Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Research Article

J Exp Clin Med
2023; 40(4): 703-709
doi: 10.52142/omujecm.40.4.7

Effect of COVID-19 on neuromotor development of infants: A case control study

Emine TEKİN[1,*], Handan Ayhan AKOĞLU[2], Muhammet BULUT[2], Fuat SÖNMEZ[3] Mintaze KEREM GÜNEL[4]

[1] Department of Pediatric Neurology, Faculty of Medicine, Giresun University, Giresun, Türkiye
[2]Department of Pediatry, Faculty of Medicine, Giresun University, Giresun, Türkiye
[3]Child Physiotherapy, Physical Therapy Center, Giresun, Türkiye
[4]Department of Physical Therapy and Rehabilitation, Faculty of Physical Therapy and Rehabilitation, Hacettepe University, Ankara, Türkiye

Received: 03.05.2023 • **Accepted/Published Online:** 18.09.2023 • **Final Version:** 29.10.2023

Abstract

The effects of the COVID-19 pandemic on the neuromotor development of infants are not clear yet. Based on the hypothesis that COVID-19 may cause a delay in infant neuromotor development, this study aimed to evaluate and compare the neuromotor development of 6-18 month-old infants hospitalized for COVID-19 and healthy children. All of the children were assessed at one point by the pediatric neurologist and pediatric physiotherapist. The Denver II developmental screening test (DDST), Hammersmith Infant Neurological Examination (HINE) test, and Alberta Infant Motor Scale (AIMS) were used to determine the neurodevelopmental status of the infants. SARS-CoV-2 PCR-positive 27 children (14 boys, 13 girls) and 29 healthy children (15 boys, 14 girls) were included in the study. The clinical findings of most of the patients were mild. The mean age of the patients was 11.4±4.2 months, and the mean length of hospital stay was 4.6±2.4 days. The most common symptom was fever in 19 patients (70%), followed by cough (25.9%), diarrhea (25.9%), vomiting (18.5%), loss of appetite (14.8%), myalgia (11.1%), dyspnea (3.7%), and sore throat (3.7%). No significant feature was detected in laboratory and imaging findings. The DDST was abnormal in 3 COVID+ patients: one was a 6-month-old patient with a birth history of asphyxia, and the others were age-retarded in language and social development with no chronic disease. There was no significant difference in the HINE and AIMS tests. In small-scale and short-term follow-up, we found that COVID-19 did not inhibit the neuromotor development of infants except for slight retardation in language and social.

Keywords: Alberta infant motor scale, COVID-19, Denver II developmental scale, Hammersmith infant neurological examination, neuromotor development

1. Introduction

The Coronavirus Disease-2019 (COVID-19) pandemic, caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) virus, still affects the entire world. Although COVID-19 usually appears with clinical findings of the respiratory system, it can affect many systems. Neurological involvement - changes in consciousness, encephalopathy, headache, cerebrovascular events, and muscle involvement- are seen less frequently (1,2).

Approximately 2-5% of the cases are pediatric patients. Excluding Multisystemic Inflammatory Syndrome in Children (MIS-C) and serious Kawasaki-like clinical conditions, they generally apply with milder symptoms (3-5). Every day, new articles about the short and long-term effects of the virus are added to the literature; however, there is no clear information on the impact of COVID-19 on neuromotor development in infants yet.

The long-term effects of the SARS-CoV-2 virus on infants are not fully known. What kind of an effect it will have on neuromotor development in the future will be clear as a result of follow-up. Considering that it may have negative effects, the neuromotor development of infants aged 6-18 months hospitalized for COVID-19 was evaluated compared to healthy infants of the same age.

2. Material and Methods

This study was designed as a case-control study to determine whether COVID-19 infection has a negative effect on the neuromotor development of infants. As the case group, 6-18 month-old infants who were hospitalized and treated at the Children's Hospital due to COVID-19 between September 2020 and June 2021 were included in the study. 27 of 42 patients who definitively tested SARS-CoV-2 PCR + based on their nasopharyngeal swab sample agreed to participate in the study. Three infants with MIS-C were excluded.

*Correspondence: dreminetekin@yahoo.com

Randomly selected healthy infants of the same age who applied to the Children's Hospital for the follow-up of healthy children were included in the study as the control group. The Denver II developmental screening test, Hammersmith Infant Neurological Examination (HINE), and Alberta Infant Motor Scale (AIMS) were used to evaluate the neuromotor development of case and control groups. All groups were examined by the same pediatric neurologist, and HINE and AIMS evaluations were made by the same pediatric physiotherapist. Sociodemographic data and clinical findings of the patients were recorded in the patient form by examining the hospital records.

Patients were examined for HINE and AIMS assessments when they reached the 6th, 9th, 12th, 15th, or 18th months at one point, and the Denver II developmental tests were performed synchronously. In addition, HINE, AIMS, and DENVER II tests were applied to the control groups in the same age range.

2.1. Tests

Hammersmith Infant Neurological Examination (HINE): The test was developed for infants aged two months to 24 months. It consists of three steps and three subsections. The section consists of 26 steps and aims to evaluate the neurological status of the infant. This section is used when calculating the optimal score. Other sections include developmental motor milestones and behavioral status but are not included in the scoring.

Alberta Infant Motor Scale (AIMS): This observational scale evaluates the motor development of infants from birth to independent walking. It consists of 58 items observed in prone, supine, sitting, and standing positions. A validity study was conducted for Turkish infants, and the norms are valid for Turkish infants (6).

Denver-II developmental screening test (DDST): It evaluates four main areas, personal-social, language, fine and gross motor, in children and infants aged between 0 and 60 months and offers norm values for all areas.

2.2. COVID-19 clinical classification

Based on the clinical classification of Dong et al. (3,7), the disease is classified as asymptomatic (no symptoms, SARS-CoV-2 +), mild (fever, mild upper respiratory tract infection (URTI) and gastrointestinal system (GIS) problems), moderate (dyspnea, need for intensive care), and severe (multiple organ failure, MIS-C).

2.3. Statistical Analysis

Statistical analyses were performed using the SPSS package program 25th Edition (trial version). The Shapiro-Wilk test was used to determine whether the quantitative variables were suitable for normal distribution. The Independent sample t-test was used for normally distributed quantitative variables, and quantitative variables without normal distribution were compared with the Mann-Whitney U test. Descriptive statistics of quantitative variables conforming to normal distribution were shown as mean±standard deviation, and descriptive statistics of non-normally distributed quantitative variables were shown as median (25-75th percentile) or (IQR) or (min-max). Descriptive statistics on qualitative variables were expressed as frequency (%). $p<0.05$ was considered statistically significant.

2.4. Ethics

Informed consent was taken from the parents/guardians of the patients. The study was conducted in concordance with the Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects.

Ethical approval was obtained from the local Clinical Research Ethics Committee for the study (Date: 04.03.2021, Number: 16).

3. Results

SARS-CoV-2 PCR-positive 27 children (14 boys, 13 girls) and 29 healthy children (15 boys, 14 girls) were included in the study. SARS-CoV-2 PCR + was detected in the families of 23 (85.2%) infants with SARS-CoV-2 PCR +. Only three infants with COVID-19 infection had a chronic disease (12 months with cerebral palsy, 6 months with a history of birth asphyxia, 15 months with atrial septal defect requiring medical treatment). Five (18.5%) of the children were asymptomatic; 20 (74.1%) had mild, and two (7.4%) had moderate COVID infections. The most common symptom was fever in 19 patients (70%), followed by cough (25.9%), diarrhea (25.9%), vomiting (18.5%), loss of appetite (14.8%), myalgia (11.1%), fatigue (7.4%), dyspnea (3.7%), and sore throat (3.7%). Abdominal pain, chest pain, arrhythmia, and seizures were not seen.

The mean age of the patients was 11.4±4.2 months, and the mean length of hospital stay was 4.6±2.4 days. Detailed laboratory findings of our patients are summarized in Table 1. Only one patient had lymphopenia (1200 /mm3). D-dimer was detected at >500 IU in nine patients. Vitamin D was above 20 pg/ml in all patients. Three patients were deficient in vitamin B12 (<200 pg/ml).

Table 1. Laboratory data findings of our patients

Lab	n	Median	25-75th percentil
Sedimentation (mm/h)	17	8	5,5-21,5
CRP (mg/L)	26	1,29	0,4-12
WBC (10^3 /ml)	26	8600	7445-9840
PLT (10^3 /ml)	26	282000	231000-399000
Ferritin (ng/ml)	24	167	66-262
D-dimer (ng/ml)	22	428	306-1039
Fibrinogen (mg/dl)	16	216	171-294
Vitamin B12 (pg/ml)	19	289	228-577
Vitamin D (ng/ml)	18	35	26-51
TSH (µU/ml)	19	4,6	2,24-6,45
fT4 (ng/dl)	19	1,17	0,93-1,39

CRP: C-reactive protein, fT4: Free tyroxine, PLT: Platelet, TSH: Thyroid stimulating hormone, WBC: White blood cell

Chest radiography was performed on 17 of the hospitalized patients, thorax computed tomography was performed on four, and all were reported as normal.

Patients were mostly treated symptomatically. Twenty-one patients received antibiotic treatment; 13 were given antivirals; eight were given zinc; four received steroid treatment.

The DDST was abnormal in three COVID+ patients: one was a 6-month-old patient with a history of asphyxia, and the others were infants without chronic diseases, who were age-retarded in language and social development. On the other hand, a healthy 12-month-old patient had an abnormal DDST and was retarded in gross motor development. In the 15th month, the median of the group with COVID in the gross motor step of the DDST was consistent with 17 months, while the healthy group was compatible with 16 months. Similarly, at the 9th month, the median of the group with COVID-19 at language development was compatible with 9.5 months, while the healthy group was compatible with 9 months. The comparison of DDST results of infants with COVID-19 and the control group is shown in Table 2.

Table 2. Comparison of Denver developmental screening test between COVID-19 positive and healthy infants

Age (Median)	6 months			9 months			12 months			15 months			18 months		
Denver	C (n=7)	H (n=8)	p	C (n=4)	H (n=4)	p	C (n=7)	H (n=9)	p	C (n=5)	H (n=3)	p	C (n=4)	H (n=5)	p
Examination time after COVID infection (Months)	4.4 (3.5-5.5)			6.1 (3.5-8)			5.6 (3-8)			8.5 (7-10.5)			4.8 (2.5-11.5)		
Gross motor	6	6.5	0.15*	9.5	10	1**	12	12	0.84*	17	16	0,4*	19	20	0,56*
Fine motor	6	7	0.12*	9.5	10	0.69*	12	12	0.76*	15	16	0.14*	18.5	22	0.35**
Language	6*	7.5*	0.04*	9.5	9	1*	12	13	0.47*	15	20	0,15**	19.5	20	0.72**
Social	7	7,5	0.28*	9	9	0.78**	12	13	0.17*	16	17	0.3**	18	24	0.56*

C=Infants with COVID-19, H= Healty infants, * Mann Whitney U test **Independent T test

Contrary to expectations, median and mean HINE scores at 15 and 18 months were higher in COVID+ compared to the healthy children. This difference was not statistically significant. Evaluation of the results of the HINE test is given in Table 3 (Fig.1).

AIMS score of 6,9,15, and 18 months was slightly higher in healthy children, but in the 12th month, a slight, not statistically significant elevation was unexpectedly found in COVID + children. Evaluation of the results of the AIMS test is given in Table 4 (Fig. 2).

Table 3. Comparison of HINE test between COVID-19 positive and healthy infants

	HINE COVID-19 infants				HINE healthy infants				
Age	n	Mean	Median	Min-max	n	Mean	Median	Min-max	p
6 mo	7	69.5±7.1	72	57-78	8	73±2.7	72.5	70-77	0.25*
9 mo	4	74.5±3	75	71-77	4	75.5±0.6	75.5	75-76	1.0**
12 mo	7	72.2±4.3	74	65-77	9	75.2±2.3	76	70-78	0.10*
15 mo	5	76.8±1.8	78	74-78	3	75.3±1.2	76	74-76	0.25**
18 mo	4	77.5±0,6	77.5	77-78	5	76±1.4	76	74-78	0.11**

*Independent T test, **Mann Whitney U test

HINE optimal score cut off value is 69 for 6 months 69, and 71 for the 9,12,15 and 18 months

Table 4. Comparison of AIMS test between COVID-19 positive and healthy infants

	AIMS COVID-19 infants				AIMS healthy infants				
Age	n	Mean	Median	Min-max	n	Mean	Median	Min-max	p
6 mo	7	25.4±5.8	27	15-33	8	27.7±1.6	27.5	26-30	0.34*
9 mo	4	42.7±6.8	44	34-49	4	45.5±5.6	44.5	40-53	0.55*
12 mo	7	49.5±14.2	55	18-58	9	50.8±7.2	53	33-58	0.35**
15 mo	5	57.6±0,5	58	57-58	3	57±3.6	58	53-60	0.78**
18 mo	4	58±0.0	58	58-58	5	58.4±0.9	58	58-60	0.73**

*Independent T test, **Mann Whitney U test

AIMS 50th percentile values for 6 months: 25, for 9 months:46, for 12 months:56, for 15 months: 58, for 18 months: 58

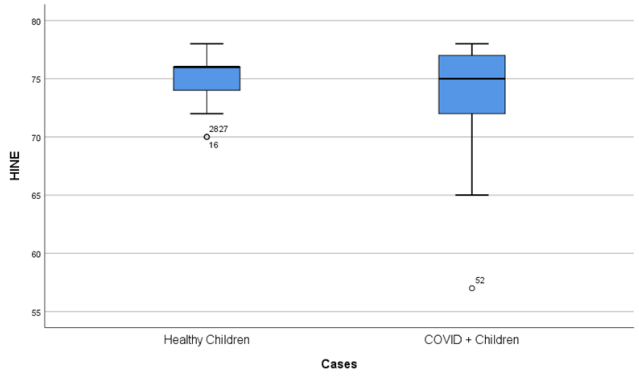

Fig. 1. Comparison of Hammersmith Infant Neurological Examination (HINE) test between healthy (median 76 points) and COVID-19-positive children (median 75 points)

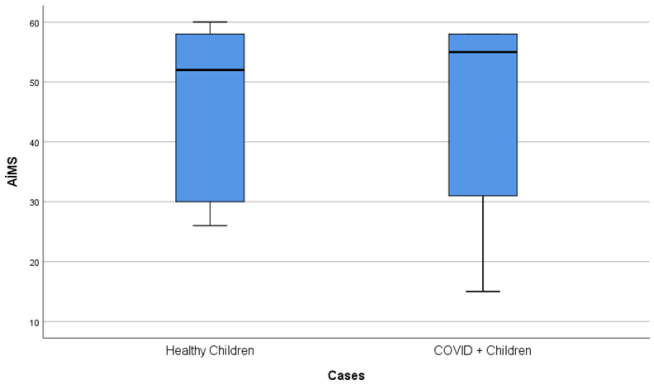

Fig. 2. Comparison of Alberta Infant Motor Scale (AIMS) test between healthy (median 52 points) and COVID-19-positive children (median 55 points)

4. Discussion

This study showed that COVID-19 does not affect neuromotor development except in the language domain in the short term period.

COVID-19 infection usually produces a milder clinical picture in children (8,9). When we compare children with adult patients, smaller numbers, lower incidence, milder symptoms, lower mortality (about 0–0.2%), and better prognosis are seen in pediatric patients. Current studies show that approximately 5% are infected with SARS-CoV-2. But also, children may become critically ill or show increased inflammatory response and experience MIS-C (10,11).

Many hypotheses have been suggested that may be the reason for the mild disease course in children, including the difference in the immune system and angiotensin-converting enzyme (ACE) receptors in adults, Bacillus Calmette-Guerin (BCG) vaccination in children, second-third generation viral exposure after adults (12,13).

Severe course of the COVID-19 disease in childhood has been associated with immunodeficiency or concomitant diseases such as type 1 diabetes mellitus, asthma, congenital heart diseases, obesity, hypertension, epileptic and neuropsychiatric disorders (14).

Malnutrition is also a risk factor for severe SARS-CoV-2 infection (15).

In our patient group, only three patients had a chronic disease, none of whom had severe COVID-19 disease. One of them was found to be retarded in the Denver developmental scale. Since one of the patients diagnosed with MIS-C died and the others were referred to an advanced center, they were not included in the study. These patients did not have any known chronic disease.

Considering the clinical table of COVID-19, pulmonary, cardiovascular, gastrointestinal, neurological, renal, ocular, and dermatological findings can be seen in addition to general findings (16). In a meta-analysis that included children aged under five, half of which were infants, respiratory and gastrointestinal system complaints were observed most frequently after fever (17). Many publications in the literature confirm this finding (10,11,18). In the study conducted by Al Yazidi et al. (19), these complaints (fever, respiratory, and GIS problems) were seen at a rate of 46.8%, 33.5%, and 31.5%, respectively. In our study, fever was seen at a higher rate (70%), whereas the others were similar. In the study conducted by Panetta et al. (20) in Canada with only infants, GIS symptoms were found at the highest rate, 85%, followed by fever and respiratory symptoms. In the study of Iijima et al. (21) in Japan, including little infants under three months, the most common symptom was respiratory symptoms, followed by fever and GIS symptoms. The same study reported that GIS involvement was less in their studies in which infants under three months were examined as a literature review (from different countries such as the USA, Saudi Arabia, and China). (21) In a study examining the clinical findings of 15-day-24-month-old infants in Turkey, the most frequently seen symptoms were fever by 65.5%, cough by 48.3%, and diarrhea by 20.7%, and it was reported that diarrhea was seen much less frequently in older children (22). Both outpatients and inpatients were included in the above-mentioned study. Although only inpatients were included in our study, similar rates indicate that the disease is generally mild. The presence of different clinical findings in different centers can be interpreted as the changes in the clinical picture due to SARS-CoV-2 variants and the changes in findings due to age.

Consistent with the literature, there were no serious abnormalities in laboratory and imaging findings (23,24). In the study in which hospitalized children were evaluated after four months of follow-up, the distribution of boys and girls and laboratory data were similar to our study. There were no patients with severe sequelae (25).

In the later stages of the pandemic, severe cases also began to be seen among children. Blazkova et al. (26) reported an infant with cerebral venous sinus thrombosis who applied with focal seizure, and Fraser et al. (27) reported a 6-month-old infant with middle cerebral artery and multi-organ infarctions after fever. Some studies reported COVID-19-related stroke

and its forms in older people (28). Bulging fontanel in a 4-month-old infant-intracranial hypertension case was reported (29). In another study, 24-, 15-, and 8-month-old patients with acute febrile encephalopathy and febrile status epilepticus were reported (30). No neurological involvement was observed in our inpatient group, but we witnessed that the patients who applied to the pediatric neurology outpatient clinic with febrile seizures tested COVID-19 positive.

Although rare, neurological damage caused by COVID-19 infection may lead to permanent pictures in infants and children. Singer et al. (31) reported in their article in which they mentioned the neurological involvement of COVID-19 decreased/absence of cognitive object examination, inability to develop imitation games, retardation in language, difficulty in learning numbers and colors in an academic sense, retardation of fine and gross motor milestones in terms of motor sense, irritability and sleep disorders in terms of behavior and mood for those between the ages of 0-3 in the signs of potential neurodevelopmental impairment following acquired brain injury table.

Since it is known that early diagnosis and intervention in neuromotor disorders will increase the success of rehabilitation, we tried to determine the neuromotor development of infants with different tests (HINE on cerebral involvement and its sequelae, AIMS on motor skills, DDST on status in four developmental stages) in our study.

Snyder et al. (32) interviewed families, babysitters, and health professionals. All of these groups thought that the pandemic period negatively impacted the environmental conditions children would need for their social, language, and motor development. The aforementioned study suggested investigating whether infants are negatively affected by pandemic conditions in areas such as muscle strength, activity level, and social development.

Shuffrey et al. (33) found that the neuromotor development of 6-month-old infants during the pandemic was retarded compared to pre-pandemic, regardless of COVID-19. The 6th-month neuromotor development of infants exposed to SARS-CoV-2 in the intrauterine period and infants born during the COVID-19 pandemic independent of the mother's SARS-CoV-2 status were evaluated and compared with children whose neuromotor development was checked with the same test before the pandemic. It was observed that the gross motor, fine motor, and social development of 114 infants with and without intrauterine exposure during the COVID-19 pandemic were statistically significantly lower at six months compared to 62 children before the pandemic.

Our study evaluated infants of different ages with and without COVID-19 infection. Language development in the sixth month was significantly lower in patients with COVID-19, and there was no statistical difference in other developmental areas. We attribute this to the fact that the study was cross-sectional, that the tests were performed at a single center, and that the disease did not affect children since it was mostly asymptomatic or mild. Repeating the test with the same infant at different months would be more reliable. However, we think that long-term follow-up is necessary for these infants.

The infection directly affects the body functions; however, we cannot ignore the fact that social and child psychology are affected, the care is completely left to the responsibility of the nuclear family during infancy, and the screen exposure increases because people stay at home. It is known that prolonged screen time causes retardation in cognitive, language, and motor development (34). Although it is generally thought that children fall behind in language, cognitive, and motor skills, it has been observed that children are not adversely affected by this situation and are resilient. (35) We will be able to see the results of the studies on this subject in the literature in the near future.

Limitations of research **:** There are some limitations of our study. The sampling size is small, and the study was carried out with patient data from only one center; a total of 56 children (27 COVID+, 29 healthy children) were included. Results may vary with larger sample sizes and multicentric data from different regions. The neurodevelopmental assessment was done at one point, and the infants' previous developmental state is unknown. However, the tests used in this study are not routinely recommended for the healthy children examination. Further studies on this subject are needed.

Strengths of research: All babies were examined by the same pediatric neurologist, and three identical tests measuring neuromotor development (DDST II, HINE, and AIMS) were used to provide objective data.

This case-control study investigated whether there was a pause or regression in the neuromotor development of infants who had COVID-19.

Neuromotor retardation was not detected in our examination and the results of objective tests such as DDST II, HINE, and AIMS. There was a statistical significance only in the language section of DDST II of the 6-month-old babies with COVID-19 who were behind the healthy ones, but they were not out of the normal. (6-7.5 months) During the small-scale and short-term follow-up, we found that COVID-19 did not pose an obvious obstacle to the neuromotor development of infants.

Conflict of interest

The authors declare no conflict of interest.

Funding

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical statement

Ethical approval was obtained from the local (Giresun

University) Clinical Research Ethics Committee for the study (Date: 04.03.2021, Number: 16). Informed consent were taken from the parents/guardians of the patients. The study was conducted in concordance with the Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects.

Acknowledgments

We thank Doctor Kıvanç Çelikkalkan for his support and assistance.

Authors' contributions

Concept: E.T., F.S., Design E.T., F.S., Data Collection or Processing: E.T., H.A.A., M.B., F.S., M.K.G., Analysis or Interpretation: E.T., H.A.A., M.B., F.S., M.K.G., Literature Search: E.T., H.A.A., M.B., F.S., M.K.G., Writing: E.T., H.A.A., M.B., F.S., M.K.G.

References

1. Mao L, Jin H, Wang M et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol. 2020;77(6):683-690. doi: 10.1001/jamaneurol.2020.1127. PMID: 32275288; PMCID: PMC7149362.

2. Wu Y, Xu X, Chen Z et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun. 2020;87:18-22. doi: 10.1016/j.bbi.2020.03.031. Epub 2020 Mar 30. PMID: 32240762; PMCID: PMC7146689.

3. Dong Y, Mo X, Hu Y et al. Epidemiology of COVID-19 Among Children in China. Pediatrics. 2020;145(6):e20200702. doi: 10.1542/peds.2020-0702. Epub 2020 Mar 16. PMID: 32179660.

4. Tezer H, Bedir Demirdağ T. Novel coronavirus disease (COVID-19) in children. Turk J Med Sci. 2020;50(SI-1):592-603. doi: 10.3906/sag-2004-174. PMID: 32304191; PMCID: PMC7195991.

5. Zimmermann P, Curtis N. Coronavirus Infections in Children Including COVID-19: An Overview of the Epidemiology, Clinical Features, Diagnosis, Treatment and Prevention Options in Children. Pediatr Infect Dis J. 2020;39(5):355-368. doi: 10.1097/INF.0000000000002660. PMID: 32310621; PMCID: PMC7158880.

6. Kepenek-Varol B, Hoşbay Z, Varol S, Torun E. Assessment of motor development using the Alberta Infant Motor Scale in full-term infants. Turk J Pediatr. 2020;62(1):94-102. doi: 10.24953/turkjped.2020.01.013. PMID: 32253872.

7. Society of Pediatrics Chinese Medical Association; Editorial Board Chinese Journal of Pediatrics. Recommendations for the diagnosis, prevention, and control of the 2019 novel coronavirus infection in children (first interim edition). Zhonghua Er Ke Za Zhi. 2020;58:E004. doi: 10.3760/cma.j.issn.0578-1310.2020.0004

8. Wald ER, Schmit KM, Gusland DY. A Pediatric Infectious Disease Perspective on COVID-19. Clin Infect Dis. 2021;72(9):1660-1666. doi: 10.1093/cid/ciaa1095. PMID: 32766824; PMCID: PMC7454399.

9. Mark EG, Golden WC, Gilmore MM et al. Community-Onset Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Young Infants: A Systematic Review. J Pediatr. 2021;228:94-100.e3. doi: 10.1016/j.jpeds.2020.09.008. Epub 2020 Sep 8. PMID: 32910943; PMCID: PMC7477627.

10. DeBiasi RL, Song X, Delaney M et al. Severe Coronavirus Disease-2019 in Children and Young Adults in the Washington, DC, Metropolitan Region. J Pediatr. 2020;223:199-203.e1. doi: 10.1016/j.jpeds.2020.05.007. Epub 2020 May 13. PMID: 32405091; PMCID: PMC7217783.

11. Wang L, Li G, Yuan C et al. Progress in the Diagnosis and Treatment of COVID-19 in Children: A Review. Int J Gen Med. 2021;14:8097-8108. doi: 10.2147/IJGM.S335888. PMID: 34795516; PMCID: PMC8594783.

12. Zimmermann P, Curtis N. COVID-19 in Children, Pregnancy and Neonates: A Review of Epidemiologic and Clinical Features. Pediatr Infect Dis J. 2020:469-477. doi: 10.1097/INF.0000000000002700. PMID: 32398569; PMCID: PMC7363381.

13. Felsenstein S, Hedrich CM. SARS-CoV-2 infections in children and young people. Clin Immunol. 2020;220:108588. doi: 10.1016/j.clim.2020.108588. Epub 2020 Sep 6. PMID: 32905851; PMCID: PMC7474910.

14. Kompaniyets L, Agathis NT, Nelson JM et al. Underlying medical conditions associated with severe COVID-19 illness among children. JAMA Netw Open. 2021;4(6):e2111182. doi:10.1001/jamanetworkopen.2021.11182

15. Beniwal N, Chaudhary P, Suman RL. Severe COVID-19 in an Infant with Severe Acute Malnutrition. Indian J Pediatr. 2021;88(11):1158. doi: 10.1007/s12098-021-03896-1. Epub 2021 Aug 3. PMID: 34342793; PMCID: PMC8329612.

16. Tezer H, Deniz M. From asymptomatic to critical illness - different clinical manifestations of COVID-19 in children. Turk J Med Sci. 2021;51(SI-1):3262-3272. doi: 10.3906/sag-2106-168. PMID: 34392672.

17. Bhuiyan MU, Stiboy E, Hassan MZ et al. Epidemiology of COVID-19 infection in young children under five years: A systematic review and meta-analysis. Vaccine. 2021;39(4):667-677. doi: 10.1016/j.vaccine.2020.11.078. Epub 2020 Dec 5. PMID: 33342635; PMCID: PMC7833125.

18. Mansourian M, Ghandi Y, Habibi D, Mehrabi S. COVID-19 infection in children: A systematic review and meta-analysis of clinical features and laboratory findings. Arch Pediatr. 2021;28(3):242-248. doi: 10.1016/j.arcped.2020.12.008. Epub 2021 Jan 9. PMID: 33483192; PMCID: PMC7794595.

19. Al Yazidi LS, Al Hinai Z, Al Waili B et al. Epidemiology, characteristics and outcome of children hospitalized with COVID-19 in Oman: A multicenter cohort study. Int J Infect Dis. 2021;104:655-660. doi: 10.1016/j.ijid.2021.01.036. Epub 2021 Jan 18. PMID: 33476759; PMCID: PMC7813479.

20. Panetta L, Proulx C, Drouin O et al. Clinical Characteristics and Disease Severity Among Infants With SARS-CoV-2 Infection in Montreal, Quebec, Canada. JAMA Netw Open. 2020;3(12):e2030470. doi: 10.1001/jamanetworkopen.2020.30470. Erratum in: JAMA Netw Open. 2021 Feb 1;4(2):e210356. PMID: 33315110; PMCID: PMC7737086.

21. Iijima H, Funaki T, Kubota M. Clinical features and outcomes of coronavirus disease 2019 in early infants in Japan: A case series and literature review. J Infect Chemother. 2022;28(4):582-586. doi: 10.1016/j.jiac.2021.12.026. Epub 2022 Jan 6. PMID: 35027300; PMCID: PMC8733281.

22. Kepenekli E, Yakut N, Ergenc Z et al. COVID-19 disease characteristics in different pediatric age groups. J Infect Dev Ctries. 2022;16(1):16-24. doi: 10.3855/jidc.15353. PMID: 35192517.

23. Guan WJ, Ni ZY, Hu Yet al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708-1720. doi: 10.1056/NEJMoa2002032. Epub

2020 Feb 28. PMID: 32109013; PMCID: PMC7092819..

24. Liguoro I, Pilotto C, Bonanni M et al. SARS-COV-2 infection in children and newborns: a systematic review. Eur J Pediatr. 2020;179 (7):1029–46, doi:http://dx.doi.org/10.1007/s00431-020-03684-7.

25. Denina M, Pruccoli G, Scolfaro C et al. Sequelae of COVID-19 in Hospitalized Children: A 4-Months Follow-Up. Pediatr Infect Dis J. 2020;39(12):e458-e459. doi: 10.1097/INF.0000000000002937. PMID: 33003103.

26. Blazkova J, Skalicky P, Bradac O, Benes V Jr. Cerebral venous sinus thrombosis in infant with COVID-19. Acta Neurochir (Wien). 2022;164(3):853-858. doi: 10.1007/s00701-022-05116-x. Epub 2022 Jan 19. PMID: 35043266; PMCID: PMC8766351.

27. Fraser S, Ellsworth M, Perez N et al. Cerebral Infarctions in an Infant With COVID-19 Delta Variant Infection and Disseminated Tuberculosis. Pediatr Neurol. 2022;126:112-113. doi: 10.1016/j.pediatrneurol.2021.10.014. Epub 2021 Oct 25. PMID: 34839267; PMCID: PMC8542513.

28. Appavu B, Deng D, Dowling MM et al. Arteritis and Large Vessel Occlusive Strokes in Children After COVID-19 Infection. Pediatrics. 2021;147(3):e2020023440. doi: 10.1542/peds.2020-023440. Epub 2020 Dec 4. PMID: 33277353.

29. Schiff J, Brennan C. Covid-19 presenting as a bulging fontanelle. Am J Emerg Med. 2021;43:81-82. doi: 10.1016/j.ajem.2021.01.062. Epub 2021 Jan 28. PMID: 33548683; PMCID: PMC7843070.

30. Raj SL, Vasanthi T, Baineni R, Sivabalan S. Neurological Manifestations of COVID-19 in Children. Indian Pediatr. 2020;57(12):1185-1186. doi: 10.1007/s13312-020-2079-0. PMID: 33318330; PMCID: PMC7781831.

31. Singer TG, Evankovich KD, Fisher K, Demmler-Harrison GJ, Risen SR. Coronavirus Infections in the Nervous System of Children: A Scoping Review Making the Case for Long-Term Neurodevelopmental Surveillance. Pediatr Neurol. 2021;117:47-63. doi: 10.1016/j.pediatrneurol.2021.01.007. Epub 2021 Jan 29. PMID: 33676141; PMCID: PMC7988307.

32. Snyder K, Chaudhary P, Pereira A, Masuda K, Niski J, Dinkel D. Early impact of the COVID-19 pandemic on promotion of infant activity, strength and communication: A qualitative exploration. Acta Psychol (Amst). 2022;222:103480. doi: 10.1016/j.actpsy.2021.103480. Epub 2021 Dec 22. PMID: 34971950; PMCID: PMC8719057.

33. Shuffrey LC, Firestein MR, Kyle MH et al. Association of Birth During the COVID-19 Pandemic With Neurodevelopmental Status at 6 Months in Infants With and Without In Utero Exposure to Maternal SARS-CoV-2 Infection. JAMA Pediatr. 2022:e215563. doi: 10.1001/jamapediatrics.2021.5563. Epub ahead of print. PMID: 34982107; PMCID: PMC8728661.

34. Lin LY, Cherng RJ, Chen YJ, Chen YJ, Yang HM. Effects of television exposure on developmental skills among young children. Infant Behav Dev. 2015;38:20-6. doi: 10.1016/j.infbeh.2014.12.005. Epub 2014 Dec 25. PMID: 25544743.

35. Wenner Moyer M. The COVID generation: how is the pandemic affecting kids' brains? Nature. 2022;601(7892):180-183. doi: 10.1038/d41586-022-00027-4. PMID: 35022597.