*Case Report*

# A neonatal case of cerebral venous sinus thrombosis with intrauterine onset after COVID-19 infection during pregnancy: Cause or coincidence?

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Coronavirus 19 disease (COVID-19) is known to predispose patients to increased thrombotic events and the risk is higher in pregnancy which is already a hypercoagulable state. Vertical transmission of the disease during pregnancy was neglected according to data early in the pandemic, however, despite conflicting results from different studies, there is an increasing suspicion of vertical transmission with the rise of new fetal and neonatal cases and perinatal transmission can be higher than expected. An early term neonate, with the history of maternal COVID-19 infection in the start of third trimester, was diagnosed as cerebral venous sinus thrombosis and chronic hemorrhagic ischemia, with intrauterine onset.

**Keywords:** Covid-19—Pregnancy—Newborn—Intracranial thrombosis



## Introduction

Neonatal cerebral venous sinus thrombosis ( CVST) is a rare cause of seizures in the neonatal period and is associated with significant mortality and morbidity.[1,2] Intrauterine fetal thrombosis is a rarer condition that is generally caused by hereditary thrombophilia, hypoxia, dehydration, or placental malfunction.[3,4] Coronavirus disease 19 (COVID-19), declared as a pandemic by the World Health Organization in March 2020, has been associated with increased coagulopathy and thromboembolism with adult and pediatric cases of CVST reported in the literature.[5,6,7,8] COVID-19 infections during pregnancy have been linked to preterm birth, growth restriction, miscarriage and hypercoagulability compromising fetal placental perfusion leading to thrombotic changes.[9,10,11] Since neonatal COVID-19 infections appear to be mostly the result of horizontal transmission during the postnatal period, it has been assumed that vertical transmission is uncommon, but it has become conceivable in the advanced stages of the pandemic. Herein we present a 3 days-old-neonate diagnosed postnatally with CVST, of a mother with COVID-19 infection during pregnancy.

## Case report

A three-day-old female neonate was transferred to our neonatal intensive care unit due to focal clonic seizures. She was born by cesarean section at 38 gestational weeks, weighing 3350g, to a 42-year-old multiparous mother whose pregnancy was affected by gestational diabetes mellitus and COVID-19 infection. The infection occurred in the initial weeks of the third trimester and the symptoms did not require hospitalization. There was no history of traumatic birth and the child's APGAR scores were 8 and 9 at 1$^{st}$ and 5$^{th}$ minutes, respectively. On the 2$^{nd}$ day of life, the patient was observed to have poor feeding and fever of 37.9°C. On the 3$^{rd}$ day of life, the patient was slightly lethargic and had clonic seizures on the left arm. Hemogram and sepsis work-up including blood and urine were normal. Serum biochemistry data were within

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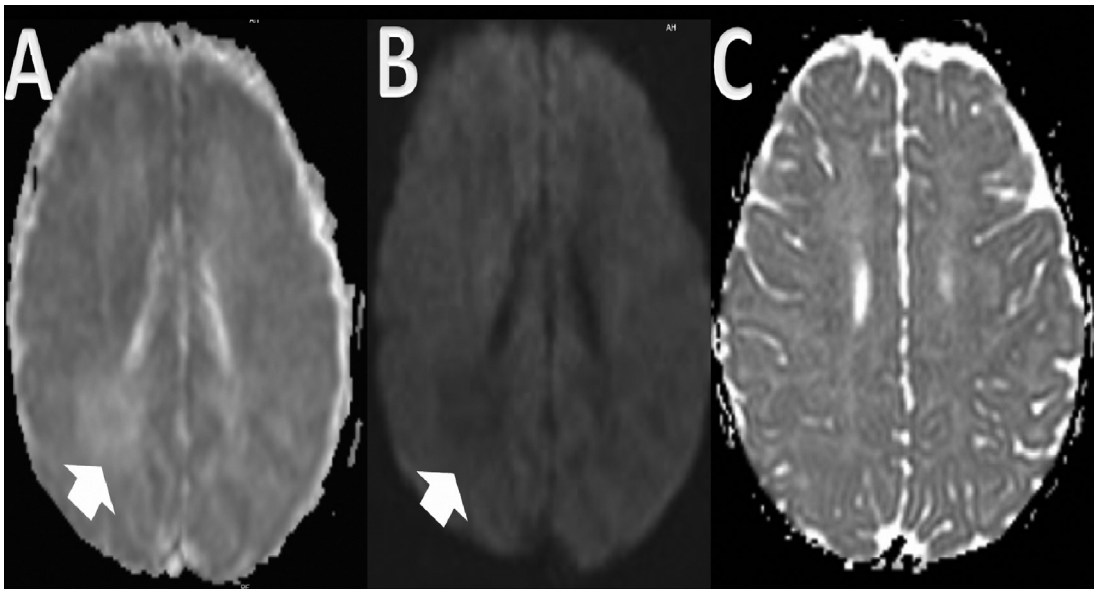


**Fig. 1.** *Magnetic Resonance images of the neonate with the suspicion of stroke. A. Axial Apparent diffusion coefficient (ADC) Magnetic Resonance Diffusion-weighted image showing partial restricted diffusion in the right parietal lobe adjacent to the occipital horn of the lateral ventricle,consistent with chronic ischemic hemorrhage (arrow). B. Axial T1-weighted Magnetic Resonance images showing approximately 16 × 16 mm in size, heterogeneous hypointense lesion with blurred borders in the right parietal lobe adjacent to the occipital horn of the lateral ventricle, consistent with chronic ischemic hemorrhage (arrow). C. The control Axial Apparent diffusion coefficient (ADC) Magnetic Resonance Diffusion-weighted image was normal at 7 months of age.*

the normal range except for magnesium (1,3 mg/dl) which was replaced immediately. Lumbar puncture revealed a xanthochromic cerebrospinal fluid with a cell count of 6 × $10^3$ cells/μl (mononuclear), protein of 100 mg/dl and glucose of 60 mg/dl. Cerebrospinal fluid remained sterile upon incubation. Intravenous antibiotics were commenced. The blood and urine cultures grew no bacteria. Phenobarbital treatment was started with a loading dose of 20 mg/kg/day and a maintenance dose of 5mg/kg/day was continued thereafter. Recurrent seizures required addition of levetiracetam as a second antiepileptic drug, with the dose of 40 mg/kg/day and seizures were controlled. Electroencephalogram (EEG) showed repetitive focal spike discharges dominant in the right parietal region in compliance with the cortical lesion. Magnetic resonance imaging (MRI) detected a hypointense lesion in T1 weighted images and partial restricted diffusion in diffusion-weighted images in the right parietal lobe, indicating chronic hemorrhagic ischemia (Fig. 1A and B). The lesion was less visible on FLAIR and T2-weighted-FSE images and could not be identified as an area of infarction on these sequences. Magnetic resonance venography showed lack of flow in the connection of right transverse sinus and confluence sinuum (Fig. 2A and B).

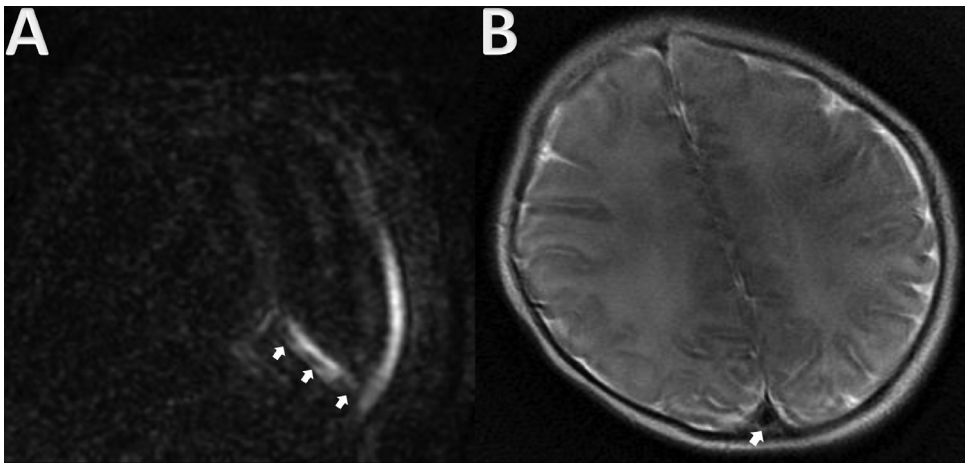


**Fig. 2.** *A. Sagittal non-contrast Magnetic Resonance Venography Inhance 3D Velocity image showing lack of flow in the connection of right transverse sinus and confluence sinuum (arrows). B. Axial T2-weighted image Magnetic Resonance image showing partially absence of flow in the right transverse sinus causing peripheral narrowing of the vein lumen (arrow)*

The coagulation tests revealed D-dimer: 1797ng/ml (0-243), PT: 10sec, PT activity: 125%, INR: 0.84, aPTT: 32sec and fibrinogen: 252mg/dl (200-393). The patient and the mother were negative for nasopharyngeal swab COVID-19 RT-PCR testing, but IgM and IgG antibody tests could not be performed due to financial constraints. Evaluation for thrombophilia showed heterozygous A1298C mutation in the methylene-tetrahydrofolate reductase (MTHFR) gene both in the patient and the mother. Homocysteine levels, protein C, protein S and antithrombin levels were all in normal ranges. Antiphospholipid antibodies were negative. The patient was diagnosed as having right transverse sinus venous thrombosis with chronic hemorrhagic ischemia in the right parietal lobe, that occurred in utero at least 14-28 days before birth. Low molecular weight heparin (enoxaparin) was commenced immediately with the dose of 1,7 mg/kg twice a day. The clinically well appearing and seizure-free baby was discharged at 15 days of age with anticonvulsant monotherapy (levetiracetam with a dose of 40 mg/kg/day) and anticoagulation therapy. At 3 months, enoxaparin was ceased and levatirecetam was discontinued after gradually tapering the dose with normalization of EEG at 7 months of age. The control MRI at 7 months was detected to have normal imaging findings (Fig. 1C). In the follow-up period to date, the neurodevelopment of the patient, at 11 months of age, appears to be normal. Informed consent has been obtained from the family of the patient to share the details of their condition.

## Discussion

Neonatal CVST is a rare disease, with an incidence ranging from 12 to 47/100,000 term neonates/year, however, comprises nearly 50% of all pediatric CVST causing a remarkable morbidity and mortality.[12,13] The diagnosis is challenging with a variable clinical presentation and needs a high degree of suspicion. It is likely to result from the combination of predisposing maternal, fetal and neonatal risk factors. These risk factors include congenital thrombophilia, preeclampsia, pregnancy induced/preexisting diabetes, perinatal asphyxia, difficult delivery, sepsis, meningitis, and placental disorders such as thrombosis, infection and fetomaternal hemorrhage.[14,15,16] COVID-19 infection, known to exacerbate thrombophilia, can be speculated in the pathogenesis of neonatal thrombosis owing to further exaggerating the hypercoagulability of pregnancy and probably infecting the fetus itself.

The neonate with CVST in our report was born to an unvaccinated mother with a history of COVID-19 infection in the beginning of the third trimester, which may have been the cause of vertical transmission. Several aspects of COVID-19 infection in pregnancy are not yet fully understood, including long-term effects and the possibility of an embryopathy.[17] Some placental pathology studies related to SARS-COV-2 during pregnancy have suggested that COVID-19 is related with a tendency towards coagulopathy with possible transplacental impact on the fetus.[10,11] Furthermore, a systematic review including 1063 pregnant women with COVID-19 during pregnancy reported higher risk of the thromboembolic complications.[18] Also a very recent review has demonstrated that COVID-19 placentitis, which may have both an infectious and immunologic basis, cause severe and diffuse placental destruction, interfering with function of oxygenation and leading to stillbirth and neonatal deaths. All mothers reported to have SARS-COV-2 placentitis were unvaccinated demonstrating viremia at some time during pregnancy.[19] The possibility of vertical transmission of COVID-19 disease during pregnancy is a topic of big debate. There is insufficient evidence to rule out vertical transmission, and data suggesting its existence have increased as the pandemic has progressed. Cases of fetal demise in the first trimester, IgM positivity at birth, neonatal limb ischemia and CVST have been reported in last two years, pointing to possible vertical transmission.[20,21,22,23]

The inability to conduct IgM and IgG antibodly tests to confirm previous COVID-19 infection in our patient and the absence of placental pathology data were the primary limitations of the present case. However, we believe IgM antibodies would have been negative, as we hypothesized that the infection took place at least 3 months before birth and presence of IgG antibodies would not be able to distinguish whether it was due to an infection or maternally derived antibodies through the placenta. Our patient was diagnosed as being heterozygous for MTHFR A1298C mutation. The published literature on intrauterine fetal thrombosis is limited to case reports and case series, it is believed that genetic prothrombotic mutations and maternal diseases such as diabetes may play a role.[3,4] However, MTHFR A1298C heterozygosity is prevalent in Turkish population and is not linked to elevated homocysteine levels and hypercoagulability unless combined with MTHFR C677T mutation.[24]

Possible effects of COVID-19 on vascular circulation raise concerns for the current neonatal case of CVST due to the possible vertical transmission of COVID-19 infection, increased hypercoagulability and the superposition of gestational diabetes.

## Author contributions

Mine Özdil, MD, contributed to the design of the work; or the acquisition, analysis, interpretation of data for the work and drafting the work revising it critically for important intellectual content; and final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

İpek Dokurel Çetin, MD, also contributed to the design of the work; the acquisition, analysis, interpretation of data for the work and drafting the work revising it critically for important intellectual content; and final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Declaration of Competing Interest

The authors report no conflict of interest.

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