quite serious public health problem. It has been declared a global pandemic by the World Health Organization.

Coronavirus is a large, enveloped, positive-sense ribonucleic acid virus that primarily targets the human respiratory system and causes upper and lower respiratory tract infections.[1] SARS-CoV-2 is primarily transmitted via respiratory droplets. Most of the patients infected by SARS-CoV-2 have presented with acute respiratory tract infection symptoms. The COVID-19 disease generally presents with a mild clinical course.[2] However, serious complications including acute respiratory distress syndrome, acute heart injury or failure, acute kidney injury, sepsis, disseminated intravascular coagulation, and even mortality can occur.[3] Typical clinical manifestations of the disease include fever, cough, sore throat, and myalgia. Besides these symptoms, gastrointestinal manifestations such as diarrhea, abdominal pain, nausea, and neurological symptoms like headache, change in mental status, convulsions, encephalitis, myositis, anosmia, and ageusia can also be seen.[4]

Neurologic manifestations of COVID-19 in adult patients have been well recognized. The literature including articles and reviews about the neurologic manifestations in adult patients is quite abundant.[4-7] However, the data related to the neurologic manifestations of COVID 19 in children are limited. It depends on the milder clinical course of the disease in children and a small number of pediatric patients.[8] Neurologic manifestations can also be seen in pediatric patients with COVID-19 and the literature on this issue is also growing day -by day.[8-11] Some neurological findings in the pediatric age group have been reported in case reports/case series.[12.13] The neurologic manifestations were also reported in the studies describing the overall clinical features of COVID-19 but these studies were especially focused on the respiratory symptoms and were generally designed retrospectively.[14-17] The frequency of the neurologic manifestations and risk factors

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in the development of these symptoms were not clear. In this respect, we intended to determine the exact frequency of the neurological symptoms in the pediatric patients with confirmed COVID-19 by interviewing with the patient and family and also to identify the risk factors for the development of the neurological manifestations.

## Methods

This prospective, descriptive, single-center study was conducted in the Ankara City Hospital. The study was approved by the Local Ethics Committee of the Ankara City Hospital (Protocol No: E1-20-563) and the Turkish Ministry of Health.

### Patients and data documentation

We prospectively analyzed 312 consecutive pediatric in-patients diagnosed with COVID-19. The first COVID-19 case was reported on March 11, 2020, in Turkey, and since then, the number of patients has been rapidly increasing. We included the pediatric patients admitted to the Children's Hospital of Ankara City Hospital between March 22 and June 1, 2020. The COVID-19 diagnosis was confirmed by the SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) assay of the nasopharyngeal swab. All laboratory tests such as a complete blood cell count, blood chemical analysis, liver, and renal function testing, coagulation testing, analysis of C-reactive protein (CRP), creatinine kinase (CK), and lactate dehydrogenase (LDH) were performed for all the patients as a part of routine testing. Radiologic assessments including chest X-rays or computerized tomography (CT) were performed based on the clinical needs of the patients. The data including age, sex, preexisting comorbidities (such as heart disease, asthma, cerebral palsy, developmental/motor delay, hematological disease), and clinical outcome were documented. Using the questionnaire, we interviewed the patients and their families regarding neurological manifestations such as headache, vertigo, impaired consciousness, delirium, agitation, seizure, presence of any neurological deficits, loss of taste and smell, blurred vision, and diplopia, myalgia. Detailed neurologic examinations were performed on all the patients within protection measures. Informed consent was obtained from the patients' families for the study and publication.

### Statistical analysis

Data analyses were performed using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States). Whether or not the distribution of continuous variables was normal was determined by the Kolmogorov–Smirnov test. Also, the Levene test was used for the evaluation of the homogeneity of variances. Unless specified otherwise, continuous data were described as mean ± standard deviation (SD) and median (interquartile range) for skewed distributions. Categorical data were described as the number of cases (%). Statistical analysis differences in not normally distributed variables between two independent groups were compared by Mann–Whitney U test. Categorical variables were compared using Pearson's Chi-square test or Fisher's exact test. Multivariate logistic regression analysis was used to determine the clinical and laboratory findings that may be associated with neurological findings.

## Results

A total of 312 pediatric patients (147 of whom were females) with the diagnosis of COVID-19 were enrolled in the study. The mean age of the patients was 110.58 ± 65.74 months (min 6 months, max 18 years) [Table 1]. Thirty-nine percent of the patients (*n*: 122) were under 7 years. None of the patients had severe COVID-19 disease and also they did not need intensive care unit or mechanical ventilation support. Some patients had underlying diseases such as epilepsy (*n*: 2), cerebral palsy (*n*: 3), asthma (*n*: 9), metabolic disease (*n*: 2), rheumatologic disease (*n*: 1), and inflammatory bowel disease (*n*: 1) [Table 1].

Sixty-six participants (21.15%) showed neurologic symptoms during the COVID-19 disease. Fifteen patients with neurologic manifestation exhibited two or three symptoms at the same time. Headache was the most common neurologic symptom and present in 14% (*n*: 44) of the cases. The other neurologic symptoms were myalgia (*n*: 30, 9.6%), anosmia/hyposmia (*n*: 6, 1.9%), ageusia (*n*: 2, 0.6%), and vertigo (*n*: 1, 0.3%) [Table 2]. The patients with neurologic manifestations were older than the patients without neurologic manifestations (149.6 ± 48.1 vs. 100.1 ± 66.0 months; $P < 0{,}001$) [Table 1]. The mean ages of the patients in different groups of neurological manifestations are also given in Table 2. There was no difference in terms of gender and presence of comorbid disease between the patients with and without neurologic manifestations [Table 1].

The laboratory findings at admission are given in Table 3. The white blood cell counts, lymphocyte counts, and platelet counts were significantly lower in patients with neurologic manifestations. The results revealed that the values of aspartate aminotransferase, lactate dehydrogenase, d-dimer, creatine kinase, and serum creatinine were significantly different between the two groups yet within the normal range. There were no statistical differences in the other laboratory parameters between these two groups.

The neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) were significantly elevated in patients with neurological symptoms when compared with the patients without the symptoms, as shown in Table 3.

We performed multivariate logistic regression (LR) analysis to determine the clinical and laboratory findings that could be associated with the neurological findings. The backward LR method of multivariate logistic regression analysis was used. In the first step of the table, the variables included in the multivariate LR analysis can be seen. The results of Step 18, which is the last step obtained by using the backward

**Table 1: Clinical characteristics of the patients**

| | All patients | Neurologic manifestations | | *P* |
|---|---|---|---|---|
| | | Yes | No | |
| Number (%) | 312 | 66 (21.1%) | 246 (78.8%) | |
| Age, months (mean±SD) | 110.58±65.74 | 149.6±48.1 | 100.1±66.0 | <0,001 |
| Gender | | | | |
| Male, *n* (%) | 165 (52.8%) | 37 (56.1%) | 128 (52%) | 0,560 |
| Female, *n* (%) | 147 (47.1%) | 29 (43.9%) | 118 (48%) | |
| Comorbidities | | 8 | 10 | 0,588 |
| Asthma | 9 | 5 | 4 | |
| Epilepsy | 2 | 1 | 1 | |
| Cerebral palsy | 3 | 1 | 2 | |
| Metabolic disease | 2 | - | 2 | |
| Rheumatologic disease | 1 | 1 | - | |
| Inflammatory bowel disease | 1 | - | 1 | |

**Table 2: Neurological findings**

| Sign and symptoms | All Patients (*n*=312, %) | Age, months (mean±SD) (min-max) |
|---|---|---|
| Headache | 44 (14%) | 153.55±43.67 (60-216) |
| Myalgia | 30 (9.6%) | 147.45±52.54 (37-242) |
| Anosmia/hyposmia | 6 (1.9%) | 173.67±59.04 (60-216) |
| Ageusia | 2 (0.3%) | 209.50±9.19 (203-216) |
| Vertigo | 1 (0.3%) | 196 |

sifting method (backward LR), are presented. According to the last step result, the PLR and platelet were statistically significant ($P < 0.05$), while the NLR was borderline significant ($0.05 < P < 0.10$) [Table 4]. As the PLR and NLR values increase and the platelet value decreases, the risk of neurological findings increases.

## Discussion

In this study, we prospectively evaluated neurological manifestations of children with COVID-19. Among the 312 pediatric patients, 21.15% had neurologic symptoms. Headache was the most common neurologic symptom. The other neurologic symptoms were myalgia, anosmia/hyposmia, ageusia, and vertigo.

The neurologic manifestations in the COVID-19 patients were frequently reported in the adult patients. In the first study conducted in Wuhan, neurological symptoms were detected in 36.4% of the adult patients.[4] The rate of the neurologic findings in the adult patients varies between 7.7 and 57.4% in different studies.[5,6] Due to the limited data, it is difficult to estimate the ratio in the pediatric age group. In a meta-analysis studying the neurological findings in the pediatric COVID-19 patients, non-specific neurologic manifestations such as headache, myalgia, and fatigue were detected in 16.7% of the patients.[8] This ratio is also compatible with our study.

The neurologic symptoms can be divided into three groups the as central nervous system (CNS), peripheral nervous system (PNS), and musculoskeletal system. CNS manifestations include headache, impaired consciousness, encephalitis, encephalopathy, ataxia, seizure, and acute cerebrovascular disease.[7] In our study, headache was the most common symptom and was seen in 14% of the patients in our study. The prevalence of headache in the adult patients varies between 13.8 and 66%.[4,7] In a cohort study involving 585 children from 21 European countries, headache was reported in 28% of the children over 5 years.[15] The frequency of headaches was reported between 3 and 9.1% of the children in the other studies.[14,18] In another study of 171 children with COVID-19, no neurologic involvement was reported.[19] CNS manifestations such as febrile and unfebrile seizures, and encephalitis were also published but we had no patients with these symptoms.[12,16]

PNS manifestations include anosmia/hyposmia, ageusia/hypogeusia, Guillain–Barre syndrome (GBS), and neuralgia.[7] In our study, anosmia/hyposmia and ageusia/hypogeusia were seen in 2.5% of the patients. Anosmia/hyposmia and ageusia/hypogeusia were the most common symptoms after headaches in the adult patients. There were high variations between the reported frequencies of these symptoms in the adult patients. A study from Wuhan reported impaired smell in 5.1% and impaired taste in 5.6% of the patients.[4] In a larger study including mild-to-moderate COVID-19 adult patients, the incidence of impaired smell and taste was 85.6 and 88.8%, respectively.[20] However, in a large cohort study including pediatric patients, anosmia or ageusia was not reported.[15] In another study, these symptoms were detected in 5% of the pediatric patients with COVID 19.[14] Anosmia or ageusia was also reported as case reports.[21] In our study, there were no patients with GBS, Miller Fisher syndrome, or cranial nerve palsy but case reports, including both the pediatric and adult patients, were published.[13,22,23]

The musculoskeletal system manifestations include myalgia, myositis, and rhabdomyolysis. In our study, myalgia was seen with a frequency of 9%. Myositis or rhabdomyolysis was not detected in our study. The estimated frequency of myalgia/fatigue in children was 14.3% in a meta-analysis.[8] Myalgia,

**Table 3: Laboratory findings of the COVID-19 patients with and without neurological signs**

| | Neurologic findings | | *P* |
|---|---|---|---|
| | Negative (*n*: 246) $\bar{X}\pm$SD | Positive (*n*: 246) $\bar{X}\pm$SD | |
| White blood cell (×10⁹/L) | 6.8±2.9 | 5.7±1.9 | **0,019** |
| Lymphocyte (×10⁹/L) | 2.9±2.4 | 1.8±0.8 | **<0,001** |
| Polymorphonuclear lymphocyte (×10⁹/L) | 3.2±2.1 | 3.3±1.9 | 0,399 |
| Platelets (×10⁹/L) | 297±198 | 260±65 | **0,041** |
| NLR | 1.80±2.26 | 3.26±5.67 | **0,002** |
| PLR | 141.93±141.25 | 211.40±252.88 | **0,001** |
| CRP, g/L | 0,004±0,001 | 0,003±0,008 | 0,131 |
| ALT, U/L | 25.4±26.4 | 22.3±13.0 | 0,177 |
| AST, U/L | 29.2±18.2 | 21.7±9.0 | **<0,001** |
| LDH, U/L | 263.8±86.0 | 220.8±54.7 | **<0,001** |
| Ferritin, µg/L | 43.5±40.4 | 52.1±47.8 | 0,171 |
| Procalcitonin, µg/L | 0.06±0.12 | 0.04±0.03 | 0,869 |
| d-dimer, mg/L | 0.57±0.53 | 0.38±0.31 | **0,019** |
| CPK, U/L | 105.8±83.5 | 86.9±32.9 | **0,022** |
| Urea, mg/dl | 24.7±7.1 | 25.9±6.7 | 0,305 |
| Creatinine, mg/dl | 0.37±0.19 | 0.47±0.24 | **<0,001** |

Continuous variables are expressed as either the mean±standard deviation (SD). Continuous variables were compared with the Mann-Whitney U test. Statistically significant. *P* values are in bold

**Table 4: Multivariate logistic regression analysis**

| | Wald | *P* | OR | 95% CI for EXP (B) | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| Step 1 | | | | | |
| Age | 0,022 | 0,881 | 1,001 | 0,988 | 1,015 |
| Gender | 0,323 | 0,570 | 0,722 | 0,234 | 2,222 |
| Comorbid disease | 0,209 | 0,648 | 1,349 | 0,374 | 4,869 |
| HGB | 0,680 | 0,410 | 0,995 | 0,984 | 1,007 |
| WCC | 0,335 | 0,562 | 1,000 | 0,999 | 1,001 |
| Lenfosit | 0,000 | 0,983 | 1,000 | 1,000 | 1,000 |
| PMNL | 0,178 | 0,673 | 1,000 | 0,999 | 1,001 |
| Platelets | 2,334 | 0,127 | 1,000 | 1,000 | 1,000 |
| NLR | 0,723 | 0,395 | 0,796 | 0,470 | 1,347 |
| PLR | 1,502 | 0,220 | 1,009 | 0,995 | 1,023 |
| CRP | 0,322 | 0,570 | 1,003 | 0,993 | 1,013 |
| ALT | 2,239 | 0,135 | 1,053 | 0,984 | 1,126 |
| AST | 0,424 | 0,515 | 0,958 | 0,841 | 1,091 |
| LDH | 0,411 | 0,522 | 1,004 | 0,992 | 1,017 |
| Ferritin | 0,004 | 0,948 | 1,000 | 0,986 | 1,015 |
| Procalsitonine | 0,490 | 0,484 | 0,906 | 0,686 | 1,195 |
| INR | 1,204 | 0,273 | 0,993 | 0,980 | 1,006 |
| D-dimer | 1,602 | 0,206 | 0,983 | 0,958 | 1,009 |
| CPK | 1,674 | 0,196 | 0,985 | 0,964 | 1,008 |
| urea | 0,919 | 0,338 | 1,044 | 0,956 | 1,141 |
| Creatinine | 0,026 | 0,871 | 0,998 | 0,970 | 1,026 |
| Step 18 | | | | | |
| NLR | 3,171 | **0,075** | 0,798 | 0,622 | 1,023 |
| PLR | 7,843 | **0,005** | 1,011 | 1,003 | 1,019 |
| Platelets | 8,130 | **0,004** | 1,000 | 1,000 | 1,000 |

Statistically significant *P* values are in bold. OR; odds radio, CI (95%); confidence interval

which is common in adults, was seen in 26–51% of the adult patients.[24]

In recent reports, multisystem inflammation syndrome in children (MIS-C) associated with COVID-19 infection has been described. This syndrome has common characteristics with toxic shock syndrome and incomplete Kawasaki disease.[25] It is a likely post-infectious syndrome seen after asymptomatic or mildly symptomatic COVID-19 disease. The children with MIS-C develop acute hypotension, cardiogenic shock, and multi-organ failure. Neurologic manifestations including headache, impaired consciousness, aseptic meningitis, encephalitis, seizure, and ataxia were reported in patients with MIS-C.[9,26] According to a systemic review, the incidence of neurologic involvement in children with MIS-C was 25–50%.[27] We had no patients with MIS-C at the time of the study.

Inflammation is an important factor in the pathogenesis of the COVID-19 disease. NLR and PLR are biomarkers that give information about the inflammatory state of the patient. In recent years, NLR and PLR have been used as prognostic markers in many diseases such as cardiac conditions, solid tumors, sepsis, pneumonia, and acute respiratory distress syndrome (ARDS).[28] The role of NLR and PLR was also studied for the COVID-19 patients. The studies revealed that the elevation of NLR and PLR could be predictive of the severity and the mortality of the COVID-19 disease.[29,30] They were easily available from the routine laboratory tests. We also found elevated NLR and PLR in children with neurologic manifestations. We suggested that NLR and PLR could be predictive for the development of neurological symptoms.

The study had some limitations. First, it was performed in a single center. Multicenter studies including more patients are preferable but our hospital's inpatient capacity is quite high. Second, neurologic manifestations are subjectively perceived

only by the patients. We interviewed each patient and family one-by-one but we could miss the patients with mild symptoms. We could not perform diagnostic procedures such as brain magnetic resonance imaging, electrophysiological tests, and lumbar puncture to reduce the risk of cross-infection. A large number of patients, conducting interviews with each patient one-by-one, and the prospective design of the study are the good aspects of our study.

## Conclusion

COVID-19 can affect the nervous system. Physicians should be alert about the neurologic involvement of the COVID-19 disease in both adults and children. Early detection of neurologic involvement may lead to better clinical outcomes. The NLR and PLR ratio could have a predictive value for the development of neurological manifestations.

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### Conflicts of interest

There are no conflicts of interest.

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