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Clinical Features in Infants Younger Than 2 Months of Age Hospitalized with Laboratory-Confirmed COVID-19

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ABSTRACT

Background: A limited number of studies described the clinical aspects of the new coronavirus outbreak in the infant population. This study was conducted to describe the clinical features and laboratory findings in infants younger than 2 months of age hospitalized with confirmed coronavirus disease 2019 (COVID-19) infection.

Methods: This observational retrospective cohort study included all infants aged <2 months, admitted to two pediatric state hospitals, north of Iran, between February 19, 2020, and January 1, 2021, with confirmed COVID-19 infection. The patients whose pharyngeal or rectal specimens examined for coronavirus disease using a real-time polymerase chain reaction (RT-PCR) assay was positive, were included in the research. All patients were followed until they were discharged from the hospital.

Results: Totally, 13 infants with an age range from 1 to 50 days have been recognized. More than one-third of the study patients (38.5%) have been hospitalized immediately after birth. Dyspnea and gastrointestinal symptoms were the most typical manifestations of the patients. One patient had positive RT-PCR results in cerebrospinal fluid examination

Conclusion: The median length of stay in the hospital was seven days. More than 90% of infants younger than 2 months of age hospitalized with confirmed COVID-19 infection are expected to be cured.

Keywords: Coronavirus, Infant, Pandemics

Introduction

Since the beginning of the coronavirus disease 2019 (COVID-19) outbreak in the world, a variable presentation and different routes for the transmission of the disease have been reported in adults and children (1-6). A wide spectrum of clinical manifestations and severity of the disease has been reported in infected neonates and children. Several reports indicate that children are usually asymptomatic or present with a milder disease course, compared to adults (7-11), and severe illness has been reported in 10.6% of children younger than 1 year (8). Cough, fever, and pharyngitis have been reported to be more common than other symptoms, such as upper respiratory symptoms, nausea and vomiting, or diarrhea in infected children (8, 12, 13).

The American Academy of Pediatrics suggests that Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) laboratory test conducted during the first 24-96 hours after birth has been positive in approximately 2% of infants born to mothers who were confirmed COVID-19 cases near the time of delivery (14). The literature review demonstrates that fetal growth does not appear to be affected in infected mothers, and the infants born to infected mothers do not present serious complications (6, 15, 16); however, in low- and middle-income countries, whenever the

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essential health care services are likely to be insufficient, the potential impact of COVID-19 on mothers and newborns might be some different (17).

The COVID-19 epidemic started in Iran on February 19, 2020, has spread to different parts of this country, and various age groups have been affected (18, 19). In the north region of Iran, three waves of COVID-19 outbreaks have been reported from February 2020 to January 2021 (20). As a limited number of studies described the clinical aspects of the new coronavirus outbreak in the infant population, this study was conducted to describe the clinical features and laboratory findings in infants younger than 2 months of age hospitalized with confirmed COVID-19 infection. This situation analysis can be helpful for the implementation of effective local strategies for future waves of the disease (21).

Methods

Study design, Setting, and Participants

This longitudinal descriptive study included all infants aged <2 months, admitted to two pediatric state hospitals affiliated to Babol University of Medical Sciences, north of Iran, between February 19, 2020, and January 1, 2021, with confirmed COVID-19 infection. If any of their pharyngeal or rectal specimens examined for COVID using a real-time polymerase chain reaction (RT-PCR) assay were positive, they would recruit for the research. No sampling was performed, and all of these eligible infants were included using the census. Designated isolated rooms of the neonatology unit were considered for the admission of the participants. They stayed in these rooms until the pharyngeal or rectal specimens were cleared from SARS-CoV-2 RNA in RT-PCR examination. The standard protective approaches for physicians and other related healthcare staff were considered (22). All patients were followed until they were discharged from the hospital.

Outcomes and Variable Assessment

Demographic and clinical characteristics, including age, gender, place of residence, comorbid disorders, and clinical manifestations were recorded in the research data sheets. In addition, the previous history of COVID-19 infection among their mothers and other close contacts was collected. The most important findings of the chest X-ray and clinical laboratory exams were recorded. Conducted treatment approaches, including medications, admission to the pediatric or neonatal intensive care units (PICUs or NICUs), mechanical ventilation, and duration of hospitalization were assessed. The final outcome was categorized as discharge from the hospital or death.

Detection of SARS-CoV-2 RNA in the participants' samples was confirmed using RT-PCR assay. Furthermore, the viral RNA was extracted using the Ribospin vRD plus kit (GeneAll, Seoul, South Korea) and analyzed with LightMix SarbecoV E-gene kit (TIB Molbiol, Berlin, Germany) and LightCycler Multiplex RNA Virus Master (Roche) (23).

Data Sources and Measurement

Data were collected by reviewing the hospital documents. In each hospital, a medical doctor and a fellowship of perinatal and neonatal care were responsible for evaluating the infants and recording data in the research data collection form.

Statistical Methods

Data analysis was performed using SPSS software package (version 17), and findings were presented as descriptive values.

Ethical Considerations

The patients' proxies gave a written informed consent form for the participation of the infants in this study. The study protocol was approved by the Ethics Committee of Babol University of Medical Sciences, Babol, Iran (IR.MUBABOL.HRI.REC.1399.073).

Results

Totally, 13 infants with an age range from 1 to 50 days were diagnosed as confirmed COVID-19 cases. Their demographic and clinical characteristics are presented in Table 1. According to this table, the number of male patients was higher than female infants. Most of them have not been hospitalized immediately after birth and had close contact with other COVID-19 patient. In seven infants (more than 50%), their mothers were reported to have COVID-19 infection.

The patients' clinical features, as well as imaging and laboratory findings, are summarized in Table 2. This table represents dyspnea and gastrointestinal manifestations (e.g., poor feeding, vomiting, abdominal pain, and diarrhea) as the most common clinical symptoms in the study population.

Blood, cerebrospinal fluid (CSF), and urinary samples were cultured to assess different microorganisms, and no positive culture was

found. Only one patient (a girl, 20 days of age, conscious and awake, without previous history of any diseases, was referred to the hospital because of fever [T=40°C], agitation, irritability, and continuous crying) had positive RT-PCR result in the CSF examination. The CSF specimen was tested again, 48 hours later in this infant, and RT-PCR was positive, for the second time. No infant was tested considering COVID-19 antibodies. Our finding showed pulmonary involvement in the chest X-ray of three patients (23.1%). In total, 12 (92.8%) patients were admitted to the NICU, and all 6 patients with ages <72 hours were admitted to the NICU. All patients (100%) underwent supportive treatment approaches according to standard guidelines (24) and received antibiotics for the coverage of probable bacterial infections. Two (15.4%) cases received mechanical ventilation, and no patient received antiviral medications.

One (7.7%) patient died, and the others were discharged from the hospitals. The infant who died was a preterm boy neonate, with a birth weight of 630 g. A congenital anomaly was observed in his lower extremities. A rare manifestation in this child was bloody tears. The infant's mother had suspicious clinical features of coronavirus disease before delivery; however, no definite diagnosis of COVID-19 was given to the mother. In addition to RT-PCR positive result, the neonate had an elevated serum C-reactive protein concentration in the laboratory tests. No other abnormal finding was found in serum lactate dehydrogenase, as well as lymphocyte and polymorphonuclear cells count. The infant received surfactant replacement therapy and underwent non-invasive mechanical ventilation. The patient died on the 18th day of birth. The exact cause of death in this infant is not clear; however, both COVID-19 and congenital abnormalities can be mentioned as the cause of mortality.

Table 1. Baseline demographic and clinical characteristics of infants with confirmed COVID-19 infection

Characteristics	Value
Age (day), median (IQR)	9.0 (1.0-18.0)
Age <72 hours, no. (%)	6 (46.2)
Age ≥72 hours, no. (%)	7 (53.8)
Weight (in gram), median (IQR)	3000.0 (2350.0-3750.0)
Gender: Male, no. (%)	7 (53.8)
Place of residence, Urban, no. (%)	10 (76.9)
Duration of stay in the hospital (day), median (IQR)	7.00 (5. 0- 14.0)
Hospitalization immediately after the birth no. (%)	5.00 (38.5)
Close contact with confirmed or suspected COVID-19 patients, no. (%)	9 (96.2)
Mother suspected of COVID-19, no. (%)	7 (53.8)
Comorbid anomalies, no. (%)	1 (7.7)

Table 2. Clinical features, as well as imaging and laboratory findings of infants with confirmed COVID-19 infection

Characteristics	Value
Body temperature (centigrade), median (IQR)	36.80 (35.8-38.0)
Fever, no. (%)	4 (30.8)
Hypothermia, no. (%)	3 (23.1)
Dry cough, no. (%)	0 (0.0)
Respiratory distress, no. (%)	4 (30.8)
Granting and dyspnea, no. (%)	9 (69.2)
Poor feeding or vomiting, no. (%)	4 (30.8)
Abdominal pain, no. (%)	1 (8.3)
Diarrhea, no. (%)	2 (16.7)
Pulmonary involvement in chest X-ray, no. (%)	3 (23.1)

Discussion

During three waves of COVID-19 outbreaks in the northern region of Iran, 13 infants with laboratory-confirmed disease have been recognized in two tertiary care academically affiliated children's hospitals. Similar studies demonstrated a low rate of infection in children, and this population is thought to be infected less likely when they are exposed to the virus, and clinical manifestations are expected to be milder than those in adults (8, 15, 25). Several mechanisms have been hypothesized for the less severity of COVID-19 disease in children, compared to adult patients. A recent review article represented these mechanisms as "different distribution and affinity in angiotensin-converting enzyme 2 receptors (ACE-2) and transmembrane serine protease; the age-related difference in endothelial damage and clotting function; pre-existing coronavirus antibodies and T cells; and the existence of comorbidities and serum levels of vitamin D" (26, 27). A lower rate of lymphocytopenia (3%-3.5% versus 63%) has been reported in children, compared to adults; in addition, children with COVID-19 generally have lower serum levels of procalcitonin and C-reactive protein than adults (28).

In our study, the number of boys was higher than that of girls. This finding is similar to another research performed at New York-Presbyterian Morgan Stanley Children's Hospital in that 54% of hospitalized patients were male (1), and a study in Tehran, Iran, on children aged from 4 months to 15 years that reported 63% of confirmed COVID-19 patients were male (19). Moreover, two recent systematic reviews and meta-analyses on

epidemiological characteristics of laboratory-confirmed COVID19 patients younger than 18-19 years old revealed that 57% of the infected children were male (8, 25), and the male to female ratio was 1.31 (25). This higher vulnerability of boys than girls might be attributed to the biological differences in the immune systems between men and women, and higher expression of coronavirus receptors ACE-2 in men (29).

More than one-third of the study patients (38.5%) have been hospitalized immediately after birth. Vertical transmission of COVID-19 has been reported in previous studies (30). Furthermore, breast milk samples from mothers with COVID-19 might be positive for SARS-CoV-2 RNA (31); however, mother-to-child transmission of infection through breastfeeding or other routes needs to be studied much further.

In this study, most patients (96.2%) had reported close contact with confirmed or suspected COVID-19 patients. Reported evidence revealed that 90% of the infected children might have family cluster exposure to COVID-19, and 82% of children might have contact with confirmed or suspected adult COVID-19 patients (25).

Nearly, one-third of children had fever, dyspnea and gastrointestinal symptoms were the most typical manifestations of the patients, and nobody had a dry cough. Contrary to our results, a systematic review and meta-analysis reported fever and cough in 51% and 41% of under-18-year-old patients, respectively (10). In a study performed at Tehran University of Medical Sciences, Tehran, Iran, cough, fever, nausea or vomiting, diarrhea, and dyspnea were reported in 80%, 77%, 26%, and 29% of children with COVID-19 in the age range from 4 months to 15 years, respectively (19).

In our research, 92.8% of patients were admitted to the NICU and more than 90% of children were discharged from the hospital with a median length of stay of seven days. Reported evidence in China represented a larger proportion of <1 year of age infants with severe disease, compared to older children (10.6% versus 4.8%). Furthermore, in the United States, individuals under one year of age had the highest rates of hospitalization among pediatric patients (15). A better prognosis of the disease is expected to occur in infants, compared to adults (8, 28). In addition, fewer comorbidities, better immune response, and regeneration capacity of alveolar epithelium have been listed as contributing factors to early recovery from COVID-19 in pediatric patients (27).

The most important strong point of this study is the tracing of all under 2-month-of-age infants during three waves of COVID-19 outbreak in a particular region of Iran. In this study, we did not categorize the severity of disease in the study participants; moreover, some specific laboratory exams have not been reported. Furthermore, we did not assess the infants' mothers to find confirmed COVID-19 individuals. These can be presented as the limitations of the research.

Conclusion

Granting, dyspnea, and gastrointestinal symptoms can be presented as the most typical manifestations of infants with confirmed COVID-19. More than 90% of infants with the disease are expected to be cured.

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Conflicts of interest

The authors declare that they have no competing interests.

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Authors' contributions

YZP, SM, MA, MH, MM, ZP, MN, and ZA contributed to the conception and design, acquisition of data, and interpretation of data.

SM drafted the article.

All authors have read the manuscript, revised it critically for important intellectual content and approved the final version of the article to be published.

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