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Hyperglycemia and Cytopenias as Signs of SARS-CoV-2 Delta Variant Infection in Preterm Infants

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Abstract

Information regarding severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in premature infants remains limited. Early in the pandemic, several studies reported that the risk of infection in infants was relatively small and that affected infants had a milder disease than what was seen in adults. Since the increase of the delta variant (SARS-CoV-2 B.1.617.2) within the population, there have been increased reports of more severe disease in infants. We present 3 cases of premature, very low birth weight infants with confirmed SARS-CoV-2 infection who presented with significant hyperglycemia and bone marrow dysfunction. Two infants had presumed vertical transmission, and 1 infant was infected by respiratory transmission. Despite the mode of transmission, symptom onset and duration were similar in all infants. All resolved with symptomatic management. In the context of the continuing pandemic, evaluation for SARS-CoV-2 infection should be considered in premature very low birth weight infants who demonstrate certain patterns of acute metabolic and hematologic abnormalities.

As the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic persists, we continue to learn more about how this disease affects vulnerable populations. Early in the pandemic, studies demonstrated a minimal risk of vertical transmission from SARS-CoV-2 positive mothers to infants.[1–4] Additionally, infants who tested positive for SARS-CoV-2 were described as having mild disease.[1,2,4,5] However, as the delta variant (SARS-CoV-2 B.1.617.2) became predominant, we began to see more infants test positive for SARS-CoV-2.[6] We present a series of premature, very low birth weight infants (birth weight <1500 g) who tested positive for SARS-CoV-2 likely due to intrapartum or postnatal respiratory transmission who have clinical signs and courses consistent with viral disease.

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METHODS

We conducted a retrospective case study of premature infants treated at a single tertiary care facility (University of Iowa, Iowa City, IA) and extracted data from the electronic medical record. SARS-CoV-2 testing was performed by real-time reverse transcription polymerase chain reaction testing on nasopharyngeal samples. The study was approved by the institutional review board at this institution (IRB# 201410743).

CASE REVIEW

Patient 1

Patient 1 (twin A) was born at 28 1/7 weeks' gestation with a birth weight of 1135 g (56th percentile per Fenton growth chart). Pregnancy was complicated by maternal coronavirus disease 2019 (COVID-19) with onset of symptoms 2 days before delivery and monochorionic diamniotic twin gestation. The infant was delivered by cesarean section due to maternal hemolysis, elevated liver enzymes, low platelets syndrome. Of note, the mother was under general anesthesia, intubated before delivery, and the father was not present. The infant was intubated due to respiratory failure. He was transported to the NICU and cared for in a closed isolette. He required mechanical ventilation and surfactant therapy for respiratory distress syndrome (RDS). He had significant metabolic acidosis (pH 7.15, lactic acid 7.1 mmol/L) following delivery, which corrected slowly with adjustments to IV fluid and ventilation management and resolved on day of life (DOL) 3. On the day of birth, neutrophil and lymphocyte counts were unremarkable. Leukopenia first developed (5500 cells/mm^3) on DOL 1 and neutrophil and lymphocyte counts reached nadirs of 620 cells/mm^3 and 1380 cells/mm^3 respectively, on DOL 4. Due to active maternal COVID-19 infection, he was tested for SARS-CoV-2 at 48 hours of life per protocol, which was positive. Genotype testing was performed which confirmed infection with SARS-CoV-2 variant B 1.617.2. Genotyping performed on the mother's sample at this time confirmed variant B 1.617.2. Lymphocyte count normalized on DOL 6. On DOL 7, he became hyperglycemic, with glucose of 175 mg/dL, while receiving a glucose infusion rate (GIR) of 8.8 mg/kg per min. Parenteral nutrition was adjusted to a GIR of 3.8 mg/kg per min, and glucose levels returned to normal within 2 days. Neutrophil count increased to normal on DOL 10. Repeat SARS-CoV-2 testing on DOL 30 was negative.

Patient 2

Patient 2 (twin B) was born at 28 1/7 weeks' gestation with a birth weight of 1015 g (36th percentile). Pregnancy and labor complications are the same as patient 1. The infant was intubated after delivery and taken to the NICU with the same precautions. He was placed on mechanical ventilation and received surfactant therapy for RDS. He initially had significant metabolic acidosis (pH 7.17, lactic acid 10.6 mmol/L) which returned to normal on DOL 3. On DOL 1, head ultrasound demonstrated bilateral grade II intraventricular hemorrhages. Initial leukocyte counts were within normal limits, however the following day he was noted to be leukopenic (white blood cell count of 5000 cells/mm^3). Neutrophil and lymphocyte counts reached nadirs of 480 cells/mm^3 and 1190 cells/mm^3 respectively on DOL 4. He underwent SARS-CoV-2 testing at 48 hours of life, which was positive. Genotyping

confirmed SARS-CoV-2 variant B 1.617.2. On DOL 3, he became hyperglycemic to 195 mg/dL while on a GIR of 4.8 mg/kg per min, requiring alteration of IV fluids to a GIR of 2.5 mg/kg per min. On DOL 4, intraventricular hemorrhage progressed to bilateral grade III with ventricular dilation. Lymphocyte and neutrophil counts returned to normal on DOL 7 and 9, respectively. Glucose levels fully normalized by DOL 12. Due to progressive ventricular dilatation, an intraventricular reservoir was placed on DOL 18. Repeat SARS-CoV-2 testing on DOL 30 and 38 remained positive. Infection control precautions continued until the infant was discharged.

Patient 3

Patient 3 was born at 24 5/7 weeks' gestation with birth weight of 670 g (50th percentile). Pregnancy and labor were complicated by lack of prenatal care, spontaneous preterm labor, and active herpes simplex virus infection at the time of delivery. The infant was intubated, placed on mechanical ventilation, and received surfactant for RDS. She was initially treated with empirical antibiotics and acyclovir, which were continued until herpes simplex virus polymerase chain reaction returned negative. On DOL 7, the mother visited the infant and reported a cough and loss of taste and smell. The mother tested positive for SARS-CoV-2 that day. On DOL 9, the infant became hyperglycemic on a GIR of 6.2 mg/kg per min, with serum glucose ranging from 277 to 379 mg/dL. The dextrose content of intravenous nutrition was reduced to achieve a GIR of 5 mg/kg per min. On DOL 11, she tested negative for SARS-CoV-2. On DOL 12, she became thrombocytopenic to 118 000/mm^3, which fell to 80 000/mm^3 by DOL 15. On DOL 16, she had a leukocytosis of 36 800/mm^3 with a significant neutrophilic predominance. A sepsis work-up was performed, with negative blood culture. On DOL 19, she was transferred to our institution for management of a patent ductus arteriosus and continued respiratory failure. Upon arrival, she was hyperglycemic to 255 mg/dL, had a leukocytosis of 28 200/mm^3 with a predominance of neutrophils. Per unit protocol, she was screened for SARS-CoV-2 and was positive. The hyperglycemia resolved within 2 days with management of IV fluids. The thrombocytopenia and leukocytosis resolved on DOL 22.

DISCUSSION

Starting in March 2020, our unit adopted special policies due to the SARS-CoV-2 pandemic. This included isolation protocols for infants born to SARS-CoV-2 positive mothers, changes to visitor policies, and decreased contact with affected mothers after delivery. Until August 2021, our unit had no neonates who tested positive for SARS-CoV-2, despite routine testing of inpatient infants every 5 days. Given our report of 3 cases in a short period of time, we believe this change may be explained for by the rising incidence of the SARS-CoV-2 delta variant. Sheth et al reviewed 39 studies with 326 COVID-19 positive mothers and their respective neonatal outcomes and reported 23 positive neonates through June 18, 2020, with no infant mortality.[7] The risk of an infant testing positive for SARS-CoV-2 in the perinatal period in the setting of a SARS-CoV-2 positive mother is relatively low, ranging from 0% to 3%.[1–4,8]

Data on SARS-CoV-2 infection in premature infants are scarce and limited to a case report.[9] So far, the literature describes a mild infection in newborns with the most common presentation being fever and respiratory symptoms,[7–11] though a new report suggests an increasing incidence of multisystem inflammatory syndrome in infants.[12] All infants included in this study became hyperglycemic 2 to 7 days following SARS-CoV-2 exposure. Hyperglycemia without diabetes has been associated with poorer outcomes in adults with SARS-CoV-2 infection.[13] A previous study found the SARS-CoV spike protein binds to angiotensin converting enzyme 2 receptors in multiple organs, including the pancreas, damaging pancreatic islet cells, resulting in acute hyperglycemia and new-onset diabetes.[14] We cannot exclude the possibility that unexpected hyperglycemia in our 3 preterm infants resulted from transient viral pancreatic injury but more likely represents a systemic response to stress.

In our patients we also identified transient bone marrow dysfunction. Infants born to mothers with preeclampsia spectrum disease are at risk for cytopenias.[15] These typically consist of a neutropenia or thrombocytopenia that is present at birth and lasts 3 to 4 days.[15] For Patients 1 and 2, the onset was at 24 hours of life, with nadir after 3 days, and duration of 10 days. For Patient 3, onset was 3 days after initial exposure, with the nadir seen 3 days later, and resolution after 10 days. The bone marrow dysfunction seen in these patients is more typical of that seen with viral infections and may be explained by their SARS-CoV-2 infection, as has been described in older children.[16]

For all 3 infants, the diagnosis of SARS-CoV-2 infection resulted from compliance with our protocol rather than due to specific clinical concern for COVID-19 disease. All 3 infants demonstrated a greater degree of illness than expected for their gestational age and exhibited similar atypical courses of laboratory abnormalities. The delta variant appears to be affecting children to a greater extent than previous variants.[17] We propose that clinicians consider the possibility of clinical SARS-CoV-2 mediated disease in preterm infants with atypical acute metabolic and hematologic abnormalities.[17,18]

We strongly suspect vertical transmission of SARS-CoV-2 in patients 1 and 2 but cannot distinguish between prenatal and intrapartum routes of transmission. They had no contact with their parents or visitors after delivery, all caretakers used respiratory precautions, but nonetheless tested positive when screened at 48 hours so that postnatal respiratory transmission is highly unlikely. Other studies have described testing amniotic fluid, cord blood or placenta to assist in evaluating for prenatal transmission in infants with clinical disease consistent with SARS-CoV-2 infection.[7,19] Our third case was most likely infected via respiratory transmission, with a known positive contact. The patient had a positive test 12 days later, though laboratory abnormalities were noted 2 days after initial exposure. Patients 1 and 2 had confirmed infection due to SARS-CoV-2 delta variant, and we highly suspect the delta variant in patient 3 due to its prevalence among infected individuals at the time of infection. Regardless of the mode of transmission, these infants had very similar clinical courses, which has not previously been described in very low birth weight infants. More data are needed about the clinical signs of SARS-CoV-2 infection in premature infants as a function of route of transmission.

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ABBREVIATIONS

COVID-19	coronavirus disease 2019
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
RDS	respiratory distress syndrome
DOL	day of life
GIR	glucose infusion rate

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