Maternal SARS-CoV-2, Placental Changes and Brain Injury in 2 Neonates

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Long-term neurodevelopmental sequelae are a potential concern in neonates following in utero exposure to severe acute respiratory syndrome coronavirus disease 2 (SARS-CoV-2). We report 2 neonates born to SARS-CoV-2 positive mothers, who displayed early-onset (day 1) seizures, acquired microcephaly, and significant developmental delay over time. Sequential MRI showed severe parenchymal atrophy and cystic encephalomalacia. At birth, neither infant was SARS-CoV-2 positive (nasopharyngeal swab, reverse transcription polymerase chain reaction), but both had detectable SARS-CoV-2 antibodies and increased blood inflammatory markers. Placentas from both mothers showed SARS-CoV-2-nucleocapsid protein and spike glycoprotein 1 in the syncytiotrophoblast, fetal vascular malperfusion, and significantly increased inflammatory and oxidative stress markers pyrin domain containing 1 protein, macrophage inflammatory protein 1 βη, stromal cell-derived factor 1, interleukin 13, and interleukin 10, whereas human chorionic gonadotropin was markedly decreased. One infant (case 1) experienced sudden unexpected infant death at 13 months of age. The deceased infant's brain showed evidence of SARS-CoV-2 by immunofluorescence, with colocalization of the nucleocapsid protein and spike glycoprotein around the nucleus as well as within the cytoplasm. The constellation of clinical findings, placental pathology, and immunohistochemical changes strongly suggests that second-trimester maternal SARS-CoV-2 infection with placentitis triggered an inflammatory response and oxidative stress injury to the fetoplacental unit that affected the fetal brain. The demonstration of SARS-CoV-2 in the deceased infant's brain also raises the possibility that SARS-CoV-2 infection of the fetal brain directly contributed to ongoing brain injury. In both infants, the neurologic findings at birth mimicked the presentation of hypoxic-ischemic encephalopathy of newborn and neurologic sequelae progressed well beyond the neonatal period.

The outbreak caused by severe acute respiratory syndrome coronavirus disease 2 (SARS-CoV-2) has had a profound effect on global health and worsened maternal and fetal outcomes.[1,2] This report summarizes severe neurologic injury in 2 infants born in the third trimester, whose mothers tested SARS-CoV-2 positive several weeks before delivery. Both infants displayed ongoing neurologic injury and developmental deficits. One infant, with sudden death at 13 months of age, had extensive loss of brain white matter, gliosis, and vacuolization at autopsy.

CASE REPORTS

Patient 1: Preterm Infant

A 32-week gestational age, appropriately grown, Hispanic male infant was born to a 21-year-old multigravida via Cesarean section. The

abstract

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Dr Benny conceptualized and designed the study, coordinated data collection, drafted the initial manuscript, reviewed and revised the manuscript; Drs Bandstra, Saad, Lopez-Alberola, Saigal. Paidas, and Jayakumar conceptualized and designed the study, contributed to data collection, reviewed and revised the manuscript; Dr Duara conceptualized and designed the study, coordinated, supervised the work, critically reviewed and revised the manuscript for important intellectual content; and all authors contributed to the concept and drafting or revising of this manuscript and approved the final version and agree to be accountable for all aspects of the work.

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mother was healthy until 27 weeks of gestation when she was admitted to the ICU for pneumonia and multisystem disease, diagnosed as SARS-CoV-2 by nasopharyngeal swab reverse transcription polymerase chain reaction (NP RT-PCR). Continuous fetal monitoring and ultrasound evaluations remained normal. At 32 weeks of gestation, a multidisciplinary decision was made to perform a Cesarean section for maternal indications after administration of antenatal corticosteroids for fetal lung maturation. The mother was SARS-CoV-2 negative by this time. The infant was born with Apgar scores of 4 and 7 at 1 and 5 minutes with an umbilical cord arterial blood gas pH 7.22, pCO2 97 mm Hg, and base excess +11. He immediately displayed seizure-like activity and poor respiratory effort, which required intubation and assisted ventilation. Continuous, conventional electroencephalography recordings on admission showed frequent multifocal epileptiform discharges consistent with status epilepticus. Initial hematologic indices and serum chemistries were normal. Early hypotension with biventricular systolic depression on echocardiography was treated with vasopressors until day 5. Significant lung disease persisted despite administration of early surfactant and broad-spectrum antibiotics; bilateral confluent densities originally presented on the initial chest radiograph did not completely resolve after full respiratory recovery (day 19). At 24 hours of age, the infant's NP RT-PCR for SARS-CoV-2 was negative. However, serum coronavirus disease 2019 (COVID-19) IgG and combined (total) IgG, IgM, and IgA reactivity to a recombinant derivative of SARS-CoV2 spike protein were present, and serum inflammatory markers and cytokines were markedly elevated (Table 1). Cerebrospinal fluid (CSF) bacterial and viral studies were negative. Bacterial cultures from blood, urine, and endotracheal sites were also negative, as was herpes simplex PCR in blood and CSF. Chromosomal microarray, newborn metabolic screen, plasma amino acids, acylcarnitines, and urine organic acid screens were also normal. An epilepsy genetic panel was noncontributory. Brain MRI on day 2 showed left germinal matrix and left intraventricular hemorrhage (Fig 1A). Follow-up brain MRI at 10 weeks showed resolution of hemorrhages, but severe parenchymal atrophy (Fig 1B). The infant was discharged after 3 months (43 weeks' postmenstrual age) with a seizure disorder and acquired microcephaly (head circumference < 2nd percentile compared with 81st percentile at birth). Eventually, the seizures resolved and antiepileptics were discontinued, but the infant was readmitted on several occasions for failure to thrive and respiratory infections. His 12-month neurologic examination remained abnormal, with head lag, truncal hypotonia, increased appendicular tone, hyperreflexia, and delayed developmental milestones. At 13 months of age, he had an emergency department visit for an upper respiratory infection. Three days later, his mother found him unresponsive in bed; paramedics who responded reported finding him in asystolic cardiac arrest, from which he could not be revived. Autopsy showed a significant reduction in brain weight and cerebral white matter volume, enlarged ventricles, extensive gliosis in the cerebrum, cerebellum and brainstem, and evidence of virus throughout the brain (Fig 1, E1–8).

Patient 2: Full-term Infant

A 39-week gestational age, appropriately grown, Hispanic female infant was born to a 20-year-old primigravida, who reported asymptomatic SARS-CoV-2 positivity (NP RT-PCR) in the late second trimester, followed by a negative test. Her prenatal assessments and ultrasound scans had all been unremarkable. Although asymptomatic, she again tested positive at the time of vaginal delivery, also complicated by clinical chorioamnionitis. The infant was awarded Apgar scores of 4 and 6 at 1 and 5 minutes, respectively, and had an umbilical cord arterial blood gas of pH 7.22, pCO2 47 torr, and base deficit −10. She required nasal continuous positive airway pressure for apnea and was begun on antibiotics for presumptive sepsis. Her physical examination revealed mild hypotonia but was otherwise normal. Initial hematologic indices and serum chemistry were also normal except for mild metabolic acidosis. At 16 hours of age, she developed clinical seizures confirmed on continuous conventional electroencephalography. A 24-hour NP SARS-CoV-2 RT-PCR was negative, but SARS-CoV-2 IgG, combined (total) IgG, IgM, and IgA reactivity to a recombinant derivative of SARS-CoV-2 spike protein, inflammatory markers, and cytokines were markedly elevated (Table 1). There was CSF pleocytosis but no detectable virus or bacteria.

TABLE 1 Key Laboratory Findings in Both Cases

Items Tested	SARS-CoV-2 RT-PCR (24 h)	COVID 19 IgG	COVID 19 Total Ab	IL 6 (pg/mL)	NT-ProBNP(pg/mL)	CRP	Ferritin (ng/mL)	Procalcitonin (ng/mL)	Lactic Acid (mmol/L)
Reference		0–0.99	0–0.99	1.5–7	1–125	0–0.9	30–400	0–0.08	0.7–2.1
Case 1	Negative	24	201	16.7	105 000	<0.5	348	1.73	0.9
Case 2	Negative	—	158	12.1	9790	0.5	354	—	4.0

—, not tested.

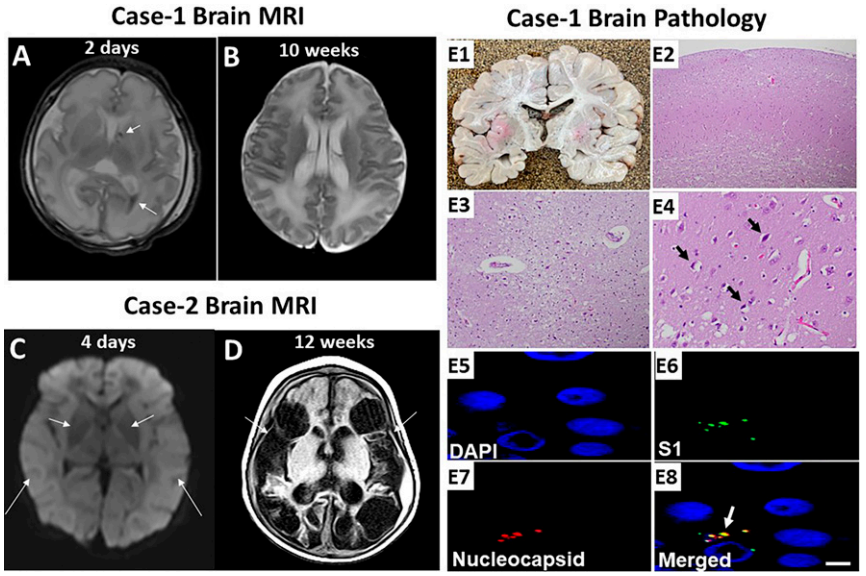

FIGURE 1

Neurologic findings in both cases. Case 1, preterm infant, (A) axial T2 weighted brain MRI on day 2, demonstrating T2 hypointensity in the left germinal matrix and dependent portion of the left occipital horn (arrows) and (B) axial T2 weighted brain MRI at 10 weeks, demonstrating significant atrophy of the brain parenchyma. In Case 2, term infant, (C) axial diffusion-weighted imaging from brain MRI done on day 4 demonstrates increased diffusion signal consistent with restricted diffusion, involving the entire supratentorial cerebral cortex bilaterally, compatible with hypoxic-ischemic injury (long white arrows), and sparing of the basal ganglia and thalami (short white arrows) and (D) axial FLAIR (fluid attenuated inversion recovery) image from brain MRI done at 12 weeks of age demonstrating severe cystic encephalomalacia bilaterally (arrows). Brain pathology of case 1 (aged 13 months), (E) showing (E1) cross section of brain with reduced white matter volume and ventriculomegaly; (E2) vacuolization of the cerebral cortex, 40X; (E3) pyramidal layer of the hippocampal cornu ammonis showing marked reduction in the number of pyramidal cells and vacuolization, 100X and (E4) hippocampal pyramidal neurons with hypoxia or ischemia (arrows), 200X. (E5–E8) Representative immunofluorescence images from case 1 brain (SARS-CoV-2 positive) showing the presence of nucleus. 4′,6-diamidino-2 phenylindole (DAPI [blue]), spike glycoprotein (green), nucleocapsid protein (red), and colocalization of (merged) nucleocapsid protein and spike glycoprotein around the nucleus as well as in the cytoplasm (arrows), illustrating the presence of virus in the brain.

Tests for inborn errors of metabolism were negative. Chromosomal microarray showed a copy number variant of uncertain clinical significance. Brain MRI on day 4 showed diffuse restricted diffusion with low apparent diffusion coefficient throughout the supratentorial brain and sparing of the basal ganglia and medial temporal lobes (Fig 1C). She was discharged at 5 weeks of age but has had multiple hospital readmissions for breakthrough seizures and respiratory infections. Repeat brain MRI at 12 weeks of age showed progressive development of severe cystic encephalomalacia (Fig 1D). Her most recent follow-up exam at 1 year of age showed microcephaly (head circumference < 3rd percentile compared with 59th percentile at birth), abnormal neurologic examination with low axial tone, head lag, increased appendicular tone, hyperreflexia, clonus, and significant neurodevelopmental delay with inability to roll over or sit unsupported. The infant is currently in hospice care.

Placental Findings

The placentas from both cases showed thrombosis and recanalization of stem villous vessels, stromal fibrosis, and increased stromal karyorrhexis of terminal villi. These widespread changes correspond to high-grade fetal vascular malperfusion (Fig 2A–B).

Presence of Viral Proteins

Immunofluorescence was done to detect the presence of SARS-CoV-2 spike glycoprotein 1 (S1) and nucleocapsid protein in the placenta and case-1 infant's brain, using Stochastic Optical Reconstruction Microscopy (Nikon Instruments, Inc. Melville, New York, USA). We detected S1 in both case placentas, colocalized with the nucleocapsid protein of the syncytiotrophoblast (Fig 2C). We also identified S1 protein, colocalized with nucleocapsid protein, throughout the brain of case-1 (Fig 1, E5–E8).

Immunofluorescence

Both placentas were also analyzed for plausible inflammatory and modulating factors, which, directly or indirectly, adversely affect fetal central nervous system development, and compared with 2 age- and gender-matched placentas of SARS-CoV-2 negative mothers. Immunofluorescence was performed[3] for hypoxia-inducible factor-α (HIF-α), a transcription factor responsive to cellular hypoxia; Nucleotide-binding oligomerization domain and leucine-rich repeat containing receptors pyrin domain containing 1 protein (NLRP1), which is formative in the assembly of inflammasomes; macrophage inflammatory protein 1 β (MIP-1β), a chemotactic cytokine; stromal cell-derived factor 1 (SDF1), an angiogenic and chemotactic chemokine; interleukin 13, an inflammatory cytokine; interleukin 10, an anti-inflammatory cytokine; and human chorionic gonadotropin (hCG), a marker of placental function. HIF-1α, NLRP1, MIP-1β, SDF-1, IL-13, interleukin 10 (IL-10) were all elevated (Fig 2D–O), whereas hCG was markedly decreased in the SARS-CoV-2 positive placentas,

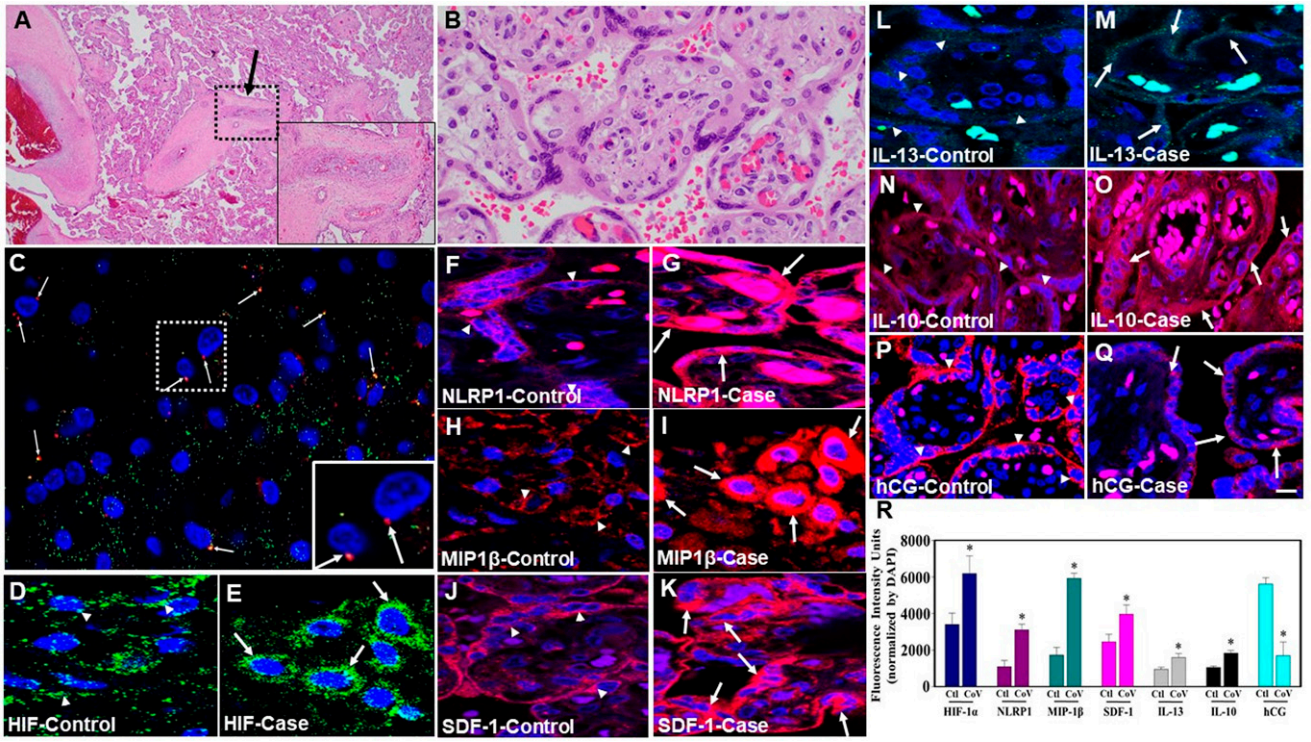

FIGURE 2

Placental findings in both cases. (A) Histopathology of both placentas demonstrated fetal vascular malperfusion with thrombosis and recanalization of the stem villous vessels (arrow). Inset: higher magnification of thrombosed and recanalized stem villous vessels. Original magnification, 200X, inset 400X (B) chorionic villi with loss of stromal vessels and apoptosis. (C) Representative immunofluorescence images from case placentas (SARS-CoV-2 positive) showing the presence of nucleocapsid protein (red), spike glycoprotein (green), and nucleus (DAPI, blue) with colocalization of (merged) nucleocapsid protein and spike glycoprotein around the nucleus as well as in the cytoplasm (arrows), illustrating the presence of virus (Inset: higher magnification of viral proteins around the nucleus). Paired placental images (left, control placenta with arrowhead and right, case SARS-CoV-2 positive placenta with arrow) showing increased HIF-1α (green, D and E), NLRP1 (red, F and G), MIP-1β (red, H & I), SDF-1 (red, J and K), IL-13 (green, L and M), IL-10 (red, N and O) and reduction in hCG (red, P and Q). (R) Bar graph showing quantification of mean fluorescence intensity of HIF, NLRP, MIF-1 β, SDF-1, IL-13, IL-10 and hCG. Two tailed t test was performed. *$P < .05$ Control versus CoV (Control = SARS-CoV-2 negative; CoV = SARS-CoV-2 positive). Scale bar = 35 μm for images D through Q.

compared with controls (Fig 2P–Q).

DISCUSSION

Exposure to intrauterine inflammation and disrupted placental programming following SARS-CoV-2 in pregnancy can have long-term consequences on the fetus.[4] To our knowledge, the 2 cases described here represent the first time that neonates born to SARS-CoV-2 positive mothers present with a neonatal clinical course mimicking hypoxic-ischemic encephalopathy of the newborn. There was no preceding clinical event in labor that heralded an acute hypoxic-ischemic event in either case, and the neurologic sequelae extended well beyond the neonatal period. Both placentas and brains showed evidence of SARS-CoV-2 infection and the placentas displayed alterations in inflammatory and oxidative stress markers.

Severe SARS-CoV-2 placental infection can impact neonatal outcome even in the absence of vertical transmission.[4–6] Although SARS-CoV-2 was absent in the nasopharyngeal swabs of our newborns, their elevated SARS-CoV-2 antibodies and proinflammatory mediators, as well as the neuropathology findings from the brain of Case 1, suggest brain injury either caused by the fetal inflammatory response to placental infection and/or the consequence of an undetected in-utero brain infection.

With respect to the timing of infection during pregnancy, both mothers initially tested positive for SARS-CoV-2 in the second trimester. However, both pregnancies continued well into the third trimester without any complications related to pregnancy or fetal compromise as could be assessed by antenatal monitoring. These observations, combined with exclusion of a lengthy list of other possible causes of the clinical and pathologic

findings, implicate SARS-CoV-2 as the etiology of the neurologic injury.

The placental histologic findings of thrombosis, loss of stromal vessels, and apoptosis are associated with maternal-fetal vascular malperfusion, placental ischemia, and insufficiency, which result in deterioration of placental function.[7] Consequences of chronic placental insufficiency may underlie the neonatal course mimicking hypoxic-ischemic encephalopathy of the newborn in the absence of a sentinel event during delivery.[8]

Successful pregnancy necessitates synchronized communications between the mother and fetus, and the immune system, and cytokine signaling pathways mediate these communications.[9] Exposure to intrauterine inflammation and disrupted placental programming following SARS-CoV-2 in pregnancy can have long-term consequences on the fetus.[10] Placental insults causing tissue hypoxia and oxidative stress induce release of proinflammatory mediators and cause endothelial damage, with resulting alterations in placental blood flow and fetal brain injury.[11]

Inflammation of the feto-placental unit leads to development of the fetal inflammatory response syndrome, which causes fetal hypoxia, blood vessel damage, and blood-brain barrier compromise, and leads to white matter injury of the fetal brain.[12–14] In a proinflammatory state, cytokines directly cross the blood-brain barrier causing neuronal injury.[14–16] HIF1-α, a master regulator of oxygen homeostasis, responds to tissue hypoxia and produces placental vascular changes similar to those seen in our cases.[17] Experimental studies show HIF-1α expression is increased in the placenta and developing mouse brain during acute systemic hypoxia.[17] This suggests that elevated placental HIF-1α is an indirect tissue marker for fetal cerebral hypoxia. Oxidative stress, measured by NLRP1, may contribute to neuronal injury.[18–20] Elevated levels of placental proinflammatory NLRP1, MIP1-β, interleukin 13 (IL-13) are also known to impair fetal neurodevelopment.[21,22] Increased myometrial SDF1 recruits immune cells, that in turn produce inflammatory cytokines.[23] The placental hormone hCG plays a neuroprotective role against hypoxic-ischemic neurodegeneration in the developing brain.[24] Moreover, hCG promotes uterine angiogenesis and vasculogenesis to ensure adequate blood supply to the placenta.[25] In this light, decreased hCG levels suggest placental compromise. The constellation of placental pathology along with placental changes in HIF-1α, NLRP1, MIP1-β, SDF1, IL-13 and hCG suggest that placental SARS-CoV-2 infection triggered inflammatory and oxidative stress injury in the fetoplacental unit, which may have resulted in neurologic damage mimicking hypoxic perinatal brain injury.

We believe the extensive placental changes are sufficient to explain at least the initial neurologic presentation of both infants.[5,26] The autopsy identification of SARS-CoV-2 in the brain of case-1 raises the possibility that viral infection of the brain may have additionally directly contributed to the evolution of this infant's neurologic injury. In retrospect, testing of amniotic fluid and cord blood samples for SARS-CoV-2 as well as uniformity in testing for inflammatory markers would have been helpful.

In conclusion, our cases demonstrate that midtrimester maternal SARS-CoV-2 infection can infect the placenta and fetal or infant brain and trigger a cascade of inflammatory events in both placenta and fetus. This may be associated with major brain injury and progressive neurologic sequelae in infants beyond the neonatal period. Our cases also highlight the shortcomings of current fetal monitoring for assessment of fetal well-being, especially when the target of injury is the fetal brain. Future longitudinal studies are needed to study the impact of timing of in utero SARS-CoV-2 infection on placental inflammation, as well as the long-term consequences on the developing brain.

ABBREVIATIONS

COVID-19: coronavirus disease of 2019
CSF: cerebrospinal fluid
hCG: human chorionic gonadotropin
HIF-α: hypoxia-inducible factor-α
IL-10: interleukin 10
IL-13: interleukin 13
MIP1-β: macrophage inflammatory protein 1 βη
NLRP1: NLR pyrin domain containing 1 protein
S1: spike glycoprotein 1
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
SDF1: stromal cell-derived factor 1

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