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Clinical Profile and Short-Term Outcome of SARS-CoV-2-Infected Neonates from a Government Medical College in West Bengal, India

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ABSTRACT

Introduction: Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) has led to a terrifying global pandemic. The presentations in neonates are varied with less case severity compared to adults.
Aim: To describe the clinical and laboratory features and outcomes of neonates admitted with SARS-CoV-2 infection during the second surge of COVID-19 pandemic in a Government Medical College, West Bengal, India.
Materials and Methods: It is a hospital-based observational cross-sectional study conducted in the newborn unit of Burdwan Medical College and Hospital between 1 April 2021 and 31 July 2021 including all SARS-CoV-2 Real time RT-PCR (Reverse transcriptase polymerase chain reaction) positive neonates. The demographic, clinical and laboratory characteristics of all the neonates and their outcomes were documented and analysed.
Results: Twenty-two neonates were found to be SARS-CoV-2 RT-PCR positive out of which 9 (40.9%) were found to be asymptomatic and 6 (27.27%) required neonatal intensive care unit admissions. Among the symptomatic neonates, most common presentations were respiratory distress (40.9%) and gastrointestinal manifestations (40.9%). Eight (36.36%) neonates required respiratory support. Three (13.6%) neonates had pneumonia of which one had right middle lobe collapse. Laboratory parameters were nonspecific except for the two (9%) cases of multisystem inflammatory syndrome in neonates. High-resolution computed tomography findings in two cases were suggestive of SARS-CoV-2 infection-induced changes. Two (9%) neonates died of which one was likely due to SARS-CoV-2 infection.
Conclusion: Neonates with SARS-CoV-2 infection are mostly asymptomatic. However, clinicians must be vigilant as atypical presentations such as consolidation, collapse, meningitis or multisystem inflammatory syndrome may occur.

LAY SUMMARY

SARS-CoV-2 infection in neonates is rare with varied presentations ranging from asymptomatic neonates to a few presenting with multiorgan failure. The disease severity and case fatality are much less than in adults. We studied the clinical and laboratory features and outcomes of 22 neonates with SARS-CoV-2 infection during the second surge of COVID-19 pandemic. While nine (40.9%) neonates were asymptomatic, six (27.27%) required NICU admission. Pneumonia is a rare presentation in neonates but severe COVID-19 pneumonia resulting in consolidation and lobar collapse requiring positive pressure ventilation is a possibility. Multisystem inflammatory syndrome in neonates is also a clinical entity probably as a result of hyperinflammatory syndrome due to transplacental transfer of antibodies. They require rigorous treatment, close monitoring and regular follow-ups. Amniotic fluid, placental or cord blood testing is essential to ascertain the definite mode of transmission in these neonates.

KEYWORDS: SARS-CoV-2, neonates, MIS-N

INTRODUCTION

The coronavirus disease (COVID-19), caused by SARS-CoV-2, has been causing a pneumonia pandemic worldwide since December 2019 [1]. While the disease is less severe with lower case fatality in children as compared to adults, the affectability in neonates is even less with varied presentations. While some reports suggest infants to be more vulnerable to infection than young children, affectability in the neonatal period is different from children older than 28 days and has been much less reported and studied as they are mostly asymptomatic and go unidentified [2]. Less vulnerability and milder infection in neonates compared to older children is probably because they fail to develop a strong inflammatory reaction which is partially responsible for the lung injury [3, 4]. Other hypothesis considered are (1) lower expression of angiotensin-converting enzyme 2 receptor (ACE2) in lungs, (2) healthy lungs with less endothelial damage and (3) presence of innate immunity [5–8]. The fact that clinical severity is more in those with pre-existing comorbidities in adults applies to neonates as well, with morbidities relating to prematurity and perinatal events [9, 10]. This explains the fact that predisposed endothelial damage or weaker innate immunity in neonates enhances the inflammatory process leading to morbidity.

Very few cases of neonatal COVID-19 have been reported till date, and little is known regarding the route of infection, clinical presentation, management and outcome so much so that guidelines regarding effective management still varies from country to country. This study has been carried out to describe the clinical and laboratory features and outcomes of neonates admitted with SARS-CoV-2 infection during the second surge of COVID-19 pandemic following the national protocols in India.

METHODS

A hospital-based observational cross-sectional study was conducted in the newborn unit of Burdwan Medical College and Hospital between 1 April 2021 and 31st July 2021, after obtaining approval from The Institutional Ethics Committee [vide memo no BMC/PG/9524]. All the pregnant mothers had been tested for SARS-CoV-2 infection by real-time polymerase chain reaction (RT-PCR) within 5 days of delivery. All the neonates of RT-PCR-positive mothers were admitted in Special Newborn Care Unit (SNCU) immediately after birth. Nasopharyngeal and oropharyngeal swabs of these neonates were sent for RT-PCR within 48 h of life [11]. The neonates with some complaints while in postnatal ward were admitted in SNCU and their nasopharyngeal swab for RT-PCR was sent immediately at admission. Other than that, for all the outborn neonates admitted in SNCU, RT-PCR test was done at admission. The turnover time for the test was 24 h. The test was repeated immediately if any new symptoms appeared, even if the first test was negative. The neonates were monitored for mild symptoms such as rhinorrhoea, cough and fever and moderate to severe symptoms such as respiratory distress, poor feeding, lethargy, vomiting and diarrhoea [12]. All SARS-CoV-2-positive neonates were kept in COVID-19 isolation section of SNCU

for 17 days before being discharged. This was followed as per 'The Revised Discharge Policy' by the Ministry of Health and Family Welfare, Government of India, which recommended 10 days of hospital stay followed by 7 days of home isolation along with self-monitoring. Since monitoring of neonates would have been unreliable at home, the isolation period was kept to be 17 days by the Institution Advisory Board. Neonates requiring neonatal intensive care unit (NICU) admission were kept in the COVID-19 isolation section of NICU.

Symptomatic SARS-CoV-2-positive neonates were managed supportively. Appropriate respiratory support, such as continuous positive airway pressure (CPAP) or mechanical ventilation (MV), was given for respiratory distress [13]. A viral filter was placed in the expiratory limb of the ventilator circuit to minimize the risk of infection to health care workers by aerosolization [14].

The babies were fed breast milk exclusively by katori spoon or Ryle's tube as indicated. The babies were directly breastfed after their mothers were discharged [15–19]. The ones who were seriously ill received intravenous fluids as required. All the neonates were monitored thrice daily for the development or worsening of any SARS-CoV-2-related symptoms. Some neonates required mother–infant separation and NICU admission for underlying medical conditions or symptomatic illness. Caregivers wore appropriate personal protection equipment while giving routine newborn care to the infants who tested positive [20].

Operational definitions

Detection of SARS-CoV-2 ribonucleic acid (SARS-CoV-2 RNA) in a clinical specimen using RT-PCR was considered to be a laboratory confirmed case [21]. Postnatal transmission was defined as positive SARS-CoV-2 test results in neonatal nasopharyngeal swab between 24 h and 4 weeks of postnatal life [22].

Statistical analysis

Data regarding epidemiologic, demographic, clinical features, laboratory tests and chest radiographs of all the neonates were recorded and analysed. The collected data were entered into Microsoft Excel Worksheet (Microsoft, Redwoods, WA, USA) and double-checked. The Shapiro Wilk test was used to check normal distribution ($n < 2000$). Categorical data were expressed in proportion and continuous data in mean or median values.

RESULTS

Out of the 6232 mothers who were tested for SARS-CoV-2 infection by RT-PCR before delivery, 278 (4.5%) tested positive. RT-PCR was done from nasopharyngeal swabs of all the neonates born to these 278 SARS-CoV-2-positive mothers. Among these, 12 (4.3%) neonates tested positive: 1 within 24 h of life while 11 within 24–72 h during the birth admission period. Ten outborn neonates tested positive for SARS-CoV-2 infection: 9 within 7 days of life while 1 at 19th day of life (Fig. 1).

Out of the 12 SARS-CoV-2-positive inborn neonates, one tested positive in nasopharyngeal and oropharyngeal swab taken for RT-PCR at 12 h of life. Cord blood or placental blood sampling for SARS-CoV-2 of this neonate was not done due to lack of prior preparation. Nine neonates were asymptomatic and were kept for observation for 17 days before being discharged. They were roomed in with their mothers during the hospital stay. Among the symptomatic neonates, one developed hyperbilirubinemia within 24 h of life due to ABO incompatibility and required exchange transfusion. Two neonates were very preterm (28–32 weeks) with very low birth weight and were given surfactant; out of these, one required CPAP for 72 h and one had patent ductus arteriosus (PDA), developed Stage IIB necrotizing enterocolitis (NEC), required MV and died on 10th day of life [23].

Among the rest of the 10 SARS-CoV-2-positive neonates, either outborn and admitted via SNCU emergency or admitted from postnatal wards, four neonates presented with respiratory distress with Downe's Score > 3/10 within 7 days of life and required CPAP. None of them had meconium-stained liquor. Out of them, two neonates required positive pressure respiratory support for 4–6 days; third was radiologically diagnosed as pneumonia with consolidative changes and right middle lobe collapse seen in high-resolution computed tomography (HRCT) and required CPAP for >14 days;

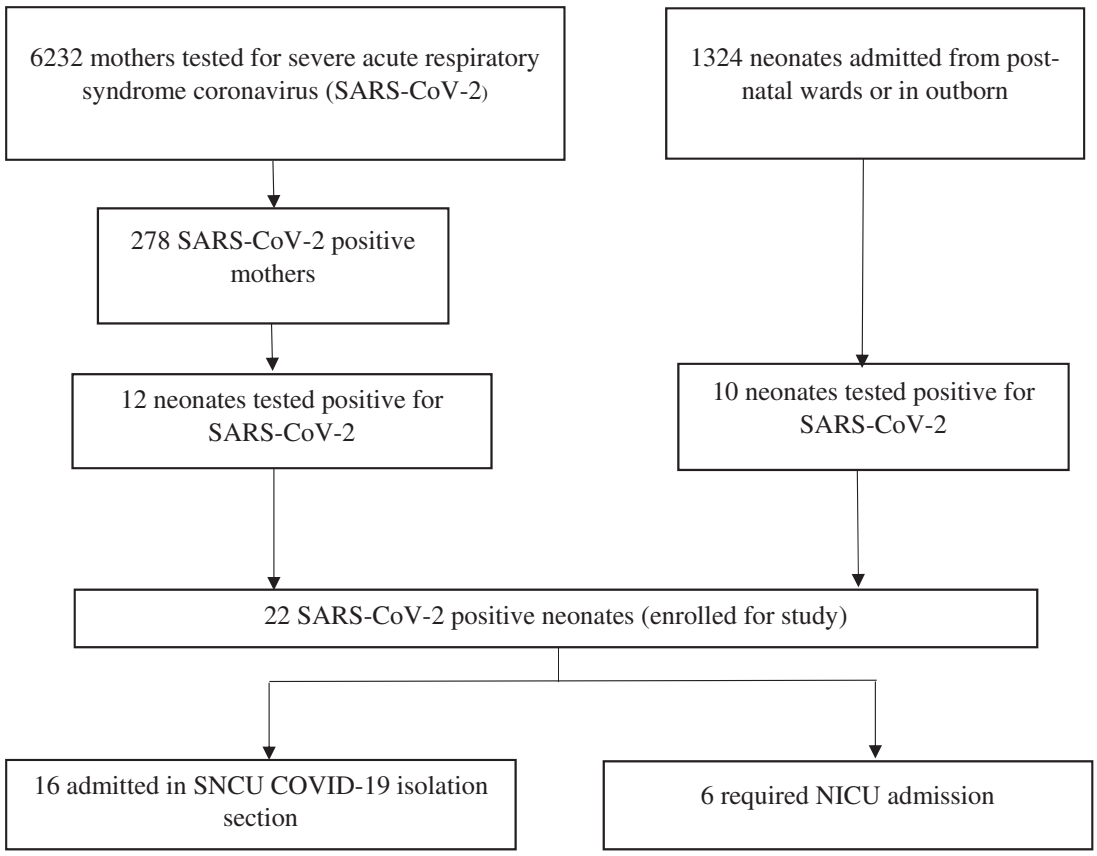

Fig. 1. Study flow chart.

fourth had refractory shock with elevated inflammatory markers, d-dimer levels and was negative on blood culture. The fourth neonate was diagnosed as a case of multisystem inflammatory syndrome in a neonate (MIS-N) and eventually died on 20th day of life after 2 days of MV. Three neonates had presented with features of sepsis, out of which two presented with hyperthermia and loose stools and one with hypoglycaemic convulsions; all these three indicated positive on blood culture and were treated accordingly. One neonate had birth asphyxia and required anticonvulsants. One had hyperbilirubinemia and required phototherapy. One was a hypotonic baby presenting with respiratory distress and lethargy on 19th day of life. This neonate was diagnosed as a case of meningitis and on further investigations had elevated inflammatory markers and d-dimer levels; had features of myocarditis with ejection fraction <70% and required inotropes while the HRCT findings showed subpleural consolidation and fibrosis. The baby was also diagnosed as MIS-N. The child was hypotonic even after recovery and was later diagnosed as spino-muscular atrophy (SMA) with homozygous deletion of exons 7 and 8 of the SMN1 gene as well as two copies of SMN2 gene through Multiplex Ligation-dependent Probe Amplification assay.

Both the diagnosed cases of MIS-N were given methylprednisolone and intravenous immunoglobulin (IVIG) as per protocol. The sociodemographic, clinical and laboratory characteristics and outcome parameters of SARS-CoV-2-infected neonates have been summarized in Tables 1 to 3, respectively. Specific details of the two neonates who died are given in Table 4.

Table 1. Sociodemographic characteristics of SARS-CoV-2-infected neonates (N = 22)

Characteristics	Values
Male	13 (59)
Gestational age in weeks[a]	35.4 (34.3, 36.8)
Birth weight (kg)[a]	2.05 (1.7, 2.4)
Length at birth (cm)[a]	46.30 (45.22, 47.85)
Caesarean section	16 (72.73)
Preterm (GA < 37 weeks)	11 (50)
Small for GA	8 (36.4)
Mother RT-PCR positive at delivery	12 (54.54)
Age at RT-PCR sampling of baby (h)[a]	30 (24, 36)
APGAR at 1 min[a]	8 (8, 8.5)
Asymptomatic	9 (40.9)
NICU admission	6 (27.27)

Data expressed as *n* (%). real time RT-PCR: Reverse Transcriptase Polymerase Chain Reaction; GA: gestational age.
[a]Data expressed as median (IQR).

Table 2. Clinical and laboratory characteristics of symptomatic SARS-CoV-2-infected neonates (N = 13)

Clinical or laboratory parameters	Values
Respiratory distress (DOWNE'S Score > 3)	9 (69.2)
Gastrointestinal manifestations (vomiting, loose stools and feed intolerance)	9 (69.2)
Poor feeding/lethargy	8 (61.5)
Neonatal jaundice requiring phototherapy/ DVET	8 (61.5)
Hyperthermia (core temperature >37.5°C)	2 (15.4)
Seizure	2 (15.4)
Birth asphyxia (APGAR < 3 at 10 min of birth or PPV > 1 min)	1 (7.7)
Hypoglycaemia (Blood glucose < 40 mg/dl)	1 (7.7)
Haemodynamically significant patent ductus arteriosus	1 (4.5)
Pre-ductal SpO_2 < 94% at admission	10 (76.9)
Haemoglobin (g/dL)[a]	15.4 (2.5)
CRP > 6.0 mg/L	8 (61.5)
Micro ESR > 15 mm in first hour	6 (46.2)
Culture positive sepsis	4 (30.8)
Hypotension/shock	4 (30.8)
Meningitis	1 (7.7)
Radiological evidence of pneumonia	3 (23.1)
LDH > 400 IU/L	2 (15.4)
Serum creatinine > 1 mg/dl	3 (23.1)
Thrombocytopenia (<150 × 10^6/L)	3 (23.1)
Ferritin > 200 ng/ml	2 (15.4)
d-dimer > 0.50 µg/ml	2 (15.4)
Liver function tests	
• ALT > 40 IU/L	1 (7.7)
• AST > 40 IU/L	1 (7.7)
Cardiac dysfunction with ejection fraction < 70%	1 (7.7)

Data expressed as *n* (%). PPV: positive pressure ventilation; DVET: double volume exchange transfusion; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase; Alt: alanine aminotransferase; AST: aspartate aminotransferase.
[a]Data expressed as median (IQR).

DISCUSSION

Neonates are said to be exposed to SARS-CoV-2 infection if they are born to the mothers diagnosed of SARS-CoV-2 between 14 days before to 28 days after delivery, or if the neonate is directly exposed to close contacts [24]. In the absence of amniotic fluid, placental or cord blood testing, it was not possible to comment on the mode of transmission of SARS-CoV-2 in the one neonate tested positive with SARS-CoV-2 RT-PCR within 24 h of life [25]. All the symptomatic SARS-CoV-2-positive neonates were premature, had comorbidities or had sepsis-like clinical manifestations, and it is difficult to interpret whether the clinical course was more influenced by the pre-existing conditions or SARS-CoV-2 infection or was aggravated by the infection on an already haemodynamically compromised neonate. We found nine babies with respiratory distress (40.9%) and nine with gastrointestinal manifestation (40.9%) as the presenting features. These findings were similar to observations by Liguoro, *et al.* [26] (40%) who found respiratory distress to be the most common manifestation among the symptomatic neonates. Gastrointestinal manifestations like diarrhoea and feed intolerance have been described in several case reports as well [27–29]. Febrile and neurologic manifestations has also been reported [30–32].

Table 3. Treatment and outcome results of symptomatic SARS-CoV-2-infected neonates (N = 13)

Respiratory support	
• Moist oxygen	4 (30.8)
• CPAP	6 (46.2)
• Invasive mechanical ventilation	2 (15.4)
Duration of oxygen (h)[a]	120 (102)
Antibiotics	10 (76.9)
Inotropic support	4 (30.8)
Methylprednisolone/IVIG/Both[b]	2 (15.4)
Anticoagulants (SC Enoxaparin)	2 (15.4)
MIS-N	2 (15.4)
Multiorgan involvement >5	1 (7.7)
Death	2 (15.4)

Data expressed as *n* (%). CPAP: continuous positive airway pressure; IVIG: intravenous immunoglobulin; SC: subcutaneous; MIS-N: multisystem inflammatory syndrome in neonates.
[a]Data expressed as median (IQR).
[b]Both the diagnosed cases of MIS-N received both methylprednisolone and IVIG.

There are very few case reports of COVID-19 pneumonia in neonates and the lung presentations are varied. While few cases of consolidation have been reported, we were not aware of any cases of lobar collapse as a result of SARS-CoV-2 in neonates while treating the baby [33, 34]. Delving into literature we found Munoz, *et al.* [35] to have dealt with a similar case of lobar collapse which required mechanical ventilation with higher positive end expiratory pressure (PEEP) which resulted in pneumothorax requiring tube thoracotomy. Contrary to this, our neonate received noninvasive ventilation (NIV) but for a duration of more than 2 weeks.

While infected neonates usually are asymptomatic or present with mild symptoms of acute viral infection, they can also present with atypical features. Encephalitic symptoms in a neonate with SARS-CoV-2 infection have been described by Lorenz, *et al.* [36] in one of the rare presentations. This case was similar to our neonate presenting with irritability, poor cry, hypotonia and refusal to feed which was later diagnosed as a case of meningitis with MIS-N in a child with SMA. Godfred Cato, *et al.* [37] described 85 infants with multisystem inflammatory syndrome in children (MIS-C) of which 83 (97.6%) tested positive for SARS-CoV-2 infection. Kappanayil, *et al.* [38] reported a case of multisystem inflammatory syndrome in a neonate with temporal association to prenatal exposure to SARS-CoV-2. Both our cases of MIS-N were similar to it in presentation with the case of hypotonic baby being more complicated due to hypotonia. Multisystem inflammatory syndrome is a postinfectious immune-mediated condition and maternal SARS-CoV-2 may potentially cause a similar hyperinflammatory syndrome due to transplacental transfer of antibodies [39–41]. The manifestations in our neonates might be related to maternal SARS-CoV-2 infection which probably went undiagnosed in cases of outborn neonates. None of these mothers had received vaccination for SARS-CoV-2, as vaccination in India above 19 years had only started during the period of study.

Treatment for MIS-N is mainly supportive. Both the neonates in our study received IVIG, steroids and low-molecular-weight heparin while the neonate that survived was followed up with Aspirin (antiplatelet therapy). This was followed as per 'The Comprehensive Guidelines for Management of COVID-19 in children below 18 years' issued by the Ministry of Health and Family Welfare, Government of India, and recommendations of American Academy of Pediatrics and Centre of Disease control and Prevention. Further studies are required to evaluate the risks and benefits of these therapies in neonates [42, 43].

The limitations of our study was the small number of subjects. It is also not prudent to use of high-dose IVIG in neonates as it is associated with a higher incidence of NEC and requires further trials to establish the risk benefit ratio in severe conditions like MIS-N [44]. Larger epidemiological and clinical cohort studies are needed to understand the implications of SARS-CoV-2 infection in neonates.

Table 4. Clinical events of the 2 SARS-CoV-2 positive neonates who died

Sl. no.	GA (weeks)	Complications	Hb (g/dl)	TLC ($\times 10^9$/L)	ANC ($\times 10^9$/L)	AST (IU/L)	ALT (IU/L)	Cr (mg/dl)	LDH (IU/L)	Ferritin (μg/L)	CXR	Treatment	Related to SARS-CoV-2
1	33	LBW with RDS and PDA. Culture positive sepsis.	8.5	3.5	1.3	75	30	1.5	264	135	GGO	Two doses of surfactant; Ibuprofen; Inotrope support; required MV.	No
2	37	Pneumonia. Elevated inflammatory markers. Developed hypotension and coagulopathy. Blood culture negative. Required MV.	7.2	11.2	3.7	82	32	1.0	1674	1540	PI with consolidation	Methylprednisolone 2 mg/kg/day × 3 days followed by 1 mg/kg/day × 2 days; IVIG 2 g/kg; Dexamethasone 0.15 mg/kg/day; Enoxaparin 0.15 mg/kg SC BID; Inotrope support; MV	Likely

GA: gestational age; LBW: low birth weight; RDS: respiratory distress syndrome; PDA: patent ductus arteriosus; MV: mechanical ventilation; IVIG: intravenous immunoglobulin; Hb: haemoglobin; TLC: total leukocyte count; ANC: absolute neutrophil count; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Cr: serum creatinine; LDH: lactate dehydrogenase; GGO: ground glass opacity; PI: pulmonary infiltrates.

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