Neonatal Cerebral Venous Thrombosis following Maternal SARS-CoV-2 Infection in Pregnancy

Francesca Campi\textsuperscript{a} Daniela Longo\textsuperscript{b} Iliana Bersani\textsuperscript{a} Immacolata Savarese\textsuperscript{a} Giulia Lucignani\textsuperscript{b} Cristina Haass\textsuperscript{c} Maria Chiara Paolino\textsuperscript{c} Sarah Vadalà\textsuperscript{c} Paola De Liso\textsuperscript{d} Matteo Di Capua\textsuperscript{d} Matteo Luciani\textsuperscript{e} Giacomo Esposito\textsuperscript{f} Paolina Giuseppina Amante\textsuperscript{f} Federico Vigevano\textsuperscript{d} Andrea Dotta\textsuperscript{a}

\textsuperscript{a}Department of Medical and Surgical Neonatology, Bambino Gesù Children’s Hospital IRCCS, Rome, Italy; \textsuperscript{b}Neuroradiology Unit, Imaging Department, Bambino Gesù Children’s Hospital IRCCS, Rome, Italy; \textsuperscript{c}Neonatal Intensive Care Unit, S. Pietro FBF Hospital, Rome, Italy; \textsuperscript{d}Division of Neurology, Bambino Gesù Children’s Hospital IRCCS, Rome, Italy; \textsuperscript{e}Department of Pediatric Hematology Oncology, Bambino Gesù Children Hospital IRCSS, Rome, Italy; \textsuperscript{f}Neurosurgery Unit, Department of Neuroscience and Neurorehabilitation, Bambino Gesù Children’s Hospital IRCSS, Rome, Italy

Established Facts

- A possible complication of SARS-CoV-2 infection is the development of an exacerbated thrombophilic status.
- Cerebral venous thrombosis may represent a rare but possible complication of SARS-CoV-2 infection both in adults and children.

Novel Insights

- We describe the case of a term neonate showing extended cerebral venous thrombosis of unclear origin, whose mother had SARS-CoV-2 infection during pregnancy.
- We believe that the prothrombotic status induced by maternal SARS-CoV-2 infection may have played a pathophysiological role in the development of such severe neonatal complication.

Keywords

SARS-CoV-2 · Cerebral venous thrombosis · Neonate · Pregnancy · Magnetic resonance imaging

Abstract

A possible consequence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is the development of an exacerbated thrombophilic status, and cerebral venous thrombosis (CVT) is a rare but possible complication of SARS-CoV-2 infection reported both in adults and in chil-
children. The present case report describes the clinical course of a term neonate showing extended CVT of unclear origin, whose mother had developed SARS-CoV-2 infection during the third trimester of pregnancy. We speculate that the prothrombotic status induced by maternal SARS-CoV-2 infection may have played a pathophysiological role in the development of such severe neonatal complication. Further investigations are required to confirm such hypothesis.

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Introduction

A possible consequence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is an exacerbated thrombophilic status [1], and cerebral venous thrombosis (CVT) may represent a rare but possible complication in adults [2, 3] and children [4]. The exact pathophysiology of SARS-CoV-2-related coagulopathy is still unclear [5].

An early diagnosis of neonatal CVT is challenging due to its rarity, different etiology, variable clinical presentation, variable location/extension, and velocity of clot formation [4, 6, 7]. CVT may lead to significant mortality/neurologic morbidity, and neonates are the most commonly affected age-group, compared to older infants/children [8].

The results of an international survey of pediatric stroke, occurred in 61 centers during the pandemic, reported that only a minority of pediatric patients with ischemic stroke were tested for SARS-CoV-2 [4]. In the present case report, we describe a possible association between maternal SARS-CoV-2 infection during pregnancy and neonatal CVT. We speculate that maternal SARS-CoV-2-related prothrombotic status, in addition to the prothrombotic tendency typical of pregnancy, may have indirectly facilitated in utero the pathophysiological mechanisms leading to perinatal CVT.

Case Report

A 27-year-old woman (gravida-II, para-1) was hospitalized at 33 weeks’ gestational age due to SARS-CoV-2 infection. Up to that moment, pregnancy and obstetric ultrasound evaluations were normal. No history of familial thrombophilia/venous thromboembolism was reported. The woman had increased fibrinogen levels (539 mg/dL) and prothrombin time 143% and received low molecular weight heparin, suspended when she left the hospital against medical advice. The following obstetric assessment detected oligo-anhydramnios, and delivery was induced. Perinatal cardiotocographic monitoring was negative. The neonate (gestational age 39\textsuperscript{5} weeks, birth weight 2,950 g) was born after dystocic delivery, requiring a single vacuum application. Cord/neonate blood gas analyses and cardiorespiratory adaptation were normal (Apgar score 7\textsuperscript{′}–9\textsuperscript{′}). Early postnatal period was silent, neonatal clinical assessment normal, and postnatal weight loss within normality range. The neonate was routinely discharged on the third day of life. One day after, however, the newborn was taken to the emergency room due to seizures development (generalized hypertonus, opisthotonus, lateral gaze deviation, and blinking), confirmed by amplitude-integrated electroencephalography and electroencephalography. Intravenous anticonvulsing therapy with phenobarbital was begun, subsequently associated with midazolam. Cerebral ultrasound showed right intraventricular hemorrhage, right thalamus infarction, the presence of blood in the third and fourth ventricles, mild midline shift, and absent Doppler signal in the cerebral internal veins. Neonatal pharyngeal swab for SARS-CoV-2 (polymerase chain reaction) was negative. Mother and child had comparable anti-SARS-CoV-2 total antibody titer (mother: 135,600 baumé/mL; neonate: 131,500 baumé/mL, Diasorin LIAISON\textsuperscript{®}). On the 8th day of life, the neonate referred to our neonatal intensive care unit for further investigations.

At arrival, cerebral ultrasound confirmed the findings detected at the transferring hospital (Fig. 1a–c). Magnetic resonance imaging (MRI) showed right thalamic infarction secondary to thrombosis of the internal cerebral veins, thrombosis of the Galen vein and venous sinuses confluence, posthemorrhagic dilation of the supratentorial ventricular system, and blood in the fourth ventricle (Fig. 1d–f). Neurosurgical evaluation excluded urgent surgical indications. Serial amplitude-integrated electroencephalography and electroencephalography monitoring confirmed the presence of seizures, responsive to the anticonvulsant treatment (midazolam administration was progressively reduced up to withdrawal, phenobarbital continued). Echocardiography only found patent foramen ovale with normal cardiac function. Ocular assessment was negative. Hemoglobin was 13.6 g/dL, stable throughout hospitalization. C-reactive protein, procalcitonin, platelet count, and coagulative profile (prothrombin time, activated partial thromboplastin time, international normalized ratio, fibrinogen, antithrombin III, and D-Dimer) were normal. Extended thrombophilic screening including homocysteine, anticardiolipin/antiphospholipid/anti-beta-2-glycoprotein antibodies, protein S, protein C, activated protein C resistance, lupus anticoagulant, factor XIII, von Willebrand factor antigen, Factor V Leiden (G1691A) mutation, and factor II prothrombin (G20210A) mutation was normal. Heterozygous mutation of the methylenetetrahydrofolate reductase (C677T and A1298C) was detected. Serial pharyngeal swabs for SARS-CoV-2 were negative. Blood/urine cultures were negative. Cytomegalovirus/rubella/ herpes simplex 1–2 toxoplasma infections were excluded. Genetic investigations for vascular abnormalities (AGGF1/ACVR1LI/SMAD4/ENG/GDF2/AKT1/PIK3CA/PTEN/SEC23B/FTAMBP/GNAO1/GLMN/RASA1/EPHBF4/TEK/GNA11/GNA14/FO5/FOSB/COL4A1) by next-generation sequences (Twin-Custom-Panel kit on NovaSeq6000; Illumina) were negative. Auditory brainstorm/short somatosensory of the upper limb/visual evoked potentials was normal. One week after admission, control MRI found comparable site/extension of the thrombotic lesions, intraventricular clots organization, and stability of the supratentorial ventricular dilatation. Considering the absence of new-onset hemorrhages, subcutaneous low-molecular-weight heparin was begun (200 UI/kg/day in two administrations), with cautious monitoring of activated Xa factor. At subsequent cerebral ultrasound evaluations serially performed during hospi-
talization, and at MRI assessment performed 3 weeks after admission (Fig. 2a, b), progressive recanalization of the cerebral internal veins and Galen vein was observed. Due to progressive enlargement of the lateral ventricles, Rickham reservoir was inserted. The subsequent control MRI documented decreased ventricular sizes and almost complete resolution of the thalamic infarction and thrombotic lesions. Clinical neurologic assessment was normal. Parents’ written informed consent for publication was obtained.

**Discussion**

The present work describes the case of a term neonate showing extended CVT of unclear origin, whose mother was hospitalized during pregnancy due to SARS-CoV-2 infection. We believe that the exacerbated thrombophilic status induced by maternal SARS-CoV-2 infection may have played a pathophysiological role in the development of CVT.
of such complication, suggesting a possible association between maternal SARS-CoV-2 infection during pregnancy and neonatal CVT. Low-molecular-weight heparin, a possible therapy for thrombophilic conditions [4, 9], was administered during maternal hospitalization due to SARS-CoV-2 infection, but discontinued prematurely after discharge, occurred against medical advice.

Our multidisciplinary team widely discussed the possible differential diagnoses leading to such extensive CVT: (i) although our neonate was born by dystocic delivery, prenatal cardiotocography was negative, vacuum application was not protracted [10], adaptation at birth was normal, and the imaging findings were not supportive for vacuum-related lesions [11]; (ii) congenital/acquired infections were excluded; (iii) malformative disorders were excluded at angio-MRI; (iv) no feto-maternal transfusion was present; (v) no neonatal dehydration was reported; and (vi) neonatal thrombophilic screening only highlighted methylenetetrahydrofolate reductase heterozygotic mutations, anyway associated with normal homocysteine levels. Such a widely diffused condition might generically increase the risk for thrombotic disorders [12], possibly due to increased plasma homocysteine levels [13], and plays a role in the pathogenesis of thrombotic events. Nevertheless, CVT development is mostly triggered by additional etiological factors [12, 14, 15]. In our opinion, maternal SARS-CoV-2-related coagulopathy may have facilitated, prenatally, a cascade of events which, in addition to predisposing factors, might have enhanced CVT development.

In conclusion, the possible risk of perinatal CVT following maternal SARS-CoV-2 infection during pregnancy deserves high clinical suspicion since a precocious diagnosis of such potentially life-threatening condition in the perinatal period may be challenging. Further investigations are required to confirm our hypothesis.

Statement of Ethics
The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The paper is exempt from Ethical Committee approval because it reports a case report and parents have given their written informed consent to publish their neonate’s case.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

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Author Contributions
Francesca Campi, Daniela Longo, Iliana Bersani, Giulia Lucignani, Cristina Hass, Maria Chiara Paolino, Sara Vadalà, Paola De Liso, Matteo Di Capua, Matteo Luciani, Immacolata Savarese, Federico Vigevano, Giacomo Esposito, Paolina Giuseppina Amante, and Andrea Dotta contributed to conceptualization, investigation, and writing (first draft, review, and editing). All the authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data Availability Statement
All data related to the case report and included in this article are stored in a repository secured by the corresponding author. Further inquiries can be directed to the corresponding author.

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