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Original Article

Short and Medium Term Neurological Outcomes of Children with Antenatal or Neonatal Exposure to Severe Acute Respiratory Syndrome Coronavirus 2

Antenatal veya Yenidoğan Döneminde Şiddetli Akut Solunum Yolu Enfeksiyonu Sendromu Koronavirüs 2'ye Maruz Kalan Çocukların Kısa ve Orta Dönem Nörolojik Sonuçları

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ABSTRACT

Objective: Neurological complications are among the main causes of mortality and morbidity in antenatal infections. Data on the long-term outcomes of infants exposed to severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection in the antenatal or neonatal period are limited. This study aimed to investigate potential neurological complications in children with antenatal or neonatal exposure to SARS-CoV-2.

Method: In this prospective cross-sectional study, infants and toddlers with a history of antenatal or neonatal SARS-CoV-2 exposure underwent neurological evaluation by a pediatric neurologist.

Results: Of 31 children (19 males, median age 9.3 months) included in the study, maternal coronavirus disease-2019 (COVID-19) diagnosis was made in the first trimester of pregnancy in 1, the second trimester in 3, and the third trimester in 25 children. Two children were diagnosed with COVID-19 in the neonatal period, and 3 children with maternal COVID-19 diagnosis during pregnancy were also diagnosed with COVID-19 neonatally. On neurological examination, hypotonia and motor/social delays were observed in 1, microcephaly in 2, and macrocephaly in 1 child. Of the 8 children evaluated with magnetic resonance imaging, 1 had findings consistent with Joubert syndrome and the others were normal. All infants passed the standard auditory brainstem response test. The only ocular abnormalities detected were retinopathy of prematurity (stage 3) in 1 infant and poor eye contact and object tracking in the child with Joubert syndrome.

Conclusion: Our study suggests that neurological development is mostly favorable in infants and toddlers exposed to SARS-CoV-2 in the antenatal or neonatal period.

Keywords: COVID-19, newborns, pregnancy, prognosis

ÖZ

Amaç: Gebelikte geçirilen enfeksiyonlarda mortalite ve morbiditenin en önemli nedenlerinden biri nörolojik komplikasyonlardır. Şiddetli akut solunum yolu enfeksiyonu sendromu-koronavirüs-2 (SARS-CoV-2) enfeksiyonuna antenatal veya yenidoğan döneminde maruz kalan bebeklerin uzun vadeli sonuçları ile ilgili veriler kısıtlıdır. Bu çalışmanın amacı antenatal veya yenidoğan döneminde SARS-CoV-2'ye maruz kalan bebeklerde olası nörolojik komplikasyonların araştırılmasıdır.

Yöntem: Bu kesitsel, prospektif araştırmada antenatal veya yenidoğan döneminde SARS-CoV-2'ye maruz kalan bebeklere çocuk nöroloji uzmanı tarafından nörolojik değerlendirme yapıldı.

Bulgular: Çalışmaya alınan 19'u erkek toplam 31 bebeğin annelerinin 1'i ilk, 3'ü ikinci ve 25'i üçüncü trimesterde koronavirüs hastalığı-2019 (COVID-19) tanısı almıştı. İki bebek yenidoğan döneminde COVID-19 tanısı almış, 3 bebek ise annesi gebelikte COVID-19 geçirmekle birlikte yenidoğan döneminde COVID-19 tanısı almıştı. Nörolojik bakıda bebeklerin birinde hipotoni, motor ve kişisel/sosyal, ikisinde mikrosefali, birinde makrosefali saptandı. Manyetik rezonans görüntüleme ile değerlendirilen 8 bebeğin 1'inde Joubert sendromu ile uyumlu bulgular mevcut olup diğerleri normaldi. Tüm bebekler standart işitsel beyinsapı yanıtı testinden geçmişti. Bir bebekte prematüre retinopatisi (evre 3) saptanması, ayrıca Joubert sendrom tanısı alan 1 hastamızda göz teması ve obje takibinin zayıf olması dışında göz anomalisi saptanmadı.

Sonuç: Çalışmamız, antenatal veya yenidoğan döneminde SARS-CoV-2'ye maruz kalan bebeklerde nörolojik gelişimin çoğunlukla pozitif olduğunu göstermektedir.

Anahtar kelimeler: COVID-19, yenidoğan, gebelik, prognoz

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INTRODUCTION

It is not clear what effects coronavirus disease-2019 (COVID-19) infection in mothers during pregnancy or in infants during the neonatal period may have in early childhood. Several studies have shown that antenatal vertical transmission is possible but rare, and most perinatal infections are asymptomatic or progress with mild symptoms[1-7]. The available data increase our knowledge about the outcomes of infants born to mothers with COVID-19 and enable better treatment of the mother-neonate dyad (in most cases allowing room entry and breastfeeding) while also highlighting the lack of knowledge about the possible medium- and long-term effects of perinatal or transplacental severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) neonatal infection[8,9].

In the face of this ambiguity, it might be helpful to refer to other congenital infections such as cytomegalovirus (CMV) to make an educated guess about how best to monitor infants born to mothers infected with SARS-CoV-2 and infants with COVID-19 during the neonatal period[10]. Studies conducted in the last decade have linked congenital CMV infection to sensorineural hearing loss (SNHL) and neuropsychiatric involvement, even in completely asymptomatic newborns[11]. Recent studies on the long-term effects of the newly identified Zika virus also demonstrated clinical sequelae in children[12].

The neurotropism of SARS-CoV-2 could result in a broad spectrum of neuropathic effects, including potentially affecting hearing[13]. Other coronavirus infections were shown to cause neurologic invasion via retrograde neuronal pathways or the blood, and the nervous system has a recognized receptor for SARS-CoV-2[14]. Evidence also suggests that COVID-19 infection may have a negative impact on the function of cochlear hair cells in asymptomatic adult patients, potentially affecting their hearing abilities[15]. In addition, a recent study in Turkey showed that the only presenting signs of COVID-19 infection may be non-specific symptoms such as sudden SNHL[16]. These studies showed that prenatal or neonatal exposure to SARS-CoV-2 may cause neurodevelopmental harm in infants. Another study showed that the placentas of SARS-CoV-2-infected women exhibited strong immune responses such as increased expression of interferon-associated genes and increased natural killer and T-cell activation[17]. Placental changes resulting from antenatal SARS-CoV-2 infection may create a pro-inflammatory environment that exposes the fetus to potential neurological sequelae. This is due to both the inflammatory responses that occur during the infection and direct viral infection, which can lead to pathological effects in vulnerable organs such as the eyes.

The present study investigated the short- and medium-term neurological characteristics of children with intrauterine or neonatal exposure to SARS-CoV-2 infection.

MATERIALS and METHODS

This observational, prospective, cross-sectional study included children born to women who were diagnosed with SARS-CoV-2 infection during pregnancy or at the time of delivery via molecular polymerase chain reaction (PCR) test of a nasopharyngeal swab and children with a history of COVID-19 infection confirmed by nasopharyngeal swab PCR during the neonatal period since the start of the pandemic in Turkey. A total of 107 families of women who were antenatally diagnosed as having SARS-CoV-2 infection and/or children infected with COVID-19 in the neonatal period in our hospital were contacted by phone. The study was explained, and 31 infants whose families provided informed consent to participate in the study underwent neurological and developmental assessments performed by a pediatric neurologist between May and August 2022. The developmental assessment evaluated fine motor, gross motor, personal-social, and language delays and was conducted by a pediatric neurologist based on history and neurological examination[18]. Developmental tests such as the Denver or Bayley tests were not routinely administered to all patients within the scope of the study.

The children's current age, sex, self and family history, head circumference, neurological examination findings, neuroimaging [e.g., brain magnetic resonance imaging (MRI), brain computed tomography (CT), transfontanel ultrasonography], electroencephalography (EEG), blood and urine analyses (biochemistry, complete blood count, thyroxine, thyroid-stimulating hormone, infectious, nutritional, and metabolic examinations), eye examination findings, and hearing test results (Ministry of Health routine neonatal screening) were recorded in the patient follow-up form. In the presence of clinical indications, brain CT (e.g., head trauma history), brain MRI (e.g., focal seizure, prematurity, risky procedures such as mechanical ventilation, abnormal physical examination findings such as toe walking, developmental delay, microcephaly, paresis), EEG (e.g., seizure or suspected seizure) were planned.

Inclusion Criteria

- Aged 0-3 years,

- History of PCR-confirmed neonatal SARS-CoV-2 infection in child or antenatal SARS-CoV-2 in mother who had antenatal follow-up and/or delivery at our hospital,

- Informed consent obtained from a parent/legal guardian for study inclusion.

Exclusion Criteria

- Suspected but unconfirmed neonatal or maternal antenatal SARS-CoV-2 infection,

- Lack of informed consent from parent/legal guardian.

Approval for the study was received by Necmettin Erbakan University Pharmaceutical and Medical Device Research Ethics Committee [date: 13.05.2022, decision no: 2022/3785:(9696)].

The parents/legal guardians of the children provided informed consent.

Statistical Analysis

Quantitative data were analyzed using IBM SPSS Statistics version 23 and presented as mean ± standard deviation or median and range. Categorical data were presented as frequency and percentage.

RESULTS

A total of 31 infants, 19 (61.3%) of which were males, were included in the study. The clinical characteristics of the infants and mothers are summarized in Tables 1 and 2.

Of the infants included in the study, 1 of the mothers was diagnosed with COVID-19 in the first trimester, 3 were diagnosed in the second trimester, and 25 were diagnosed in the third trimester. Two infants had COVID-19 during the neonatal period without a maternal history of COVID-19 during pregnancy, and 3 infants whose mothers were diagnosed with COVID-19 during pregnancy were also diagnosed with COVID-19 during the neonatal period. On neurological examination, motor and personal-social delays and hypotonia were observed in 1 child, microcephaly in 2, and macrocephaly in 1 child.

Transfontanel ultrasonography was performed in 18 children (58%) and brain CT was performed in 1 child (3.2%), and all were found to be normal. Brain MRI was performed on 8 (25.8%) of the infants; 1 had findings consistent with Joubert syndrome and the others were normal. EEG was performed in 4 children (12.9%) and was normal in all cases. All infants passed the hearing screening test of standard auditory brainstem response (ABR). The only ocular abnormalities detected were retinopathy of prematurity (stage 3) in 1 infant and poor eye contact and object tracking in the child with Joubert syndrome.

DISCUSSION

Managing pregnant women and their babies during a pandemic is challenging. The first case series from

Table 1. Clinical characteristics of children with antenatal or neonatal exposure to SARS-CoV-2

Age (months), median (range)	9.3 (1-15.9)
Male sex, n (%)	19 (61.3)
Cesarean delivery, n (%)	9 (70.9)
Neonatal COVID-19 transmission, n (%)	5 (16.1)
Symptomatic COVID-19 transmission, n (%)	4 (12.9)
Received medical treatment for COVID-19, n (%)	4 (12.9)
Preterm birth, n (%)	12 (38.7)
Concomitant infection, n (%)	15 (48.4)
Presence of symptoms at birth/in the neonatal period, n (%)	20 (64.5)
Meconium aspiration, n (%)	3 (9.7)
Neonatal pneumonia, n (%)	14 (45.2)
Transient tachypnea of the newborn, n (%)	4 (12.9)
Seizures, n (%)	2 (6.5)
Dysmorphia, n (%)	1 (3.2)
Microcephaly/macrocephaly, n (%)	2 (6.5) / 1 (3.2)
Developmental delay: motor and social/adaptive, n (%)	1 (3.2)
Hypotonia, n (%)	1 (3.2)
Anemia/polycythemia, n (%)	9 (29) / 1 (3.2)
Thrombocytopenia/thrombocytosis, n (%)	1 (3.2) / 12 (38.7)
Leukocytosis/neutropenia, n (%)	16 (51.6) / 3 (9.6)
Jaundice, n (%)	9 (29)
Ocular findings: retinopathy of prematurity, n (%)	1 (3.2)
Sensorineural hearing loss, n (%)	0 (0)
Epilepsy, n (%)	1 (3.2)

SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, COVID-19: Coronavirus disease-2019

China provided some promising results about COVID-19 pneumonia in pregnant women, which had similar clinical features to non-pregnant adult patients and did not show vertical transmission. However, most centers adopted a cautious approach in terms of isolation during the first wave of the pandemic[19-22].

Not many studies have been done regarding the long-term effects of COVID-19 during pregnancy or its effect on infants. Previous studies on congenital infectious diseases have shown that even those without symptoms of the disease may be at risk of long-term sequelae such as vision, hearing, and neuropsychological problems [11,23,24]. Results showing strong placental inflammation during maternal SARS-CoV-2 infection strengthen this hypothesis[17].

Our study showed that neurological development is generally normal in infants exposed to SARS-CoV-2 in the antenatal or neonatal period. In comparison to a study that reported developmental delay in 13.2%, microcephaly in 5.3%, and SNHL in 5.3% of infants with in-utero Zika virus exposure over 3-year follow-up, the shorter follow-up of our patients (whose median age was 9.3 months) is a limitation in terms of monitoring language and cognitive development, but our findings are encouraging in terms of neurodevelopment[12].

Table 2. Clinical characteristics of the mothers of children with antenatal or neonatal exposure to SARS-CoV-2

Age (years), median (range)	27 (18-44)
Weeks of gestation at birth, median (range)	38 (22-40)
Advanced maternal age at birth (>35 years), n (%)	6 (19.4)
Parity-primigravida, n (%)	6 (19.4)
Consanguinity, n (%)	7 (22.6)
Antenatal fever, n (%)	11 (35.5)
Antenatal coinfection, n (%)	6 (19.4)
Multiple pregnancy, n (%)	2 (6.5)
COVID-19 vaccination status (BNT162b2), n (%)	3 (9.7)
COVID-19 vaccination timing: before pregnancy/first trimester, n (%)	2 (6.5) / 1 (3.2)
Weeks of gestation at the time of COVID-19 diagnosis, median (range)	32 (8-40)
Trimester at time of COVID-19 diagnosis, median (range)	3 (1-3)
Symptomatic COVID-19 infection, n (%)	25 (86.2)
Required medical treatment for COVID-19, n (%)	9 (29)
Radiologically documented pneumonia, n (%)	2 (6.5)

SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, COVID-19: Coronavirus disease-2019

In a study evaluating infants with intrauterine COVID-19 exposure early in the pandemic, brain MRI findings of delayed myelination with brain hypoplasia, abnormal white matter signals, and bilateral periventricular abnormal signals suggestive of hypoxic effects were reported[2]. Neuroimaging in our study consisted of transfontanel ultrasonography in 18, brain CT in 1, and brain MRI in 8 children, and the only abnormal result in all of these examinations was MRI findings consistent with Joubert syndrome in 1 child. In the literature, Joubert syndrome in a patient with congenital rubella was reported as a cerebellar anomaly believed to possibly be associated with congenital infections[25]. However, we think Joubert syndrome was coincidental in our patient rather than related to COVID-19 exposure because the mother had COVID-19 at 36 weeks of gestation (third trimester), and the formation of the cerebellum is expected to be completed before this stage.

As antenatal COVID-19 exposure happened in the third trimester in most of the patients in our study (n=25, 80.6%), a statistically significant comparison could not be made with COVID-19 exposure in the first two trimesters or during the neonatal period. In a study by Rosen et al.[26] evaluating 55 pregnant women (similar in age to our maternal population) who had COVID-19 in the first 2 trimesters, no abnormalities in central nervous system development were detected by fetal ultrasound or brain MRI. The preterm birth rate was 3.4% in that study and 38.7% in our study, suggesting maternal COVID-19 in the third trimester could be a risk factor for preterm birth compared to infection in the first 2 trimesters. A study conducted on 388 pregnant women who were confirmed to have SARS-CoV-2 infection found that most cases were diagnosed in the third trimester and 26.3% gave birth before term[27].

In the study by Rosen et al.[26] cited above, all but 1 of the 55 infants were reported to be asymptomatic or mildly symptomatic during the neonatal period. In contrast, approximately 65% of the patients in the present study were symptomatic in the neonatal period, 16% were diagnosed with COVID-19 in the neonatal period (13% of which were symptomatic), 10% had meconium aspiration syndrome, 45% had neonatal pneumonia, 13% had transient tachypnea of the newborn,

29% had neonatal jaundice, and 1 patient developed *Streptococcus agalactiae* meningitis and associated focal seizure (based on the ILAE 2017 classification: focal impaired awareness with motor onset) and epilepsy (based on the ILAE 2017 classification: focal epilepsy, etiology: infectious) during the neonatal period[28]. However, except for the patient with Joubert syndrome, all children showed age-appropriate neurological development, and the patient with neonatal meningitis exhibited no seizures after the neonatal period. Compared to the results reported by Rosen et al.[26], these data suggest a risk of neonatal complications in third-trimester maternal COVID-19 infection compared to the first 2 trimesters but make no difference in terms of longer-term neurological outcomes. The patient samples in their study and the present study were similar in terms of the rate of symptomatic COVID-19 (90.4% and 86.2%, respectively) and prevalence of antenatal maternal fever during COVID-19 (31.4% and 35.5%, respectively)[26]. However, while Rosen et al.[26] reported a 10.3% rate of cesarean delivery in their study, this rate was 70.9% in our study. This may be related to the possible negative impacts of COVID-19 on fetal and maternal well-being in the last trimester, as well as physicians and families being worried about COVID-19 vertical transmission. Rosen et al.[26] showed that COVID-19 in the first two trimesters was not associated with vertical transition.

In our study, apart from our patient who developed symptomatic seizures due to neonatal meningitis (*S. agalactiae*), one child with neonatal COVID-19 infection had febrile seizures (focal impaired awareness with motor onset according to the ILAE 2017 classification) three times, at 7, 10, and 12 months of age[28]. Both of these patients had normal neurological examination findings during follow-up and normal EEG and brain MRI. An epileptic seizure is a frequent symptom in COVID-19. In a study using EEG in critical COVID-19, seizures were documented in 63.6% of patients[29]. Epileptiform activity is reported to be mainly focal (most commonly frontal) in the EEGs of COVID-19 patients[29,30]. Few studies have focused on the relationship between antenatal and neonatal COVID-19 and the occurrence of seizures and epilepsy development in children. However, our patient with antenatal COVID-19 exposure and meningitis-related seizures in the neonatal period and our patient with neonatal COVID-19 and febrile seizures both exhibited normal neurological development during follow-up, with normal EEG and brain MRI findings.

In our study, ABR screening at birth demonstrated normal hearing in all children. These outcomes were more favorable than those in a previous study on infants with intrauterine SARS-CoV-2 exposure, which reported defects in the medial olivocochlear efferent system[31]. However, this discrepancy may be due to methodological differences, as that study used otoacoustic emission tests, and our study used ABR. A retrospective study suggested that antenatal COVID-19 exposure caused transient abnormalities in ABR test results[32]. Considering the different results reported for audiological outcomes in adults with SARS-CoV-2 infection, we recommend longer-term studies including more patients to clarify this issue[33].

In a study in which 20 infants with intrauterine and perinatal COVID-19 exposure underwent ophthalmological assessments using fundus fluorescence angiography (FFA), optical coherence tomography (OCT), and behavioral assessment of visual functions at 3-7 months, OCT in all infants was normal, while abnormal FFA findings such as choroidal perfusion abnormalities, peripheral choroidal hypofluorescence, mild obliteration of the capillary bed, and vascular tortuosity were observed in up to 15% of the infants[1]. In a visual function study, although most infants showed normal behavioral assessments, 30% of them had reduced attention at a distance, and 15% had reduced contrast sensitivity[1]. Compared to that study, the lack of OCT and FFA data is a limitation of our study. However, eye examinations were normal in our patients except for the detection of stage 3 retinopathy of prematurity in a preterm infant (gestational age of 29 weeks) and poor eye contact and object tracking in a patient diagnosed with Joubert syndrome. In another study in the literature, ophthalmological assessment of 165 neonates with intrauterine COVID-19 exposure revealed venous engorgement and vascular tortuosity in 1, intraretinal hemorrhage in 7, and retinopathy of prematurity in 2 of the infants[34]. Again, more insight could be gained by evaluating more patients over a longer follow-up period.

Study Limitations

The strength of our study stems from its prospective, cross-sectional design. Limitations of our study are the cross-sectional evaluation of a limited number of patients, the fact that some patients were too young to assess cognitive and language development, that hearing and vision assessments were made by retrieving screening data and the lack of a control group. Also, most (86.2%) of the 29 infants with intrauterine COVID-19 exposure were born to mothers with COVID-19 in the third trimester. For this reason, our results cannot be

generalized to infants born to mothers infected at earlier stages of pregnancy, when the risk of malformations is higher in theory. Nevertheless, because of the insufficient data in this area, our observations can be considered preliminary results in this regard.

CONCLUSION

In summary, although our study showed that neurodevelopment was mostly normal in infants with antenatal or neonatal SARS-CoV-2 exposure, we believe that studies with more patients, longer follow-up periods, and control groups should be conducted to better understand these infants' long-term outcomes.

Ethics

Ethics Committee Approval: Approval for the study was received by Necmettin Erbakan University Pharmaceutical and Medical Device Research Ethics Committee [date: 13.05.2022, decision no: 2022/3785:(9696)].

Informed Consent: The parents/legal guardians of the children provided informed consent.

Peer-review: Externally peer reviewed.

Author Contributions:

Surgical and Medical Practices: F.M.A.Ö., F.H.Y., Concept: F.M.A.Ö., F.H.Y., Design: F.M.A.Ö., F.H.Y., Data Collection or Processing: F.M.A.Ö., F.H.Y., Analysis or Interpretation: F.M.A.Ö., F.H.Y., Literature Search: F.M.A.Ö., F.H.Y., Writing: F.M.A.Ö., F.H.Y.

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