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Neurological symptoms and signs associated with COVID-19 in pediatric patients: a single-center experience

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Abstract

There is insufficient evidence on SARS-CoV-2 induced neurological effects. Studies on CNS involvement during COVID-19 in children are limited. This study aims to identify and manage the neurological signs and symptoms in COVID-19-infected pediatric patients during follow up and plan future follow-ups.

Children diagnosed COVID-19 and hospitalized in the pediatric pandemic services, between March 18, 2020, and June 18, 2021, were included in the study. Children with underlying neurological disease were excluded from the study. Patient data retrieved from hospital files and medical records. Children divided into 2 groups, 1 and 2, based on the presence or absence of neurological findings.

A total of 243 children received follow-ups in the pandemic wards, 35 (14.4%) of these patients had neurological findings. Major neurological manifestations were headache (n:17, 7%), seizure (n:4, 1.6%), and anosmia/hyposmia (n:17, 7%). The number of boys (n:13, 37.1%) was smaller than the number of girls (n:22, 62.9%) in Group 1. Group 1 showed higher blood leukocyte, lymphocyte, thrombocyte, AST, LDH, d-dimer values. Anosmia/hyposmia occurred more often in girls, anosmia and headache occurred more often over 9 years of age. Pulmonary and hematologic involvement was more common in children with anosmia and headache.

Our study is one of the few studies on neurological involvement in COVID-19 in children. To the best of our knowledge, there is limited data on these subjects in the literature.

Abbrevations: AST = aspartate aminotransferase, CK = creatine kinase, CNS = central nervous system, COVID-19 = new type of coronavirus disease, CRP = C-reactive protein, CT = computed tomography, LDH = lactate dehydrogenase, NIMV = noninvasive mechanical ventilation, PICU = pediatric intensive care unit, PCR = polymerase chain reaction, SPSS = Statistical Package for the Social Sciences, WHO = world health organization.

Keywords: COVID-19, chidren, anosmia, headache, neurology, seizure.

1. Introduction

A new type of coronavirus disease, named COVID-19, emerged in Wuhan, China, at the end of 2019.[1] The virus spread rapidly worldwide, and the WHO declared COVID-19 a pandemic in March 2020.[2] Although children have a milder disease course than adults, severe clinical symptoms may develop in children and adolescents.[3–5]

Symptoms such as fever, cough, diarrhea, and myalgia due to COVID-19 constitute typical clinical findings. Neurological findings such as headache, anosmia, seizures, cerebrovascular diseases, peripheral nervous system involvement may be present in some patients.[6–26] Reports show that neurological manifestations associated with COVID-19 may arise from direct invasion of the central nervous system (CNS) by the virus, autoimmune mechanisms, worsening of preexisting neurological disease, systemic and metabolic disorders due to concomitant critical illness.[14,27,28] Studies on CNS involvement during acute infection in children are limited.[6–26] Literature shows that neurological involvement in adults during COVID-19 occurs with a varying frequency of 35–82%; however, this rate does not exceed 22% in children and is below 20% in most publications.[6,29] Most studies reported that the most common neurological findings were headache and olfactory disorders regardless of age and geographical region.[7,9,11–13,23,24,26,30,31] Evaluation of neurological manifestations according to age revealed that cerebrovascular events, encephalopathy, peripheral nervous system involvement and myelitis were more

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common in adults, while olfactory findings, seizures and headaches were more common in the pediatric age group.[9–14,23,24,26,32–41] The long-term impact of COVID-19 infection on the CNS in children remains unclear. Reports on the neurological effects of COVID-19 in adults and children are increasing day by day. A limited number of studies have reported that the long-term neurological effects of COVID-19 are also seen in children,[42–48] with insomnia, fatigue, muscle and joint pain, muscle weakness, dizziness, concentration difficulties, headache, sleep and appetite disturbances, irritability and inattention being among the most notable effects. In most of these studies, the maximum follow-up period was 6 months after the onset of the disease. However, given this short follow-up time and the novelty of the disease, it is difficult to obtain information about the neurological, cognitive and neuropsychiatric effects of COVID-19 that may occur in the future. In the subsequent years, inflammatory responses in children infected with SARS-CoV-2 may trigger mechanisms leading to an increase in neurological diseases in the long term. Data from the pediatric arm of the GCS-NeuroCOVID (NCT04379089) will be very helpful and instructive.[49] Therefore, it is critical to conduct neurological evaluation and follow-up in children with COVID-19.

Our study examined the neurological signs and symptoms detected in patients hospitalised for SARS-CoV-2. In the light of the data obtained, this study aims to identify and manage the neurological complications in COVID-19-infected pediatric patients during follow up and plan future follow-ups.

2. Material and Methods

2.1. Data collection

Children diagnosed COVID-19, according to the guidelines developed by the Turkish Republic Ministry of Health, and hospitalised in the pediatric pandemic services of State Hospital of Denizli, between March 18, 2020, and June 18, 2021, were included in the study.[50] Children with underlying neurological disease were excluded from the study. State Hospital of Denizli was designated as the pandemic hospital of Denizli for children between the specified time. SARS-CoV-2 was detected using the polymerase chain reaction (PCR) method in samples obtained from the nasopharynx and oropharynx. We retrieved retrospective patient data from hospital files and medical records. Children admitted to pandemic wards were divided into 2 groups, 1 and 2, based on the presence or absence of neurological findings. We compared the demographic features, symptoms, comorbidities, clinical and laboratory findings, treatments and prognosis between groups. We also evaluated patients' demographic characteristics, comorbidities, clinical and laboratory findings, treatments, and prognosis according to the complaints of headache, seizures and anosmia/hyposmia.

We obtained patient and parental consent for participation in research at the time of the patients' hospitalization. The study received health ethics committee approval (Ethical Committee of Pamukkale University Faculty of Medicine, date of approval 28/12/2021 and 23 approval number).

2.2. Statistical analysis

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) 22.0 software (IBM SPSS Statistics, IBM Corporation). The Chi-square test, Student *t*-test, and Mann–Whitney U-test were used; $P < .05$ was considered statistically significant.

3. Results

During our study, a total of 243 children received follow-ups in the pandemic wards. Neurological symptoms and signs developed in 35 (14.4%) of these patients. Major neurological manifestations were headache (n:17, 7%), seizure (n:4, 1.6%), and anosmia/hyposmia (n:17, 7%).

3.1. Demographic features

The number of boys (n:13, 37.1%) was slightly smaller than the number of girls (n:22, 62.9%) in Group 1. Among these patients, only 2 (5.7 %) were foreign. Assessment of the age distribution in Group 1 showed 5.7% (n:2) children below 2 years and 91.4 % (n:32) over 9 years. Underlying disease was present in 17.1 % (n:6) of children in Group 1. Major comorbidities were obesity, diabetes mellitus and hypertension. On comparing demographic characteristics, there was no statistically significant difference between the 2 groups for gender ($P = .23$) and nationality ($P = .62$), comorbidity ($P = .91$) but there was a significant difference for mean age ($P < .001$) and age distribution ($P < .001$) (Table 1).

3.2. Symptoms and physical examination

Evaluation of symptoms in Group 1 showed that 22 (62.9%) patients had fever, 13 (37.1%) had cough, 13 had myalgia (37.1%), 5 had dyspnea (14.3%), 3 had diarrhea (8.6%). The mean duration of fever in these children was 1.8 ± 1.73 (0–5) days. Comparison with the other group showed a statistically significant difference between the 2 groups for myalgia ($P = 0.03$).

In Group 1 patients, physical examination revealed fever in 22 (62.9%), abnormal respiratory sounds in 10 (28.6%), hypoxemia in 4 (11.4%), obesity in 5 (14.3%), hypertension in 3 (8.6%) patient. There was no significant difference between the 2 groups for physical examination findings. However, the

Table 1

Demographic features.

		Group 1		Group 2		
		n	%	n	%	*P*
Gender	Male	13	37.1	100	48.1	0.23
	Female	22	62.9	108	51.9	
Nationality	Immigrant	2	5.7	7	3.4	0.62
	Nonimmigrant	33	94.3	201	96.6	
Comorbidity		6	17.1	34	16.3	0.91
Age distribution	≤2 yr	2	5.7	76	36.5	<0.001
	≥9 yr	32	91.4	90	43.3	
	Mean ± SD	**Median(min–max)**		**Mean ± SD**	**Median(min–max)**	
Age (mo)	162.86 ± 49.34	180(3–212)		89.53 ± 75.79	73 (1–214)	<0.001

mean weight ($P < .001$) and mean height ($P < .001$) values were significantly different between the 2 groups. In Group 1, the mean weight was 50.06 ± 19.2 (6–85) kg, and the mean height was 155.51 ± 22.81 (68–185) cm; mean height and mean weight values were higher in Group 1. In Group 2, the mean weight was 31.4 ± 26.08 (3–110) kg, and the mean height was 116.94 ± 41.34 (46–185) cm.

3.3. Laboratory and radiology

Although no abnormalities were present in the mean values in the hemogram results, there were leukopenic, lymphopenic, neutropenic, and anemic children among the patients in each group included in our study. On comparing the laboratory findings between the 2 groups, we found statistically significant differences in blood hemoglobin ($P = .01$), leucocyte ($P = .02$), lymphocyte ($P = .01$), thrombocyte ($P < .001$), serum AST (aspartate aminotransferase) ($P = .01$), LDH (lactate dehydrogenase) ($P = .01$), d-dimer ($P < .001$), CK (creatine kinase) ($P = .02$), urea ($P = .01$) and creatinine ($P < .001$) values. The first group showed higher blood hemoglobin, serum urea and creatinine values and lower blood leukocyte, lymphocyte, thrombocyte, AST, LDH, CK and d-dimer values. When a covariance analysis was performed in terms of age, height, weight in children with and without neurological findings, it was observed that there was no statistically significant difference between serum urea and creatinine values (Table 2).

For Group 1, we detected an appearance compatible with COVID-19 in 31.4% (n:11) patients using chest radiography and 37.1% (n:13) of patients using chest computed tomography (CT). Radiological examinations showed a statistically significant difference between the 2 groups for COVID-19 pulmonary involvement in radiographs ($P = .047$) and tomography ($P < .001$). (Table 2). Of the patients included in our study, only those with headaches and seizures underwent brain MRI. It was not applied to those with anosmia/hyposmia. There were no findings to explain the neurological symptoms in patients who underwent MRI.

3.4. Treatment and follow-up

Of the patients in Group 1, 14 (40%) received favipiravir, 31 (88.6%) received antibiotics, and 5 (14.3%) received systemic steroids for medical treatment. The favipiravir (14 vs 38, 40% vs 18.3%, $P = .01$) and the systemic steroid (5 vs 8, 14.3% vs 3.9%, $P = .03$) treatments' rates showed a statistically significant difference between groups. Three children in group 1 (8.6%) had severe COVID-19 and received follow-up in the pediatric intensive care unit (PICU); 2 (5.7%) needed noninvasive mechanical ventilation (NIMV). In group 2, 7 (3.4%) patients had severe COVID-19 and received follow-up in the PICU; 1 (0.5%) needed NIMV. There was no statistically significant differences between the 2 groups for disease severity ($P = .66$), need for intensive care ($P = .16$), need for NIMV ($P = .06$).

Patients in Group 1 received follow-ups for a mean of 0.37 ± 1.46 days in the PICU and 6.11 ± 2.48 days in the hospital; patients in group 2 received follow-ups for a mean of 0.09 ± 0.69 days in the PICU and 5.44 ± 2.18 days in the hospital. Of these 2 parameters, there was no statistically significant difference between the 2 groups ($P = .07$, $P = .24$). None of the patients in either Group 1 or Group 2 died.

3.5. Clinical findings according to neurological manifestations

Anosmia/hyposmia was more common in girls (13 vs 4, 76.5% vs 23.5 %, $P = .04$) and over 9 years of age (n:16, 94.1%, $P < .001$). The frequency of COVID-19 involvement on chest CT was higher in children with anosmia (n:9, 52.9%) than in other children (n:31, 13.7%), with statistical significance ($P < .001$). Mean values of height ($P < .001$), weight ($P < .001$), blood leucocyte ($P = .03$), lymphocyte ($P = .01$), thrombocyte ($P < .001$), mean CRP (C-reactive protein) ($P = .02$), AST ($P = .02$), LDH ($P = .01$), d-dimer ($P = .03$), urea ($P = .05$) and creatinine ($P = .01$) were statistically significantly different from those of children without these complaints. When a covariance analysis was performed in terms of age, height, weight in children with and without anosmia/hyposmia, it was observed that there was no statistically significant difference between serum urea and creatinine values. When other laboratory findings were examined, it was found that the group with anosmia/hyposmia was more leukopenic, lymphopenic and thrombocytopenic than the other group. In addition, serum CRP, AST, LDH and d-dimer values were higher in the group without anosmia/hyposmia than in the other group. Moreover, it was observed that 2 of the children in the anosmia/hyposmia group had severe illness ($P = .04$).

Similarly, the majority of patients in the group with headache were over 9 years of age (n:17, 100%, $P < .001$), and COVID-19 involvement on chest CT was higher in children with headache (n:5, 29.4% vs n:35, 15.5%, $P = .01$). Although there was no statistically significant gender difference in this group ($P = .65$), mean values of height ($P < .001$), weight ($P = .01$), age ($P < .001$), blood hemoglobin ($P = .01$), leucocyte ($P = .03$), lymphocyte ($P = .01$), thrombocyte ($P = .02$), serum

Table 2

Laboratory and radiology.

	Group 1		Group 2		
	Mean	Min-max	Mean	Min–max	*P*
Heamoglobin (g/L)	13.52 ± 1.62	9.6–17.3	12.68 ± 1.63	7.3–17.4	0.01
Leukocyte count (/mm^3)	6542.86 ± 3177.98	3200–18,400	7925.44 ± 3913.49	2500–28,100	0.02
Lymphocyte count (/mm^3)	2036 ± 876.79	480–4880	3357.38 ± 2398.13	450–12,400	0.01
Thrombocyte count (/mm3)	213114.29 ± 60074.84	88,000–402,000	270355.34 ± 89795.49	79,000–623,000	<0.001
AST (U/L)	24.49 ± 10.56	10–53	32.27 ± 18.83	7–138	0.01
LDH (U/L)	232 ± 89.48	132–514	269.66 ± 81.97	74–563	0.01
D--dimer	0.44 ± 0.46	0.19 ± 2.36	1.34 ± 3.74	0.19–33.93	0.001
Creatinin kinase (U/L)	88.36 ± 95.95	26,525	100.54 ± 90.82	5.1–969	0.02

	Group 1		Group 2		
	n	%	n	%	*P*
X-ray compatible with covid	11	31.4	36	17.3	0.047
CT compatible with covid	13	37.1	27	13	<0.001

AST ($P = .04$), d-dimer ($P = .01$), troponin ($P = .01$) and creatinine ($P < .001$) were statistically different compared to other children in this group. The covariance analysis revealed that the differences in serum creatinine and blood hemoglobin values were also related to age, height, weight in these children. Blood leukocyte, lymphocyte and thrombocyte levels were found to be lower in children with headache compared to those without headache, and serum AST, d-dimer and troponin values were found to be higher in children with headache compared to children without headache.

As mentioned above, there were only 4 patients in the seizure group. Among these patients, only one was girl. The mean age of the children in this group was 79.00 ± 88.71 (3–190) months. Assessment of the age distribution in seizure group showed 2 children below 2 years and 2 over 9 years. None of the patients in seizure group received favipiravir, antibiotics and/or systemic steroids, for medical treatment. Moreover, none of them needed PICU follow-up and/or NIMV support.

4. Discussion

In our study, 35 (14.4%) children hospitalized for COVID-19 developed neurological symptoms and signs. Studies based on the neurological manifestations of COVID-19 in the literature show that the frequency reaches 36% in adults, while a limited number of pediatric reports show variations between 4–28%, similar to our study.[6–26] Similar to the literature, major neurological manifestations among our patients were headache (n:17, 7%), anosmia/hyposmia (n:17, 7%) and seizure (n:4, 1.6%). However, unlike some studies, headache and hyposmia/anosmia were found with equal frequency in our study. Some studies showed the frequency of hyposmia in pediatric COVID-19 patients between 2–46% (less common than headache).[7,9–12,14,15,23,24,31,51–55] However, other studies (regardless of geographical region differences) showed that hyposmia was more common than headache.[31] Moreover, olfactory involvement was more common among younger ages in most studies.[7,9–12,14,15,23,24,31,51–55] Literature shows that the frequency of seizures in patients diagnosed with COVID-19 is less than the other 2 neurological findings and more common in hospitalised patients and those with underlying neurological disease. The frequency of seizures in children with COVID-19 varies between 0.7% and 52.9%.[6,9–12,15,23,26,53–55] Reports show that seizures are observed more frequently in patients with underlying neurological disease and/or hospitalised for severe illness.[6,9–12,15,23,26,53–55]

Unlike the literature, in our study, the number of boys (n:13, 37.1%) was slightly smaller than the number of girls (n:22, 62.9%) in Group 1.[6–26] Most studies have reported that there is no gender difference in terms of neurological findings among children.[6–26] However, 1 study reported that headache was more common in girls.[9] Interestingly, in our study, no statistically significant difference was found between children with and without headache in terms of gender. In addition, anosmia/hyposmia was more common in girls in our study. Assessment of the age distribution in group 1 showed that 5.7 % (n:2) of children were below 2 years and 91.4 % (n:32) were above 9 years; in the other group, these rates were (n:76) 36.5% and (n:90) 43.3%, respectively, with no significant difference between age groups. Although data on the age of COVID-19-infected children with neurological findings are limited, reports show that these findings are more common in young children.[6–26] The literature also shows the occurrence of seizures in older children.[24,26,56,57] However, a study reported that the frequency of seizures increased in young children, occurring at a rate of 38% under the age of 5 years.[11] Our study findings are inconsistent with literature reports as most of our patients were over 9 years. In addition; the number of children below 2 years was equal to the number of children above 9 years in the seizure group.

Evaluation of symptoms other than neurological findings showed a statistically significant difference between the 2 groups for myalgia ($P = 0.04$), suggesting that myalgia reflected neurological system involvement.

There was no significant difference between the 2 groups for physical examination findings. However, the mean weight ($P < .001$) and mean height ($P < .001$) values were significantly different between the 2 groups. Mean height and mean weight values were higher in group 1, probably because this group had a higher number of children over 9 years. Notably, neurological findings are more common in obese patients in the literature.[6,9–12,15,23,26,53–55]

Laboratory results showed statistically significant differences in blood leucocyte ($P = .02$), lymphocyte ($P = .01$), thrombocyte ($P < .001$), serum AST ($P = .02$), LDH ($P = .01$), d-dimer ($P < .001$) and CK ($P = .02$) values. The first group showed lower blood leucocyte, lymphocyte, thrombocyte, AST, d-dimer, CK and LDH values. The low blood lymphocyte and thrombocyte counts could be attributed to a higher degree of hematologic system involvement in Group 1. High serum AST, d-dimer and LDH levels may be associated with a high degree of inflammation in Group 2. However, further studies are needed to elucidate these findings. Radiological examinations showed a statistically significant difference between the 2 groups for pulmonary involvement in COVID-19 on tomography ($P < .001$).

The rates of favipiravir (14 vs 38, 40% vs 18.3%, $P = .02$) and systemic steroid (5 vs 8, 14.3% vs 3.9%, $P = .03$) treatments were statistically significantly different between the groups. These findings indicate that pulmonary involvement may be more severe in COVID-19-infected children with neurological findings. To the best of our knowledge, there is no data on this subject in the literature. In this respect, our study makes an important contribution to the literature.

Anosmia/hyposmia occurred more often in girls ($P = .04$) and over 9 years of age ($P < .001$). Dyspnea was more common among these children ($P = .02$). The frequency of COVID-19 involvement on chest CT was statistically significantly higher in children with anosmia (n:9, 52.9%) ($P < .001$). Mean values of height ($P < .001$), weight ($P = .01$), blood leukocyte ($P = .03$), lymphocyte ($P = .01$), thrombocyte ($P < .001$) and mean serum CRP ($P = .02$), AST ($P = .02$), LDH ($P = .01$), d-dimer ($P = .03$) showed a statistically significant difference compared to children without anosmia. All these findings indicate that pulmonary and hematologic involvement of COVID-19 is more common in children with anosmia. On the other hand, although systemic inflammation indicators were higher in the group without anosmia, there was not as much lung involvement as there was in the other group. In addition, unlike the analyses made according to the presence of neurological signs or headaches, high CRP in children with anosmia may be associated with olfactory system inflammation. Clearly, more studies are needed on this subject.

Most patients in the group with headache were over 9 years of age ($P < .001$), and COVID-19 involvement on chest CT was higher in children with headache ($P = .01$). However, there was no statistically significant gender difference in this group ($P = .65$). In this group, mean values for height ($P < .001$), weight ($P = .01$), blood leucocyte ($P = .03$), lymphocyte ($P = .01$), thrombocyte ($P = .02$), serum AST ($P = .04$), d-dimer ($P = .01$) and troponin ($P = .01$) were statistically different compared to other children. Similar to children describing anosmia, within the group of children with neurologic findings, lung and hematologic system involvement was more prominent in children with headache. Although laboratory findings showing systemic inflammation were higher in patients without headache, there was less lung and hematological system involvement compared to those with headache.

Anosmia and headache were observed more often in older children, probably because older children could express their complaints.

The main limitations of our study are the small sample size and the retrospective study design.

Our center is the largest pandemic hospital for children in our city. Majority of pediatric patients with neurological findings in our city were included in our study during the 3 peak periods of the pandemic. However, the number of patients we could include in the study was small.

Our study is retrospective, and the long-term neurological effects of COVID-19 on our patients have not been examined. However, the information we obtained from the literature raised our awareness of the need to pay attention to this aspect in the follow-up of our patients.

It has once again become clear that there is a need for well-planned, multicenter prospective studies on this subject.

5. Conclusions

Our study is one of the few studies on neurological involvement in COVID-19 in children. In our study, most patients were over 9 years old, and there were slightly more girls than boys, unlike other studies in the literature. Furthermore, more severe pulmonary and more frequent hematologic system involvement occurred in children with neurological manifestations. The same findings drew our attention even when children were divided into subgroups with anosmia and/or headache. To the best of our knowledge, there is limited data on these subjects in the literature.

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Author contributions

Conceptualization: Dicle Sener Okur (DSO), data curation: DSO, investigation: DSO, methodology: DSO, project administration: DSO, writing – original draft: DSO.

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