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Original Research Article

Comparison of clinical presentation and outcome of neonatal SARS-COV2 during second wave from April-May 2021 and third wave from December 2021 to January 2022 in a tertiary care hospital in Eastern India

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ABSTRACT

Background: SARS-COV-2 manifestations in neonates acquired in the later part of neonatal life, were compared over 2 peaks over April-May 2021 (2nd wave) and (December 2021 to January 2022) (3rd wave). Setting: Study was done in Calcutta National Medical College, a tertiary care center of eastern India.
Methods: Cross sectional study was done among the admitted neonatal cases in COVID designated NICU. Neonates acquired the COVID-19 infection after birth. All mothers were tested negative during delivery.
Results: 40 neonates were admitted in April-May 2021 in COVID designated NICU and 42 neonates were admitted in December to January 2022. 66.6% mothers were COVID-19 RTPCR positive in December-January 2022 cases than 49.3% mothers in April-May 2021. These mothers were tested as COVID-19 negative at the time of delivery. None of the mothers were vaccinated in 2021 cases. Only 13.3% mothers received two doses of COVID-19 vaccination in December-January 2022 cases. Initial complaints were lethargic, not arousable (22.7%) and poor respiratory effort (27.5%) in December-January 22 cases. Respiratory (rapid breathing 40%) and gastrointestinal symptoms (diarrhoea 25.3%) were more predominant in neonates who were admitted in April-May 2021 than neonates who presented on January 2022. Hospital stay was significantly less in neonates in December-January 2022 (p=0.005). Genome sequencing revealed Omicron BA-2 in January 2022.
Conclusions: Clinical presentations differ in neonates in April-May 2021 and December-January 2022 probably due to difference in the nature of the virus.

Keywords: COVID-19, Horizontal-transmission, Lethargy, Diarrhea, Unconsciousness, Length of stay, Respiratory distress

INTRODUCTION

Novel coronavirus infection is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was named COVID-19 by the World Health Organization on January 7, 2020. Children appears to be less severely affected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) than adults.[1] However, there is a paucity of data describing the effect of the virus on babies in the first 28 days after birth. Neonates are likely to differ from older groups in their exposure to the virus: although they can contract SARS-CoV-2 through close personal contact in much the same way as other groups, they might also contract the virus vertically

before or at birth.[2] As per Raschetii et al clinical features in COVID-19 in newborn mostly respiratory (52.5%) as tachypnea, subcostal retraction, rhinitis, followed by fever (44.3%), gastrointestinal symptoms (36%) as eating disorder, vomiting, loose-motion. Neurological manifestations were less common (18.6%) as hypotonia, hypertonia, lethargy, apnea.[3] Hemodynamic manifestations as hypotension, tachycardia and skin rash, conjunctivitis was 9-10%.[3] In the SARS-COV-2 pandemic there is episodic increase in hospital admission of COVID-19 positive neonates in April-May 2021 (2nd wave) and in December 2021-January 2022 (3rd wave) in a tertiary care hospital in Kolkata. In the present study, clinical and laboratory findings of neonates in 2nd and 3rd waves were compared. There is a probable change in the nature of the virus from 2nd wave to 3rd wave.

SARS-COV-2 which was reported initially in Wuhan China 2 years back. Coronaviruses are positive sense–enveloped, single-stranded RNA virus. Serotypes from the alpha- and beta-coronavirus genera can cause human disease. The novel severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) is a beta-coronavirus, with 80% homology to SARSCoV-1 (the agent causing severe acute respiratory syndrome, or SARS) and even greater homology to some bat coronaviruses, suggesting a zoonotic origin.[4] Like other coronaviruses, SARS-CoV-2 has a "crown" appearance on electron microscopy caused by projections of the spike (S) glycoprotein from the envelope. The S protein mediates attachment to human epithelial cells via the angiotensin converting enzyme (ACE)-2 receptor, which is distributed widely throughout the human respiratory tract epithelium and is also the target of SARS-CoV-1. SARS-CoV-2 is more transmissible than SARS-CoV-1, which may be the result of stronger binding to the ACE-2receptor and more effective transmission of virus from asymptomatic and presymptomatic hosts.[5,6] Transmission primarily occurs via respiratory droplets, though airborne and contact transmission may occur to a lesser extent.[7] Disease caused by SARS-CoV-2 tends to occur in a biphasic manner, with the initial illness thought to be the result of direct viral infection and the subsequent phase being immune-mediated.[8] In addition, SARS-CoV-2 infection is known to cause coagulopathy, which may contribute to organ dysfunction as well.[8] There are multiple variants of concern of SARS-COV-2 as alpha, beta and delta are associated with new waves of infections sometimes across the globe.[9] Delta variant is associated with high viral load, longer duration of infectiousness, high rates of reinfection due to its ability to escape natural immunity causing rapid spread all over the world.[10-12]

New variant omicron has emerged on 2022 which has some deletions and more than 30 mutations, several of which (eg, 69-70del, T95I, G142D/143-145del, K417N, T478K, N501Y, N655Y, N679K, and P681H) overlap with those in the alpha, beta, gamma, or delta variants.[13] These deletions and mutations are known to lead to increased transmissibility, higher viral binding affinity, and higher antibody escape.[14,15] In India, second peak of COVID-19 was in April-May 2021 and third peak on December-January 2021-2022. As there is global change of variants of COVID-19 from delta to omicron, there may be difference in clinical manifestations of neonates in these two peaks. Present study was planned to find out the difference in clinical manifestations of RTPCR positive postnatally acquired COVID-19 cases in 2nd and 3rd peak in a tertiary care neonatal unit catering both inborn and outborn neonates.

METHODS

It is a cross sectional study conducted over 2 peaks. The study is done in Calcutta National Medical College covid newborn unit. All covid positive neonates were included in the study. There was no exclusion criteria. All neonates admitted as RTPCR positive over April-May 2021 and December-January 22 were included in the study as convenience sample. Clinical manifestations and outcome of RTPCR positive neonates were compared in these two periods. Mostly outborn neonates and suspected inborn neonates were tested initially by rapid antigen test and followed by RTPCR. Mothers were also tested for RTPCR. Rapid antigen test was done on admission and RTPCR test was done on the next day. All mothers were tested COVID-19 negative during delivery. In the month of April-May 2021 40 RTPCR positive neonates were admitted in one month. In December-January 2022, 42 RTPCR positive neonates were admitted in COVID designated newborn care unit. During admission at triage rapid antigen test was done for all neonates and positive neonates were admitted in Covid designated newborn unit. RTPCR was sent for all neonates after admission in COVID newborn unit. Genome sequencing was done at National Institute of Biomedical Genomics, Kalyani. Blood cultures were negative in all these neonates. Initial presentations were documented by junior residents in all neonates. In the previous month, in March 2021 and parameters commonly noted in COVID positive neonates were not arousable, lethargy, not feeding well, apnoeic spells, convulsion, rapid breathing, loose motion. The initial presentations were recorded on these parameters in April-May 2021 and December-January 2022. Mean, standard deviations of the presentations were calculated. Independent samples t-test was performed for continuous variables, and they were expressed as means±standard deviation. Chi square test (or Fischer's exact test) was performed for categorical data. Statistical significance was defined as $p<0.05$. SPSS version 16 software was used.

RESULTS

Both inborn and outborn neonates were admitted in COVID designated neonatal unit. Mean age at admission was 5 to 15 days. Initial presentations were not arousable, lethargy, not feeding well, apnoeic spells, convulsion, rapid breathing, loose motion. Mean gestational age was 33.6 weeks in 2021 and 35.7 weeks in 2022. Normal delivery was 20 in 2021 and 16 in 2022. Mean birth weight was higher in 2022 as 2352.8 gms than 2021.

Table 1: The presentations in April-May (2021) peak and December-January (2022) peak.

Parameters	2021, N (%)	2022, N (%)
Gestational age (weeks) mean (±SD)	33.6 (±3.51)	35.7 (±2.75)
Normal delivery	20 (50)	26 (53.3)
Caesarean section	20 (50)	18 (46.7)
Inborn	20 (50.0)	10 (33.33)
Out born	20 (50.0)	34 (66.66)
Birth weight (gms) mean (±SD)	1777.6 (±654)	2352.8 (±772.4)
Term	20 (50)	28 (53.33)
Preterm	20 (50)	16 (46.67)
Age at admission in days, mean (±SD)	4.4 (±7.7)	9.7 (±8.4)
Boy	26 (56.25)	26 (60)
Girl	14 (43.75)	16 (40)
Maternal COVID status positive (RTPCR)	16 (49.33)	24 (66.6)
Maternal Vaccine status	0	2 doses (13.3%), 1 dose (33.3%)

Table 2: Presenting complaints during admission.

Initial presentation	2021, N (%)	2022, N (%)	P value
Poor feed acceptance	12 (30)	10 (22.7)	0.78
Not arousable	0	10 (22.7)	0.03
Rapid breathing	16 (40)	4 (9)	0.09
Convulsion	2 (6)	8 (17.2)	0.87
Apnoeic spells (not breathing well)	0	12 (27.5)	0.09
Loose motion	10 (25.3)	0	0.08

Table 3: Predominant clinical features after admission.

Parameters	2021, N (%)	2022, N (%)	P value
Shock requiring inotrope	14 (46.6)	10 (35.7)	0.75
Fever	0	0	-
Cough	10 (25.3)	10 (22.7)	1
Distress	14 (33.3)	10 (22.7)	1
Diarrhoea	10 (25.3)	0	0.78
Vomiting	8 (22.6)	0	0.86
Poor feeding	4 (13.3)	16 (42.8)	0.08
Lethargy	4 (13.3)	16 (42.8)	0.08
Unconsciousness	0	4 (7)	-
Convulsion	2 (6)	8 (17.2)	0.87
Leukocyte count	13,492 (±7720)	14150 (±7145)	0.22
Neutrophil count	7587 (±6545)	6662 (±6191)	0.19
Lymphocyte count	4434 (±2666)	5739 (±3012)	0.312
Chest X-ray showing nonspecific pulmonary infiltrates	35	5	0.05
Duration of oxygen requirement(days)	8.5 (±12.2)	2.8 (±5.4)	0.468
Hospital stays	19.3 (±18.3)	11.07 (±10.5)	0.005
Mechanical ventilation/CPAP	8 (23.3)	6 (20)	0.78
Jaundice	2 (6.3)	12 (26.66)	0.043
Rhinorrhoea	10 (25.3)	20 (45.5)	0.06
Apnoeic spell	0	12 (27.5)	0.09

More numbers of term neonates with higher birthweight were affected in 2022. Number of neonatal death in 2021 cohort was 1 and neonatal deaths were 2 in 2022 cohort. Blood cultures were negative in all these neonates. Lethergy, poor feeding, excessive sleepiness were predominant findings in January 2022 cases, but respiratory and gastrointestinal symptoms were predominant in April-May 2021 cases. Neonates presented with different complaints at newborn unit triage undergone rapid test for COVID-19 followed by RTPCR of all neonates. Positive neonates were admitted in COVID designated NICU and clinical findings were noted. Not

sucking well was the initial presentation in both the groups. Lethergy and poor feeding and not breathing well were the predominant presenting complaints in December 2021 to January 2022 cohort. Loose motion was a common reason for admission in April-May 2021 cohort. Fever was not recorded during or after admission in neonates. After admission in December-January 2022 cohort had more jaundice, altered sensorium and rhinorrhoea. Total count and lymphocyte count was higher in December-January 2022 cohort. Apnoeic spells were seen in this cohort even in term neonates.

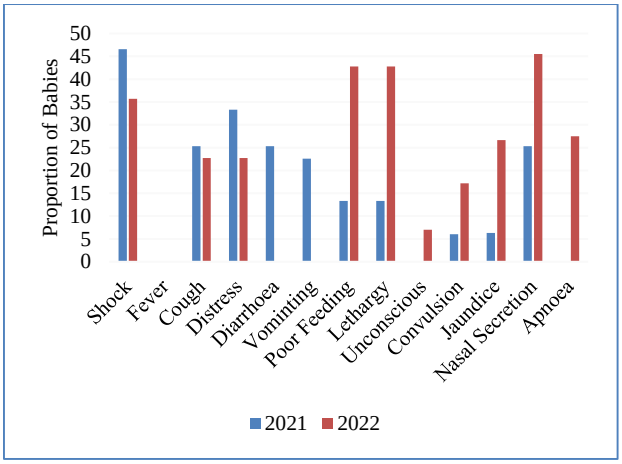

Figure 1: Different clinical features of COVID positive neonates during 2021 and 2022.

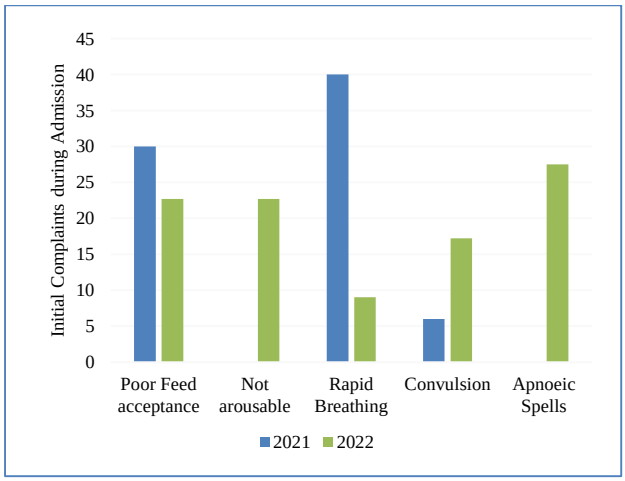

Figure 2: Clinical features of COVID positive neonates during 2021 and 2022.

Total 40 RTPCR positive sick neonates were admitted in Covid NICU in April-May 2021 with mean birth weight of 1777.6 g. 25% neonates presented with loose motions and vomiting, not seen in 2022. 10 neonates presented with bulged fontanalle and altered sensorium in 2022 in January. CSF RTPCR was done for COVID 19, influenza and para influenza virus was negative. Niserria meningitides and pneumococcus was also negative. Chest X ray revealed nonspecific infiltrates in most of the neonates in 2021 cases but seen in fewer cases in 2022. Genome sequencing was arranged at National Institute of Biomedical Genomics, Kalyani of neonates affected over 3rd peak on January 2022. Sample was accepted for 4neonates.3 cases were reported as Omicron variant BA-2. All these 3 neonates survived. One neonate was reported as (no variants) had very stormy course and expired. Hospital stay was significantly less in 2022 January cases (p=0.005).

DISCUSSION

In this study, all neonates were covid 19 RTPCR positive and virus infection was acquired probably postnatally. The clinical characteristics of COVID-19 in infected mothers and their neonates were first assessed by Chen et al. in a retrospective study.[21] All neonates in this study were born by caesarean section, and all presented with negative results for COVID-19 in all tested samples, including neonatal throat swabs, cord blood, and amniotic fluid. The authors reported fetal distress in two of the nine newborns.[21] A study conducted by Zhu et al also evaluated the clinical features of neonates born to mothers positive for COVID-19.[22] Newborns presented with fetal distress, respiratory distress, thrombocytopenia, abnormal liver function tests, and even the death of one patient occurred. The most common symptoms were dyspnea, fever, tachycardia, and vomiting. Seven out of nine neonates had abnormal chest computer tomography with the picture of neonatal respiratory distress syndrome, infection, and pneumothorax. Intrauterine fetal distress was observed in 6 out of 9 cases in this study. Zhu and colleagues speculate this is due to the hypoxemia caused by the infection that leads to birth asphyxia and premature birth.[22-25]

In 2nd wave (May 2021) GI symptoms were predominant presentation along with respiratory symptoms. In the 3rd wave (January 2022) vomiting and loose motions were not seen in neonates. The angiotensin-converting enzyme 2, a major virus receptor, is expressed in the gastrointestinal tract. Thus, in children, gastrointestinal symptoms were correlated with critical illness Tariverdi et al in his study has reported a 27-month-old child with dysentery as the only presentation.[16,25] GI symptoms have been reported in children with COVID-19 either with or without respiratory symptoms. The most common GI symptoms were anorexia, vomiting, and diarrhoea.[16-18] A few cases of GI bleeding have also been reported.[16] Neonates were more like to present with gastrointestinal symptoms (26%) compared with literature information on children and adult SARS-CoV-2 RNA shedding seems to be present in feces for a longer time than in respiratory samples.[20] Although fecal SARS-CoV-2 presence in feces does not confirm its transmissibility, the rapid and prolific spread of the COVID-19 disease worldwide indicates other transmission routes are also plausible.[24] Karabay et al described the clinical characteristics of SARS-CoV-2 positive newborns. Respiratory difficulty (74%) and fever (63%) were most common. No term infant needed mechanical ventilation, by contrast to 50% of preterm.[19] Gastrointestinal symptoms (diarrhea, feeding intolerance

and abdominal distension) were present in 50%.[19] Newborns neurologic symptoms were present in 53% in the form of irritability, hypertonia, lethargy, hyporeactivity, and hypotonia. Cough, vomiting and cyanosis were also described.[19] Jaundice was more common in 2022 case were unconjugated hyperbilirubinimea requiring phototherapy Zhao et al has hypothesised the possible reason for hyperbilirubinimea as there is impaired active transport of bilirubin uptake into the hepatocytes, or liver injury resulting from expression of the ACE-2 receptor as a target for SARS-CoV-2.[26] There may be impaired bilirubin excretion in the presence of cholangiocyte injury resulting from greater ACE-2 expression.[26] Nonspecific pulmonary infiltrates frequently seen in 2021 cohort than 2022 cohort. Iijima et al in his case series on covid affected infants documented that nonspecific pulmonary infiltrate in minimally affected infants.[27]

In the 3rd wave, neonates represented with lethargy, poor feeding, poor respiratory effort, convulsion. All neonates with convulsion, CSF examination was done and increased lymphocytes count was found. CNS symptoms were predominant finding with mild respiratory symptoms. Rhinorrhoea was commonly seen. Apneic spells were commonly seen which can be correlated to altered sensorium and excessive nasal discharge. Nathan et al reported four young infants presenting with neurological symptoms at admission, such as axial hypotonia or drowsiness and moaning sounds or both without respiratory symptoms of SARS-COV-2.[28] CSF examination was normal. Lorenz et al in his observation reported a newborn appeared lethargic, developed therapy refractory fever (38.6°C) at 24 hours after birth, progressing to encephalitic symptoms (lethargic but severely hyperexcitable, high-pitched crying) at 54 hours of life.[29] Mother and the newborn were RTPCR positive. In the present study, neonates presented during 3rd wave had depressed sensorium and lethargy causing poor respiratory effort, increased oxygen requirement and feeding difficulty. Animal models of SARS and MERS have shown that the virus can enter through epithelium of the nasopharynx and travel retrogradely to the CNS.[30,31] Interestingly, wild type mice are not vulnerable to infections and disease by human coronaviruses, but transgenic mice with human ACE-2 receptors do develop respiratory and neurological symptoms when infected.[30,32] In such transgenic mice, intranasal exposure to SARS or MERS leads to brain infection. One of the proposed portals of entry is via olfactory sensory neurons, crossing the cribiform plate into the olfactory bulb, with subsequent retrograde travel along the olfactory nerve (cranial nerve I) to the brainstem, thalamus, and basal ganglia, all areas that are connected to the olfactory cortex. In the present study, all neonates had CSF RTPCR for SARS-COV-2 as negative. CSF covid antibody was negative even in the presence COVID antibody in blood. Overall, prognosis of neonates with SARS-CoV-2 infection was good, with all of them discharged alive after a median hospital stay of 10 days. While median duration of hospitalisation was comparable among neonates, children and adults.[23]

Genome sequencing revealed Omicron BA.2 in 3 neonates. Omicron has three lineages, BA.1 (B.1.1.529.1), BA.2 (B.1.1.529.2), and BA.3 (B.1.1.529.3), which were first detected in November 2021 in South Africa.[33] Nationwide Danish data in late December 2021 and early January 2022 indicate that Omicron BA.2 is inherently substantially more transmissible than BA.1 and capable of vaccine breakthrough.[34] Israel reported a handful of cases of patients who were infected with original Omicron BA.1 strain and have reinfected with BA.2 in a short period.[35] Although BA.2 did not cause worse illness than the original Omicron BA.1 strain, its reinfection rate is very alarming.[35] Omicron BA.2 variant is about 1.5 times as infectious as BA.1 and about 4.2 times as contagious as the Delta variant. It also has a 30% higher potential than BA.1 to escape existing vaccines. The Omicron BA.2 is on its path to becoming the next dominating variant.[35] Postnatal transmission of SARS-CoV-2 to the newborn seems to occur primarily through respiratory droplets when neonates are exposed to mothers or other caregivers with SARS-CoV-2 infection, and may occur more readily than previously thought in Omicron BA.2.[36,37]

Limitations

Limitations were; It is a single centre study, Multicentric data is required for confirmation of our finding, Sample size is relatively less.

CONCLUSION

The clinical presentations of horizontally acquired COVID-19 were different on April-May 2021 peak and December-January 2022 peak. These differences could be due to difference in the nature of the virus.

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