Letter to the Editor

In reply to the letter to the editor regarding "A neonatal case of cerebral venous sinus thrombosis with intrauterine onset after COVID-19 infection during pregnancy: Cause or coincidence?"

We are grateful to Josef Finsterer for his comments on our recent case regarding the possible association of maternal COVID-19 infection during pregnancy with a neonatal case of intrauterine cerebral sinus venous thrombosis (CSVT). In the letter to editor, he had raised several arguments against a causal relationship, however our case report focused on the plausability of maternal COVID-19 infection as a triggering factor for in utero onset of CSVT.

The first comment was about the confirmation of SARS-CoV-2 infection of the fetus or neonate, negativity of nasopharygeal swab test and no presence of anti-SARS-CoV-2 antibodies. As stated in the limitations of the report, antibody test against COVID-19 infection in the neonate could not be performed in our hospital and the family did not accept this test to be performed for a fee. Although the knowledge regarding the immune response in COVID-19 infected pregnant women and their offsprings is limited, it has been postulated that IgG antibodies are positively associated with time since infection and with symptom severity of pregnants.[1] The second issue mentioned in the letter was the latency between maternal infection and fetal CSVT. The incubation period of the disease is between 0-14 days, and seroconversion usually starts between 5-7 and 14 days after the onset of symptoms.[2] Mother had the infection approximately at 28-30 weeks of gestation, confirmed with positive nasopharyngeal swab test, and after an incubation period, intrauterine infection may have occurred at 34 weeks-36 weeks resulting with CSVT 2-4 weeks before birth. We think confirmation of the antibodies would enlighten us on these situations, but presence of IgG antibodies would not be able differentiate whether they were the result of fetal infection or maternally derived IgG antibodies thorough placenta, IgM or IgA antibodies would be the most valuable, if detected positive.

Another issue mentioned in the letter was about intrauterine or transplacental transmission of the SARS-CoV-2 virus. As stated in the report, vertical transmission is a topic of debate, but the literature is expanding with recent reports of confirmed and possible cases.[3–5] Regarding the comment about differential causes of CSVT in neonate, the report includes detailed data about genetic thrombophilia causes which were excluded, there was no history of trauma or birth asphyxia, and cranial MRI did not reveal any abnormality such as hemangioma or dural sinus malformation. Pregnancy was complicated with maternal diabetes and COVID 19 infection, both of which could have prothrombotic effects on fetus already heterozygous for insignificant A1298C mutation.

Other question was about the chronic ischemic hemorrhage, which was actually defined as the venous ischemic stroke due to thrombosis with secondary bleeding in right parietal lobe, adjacent to occipital horn of the lateral ventricule. As mentioned in the paper, the ischemic infarct and venous sinus thrombosis were documented, however some of the MRI sequences defined lesion poorly due to resolution quality and was not demonstrative for publishing in the paper. We agree with the observation that the neuroimaging modalities which certainly define the hemorrhage (CT or SWI sequences) weren't performed in the patient. It is difficult to conclude the relevance of the hemorrhage with solely published images, the state of encephalopathy of an infant with documented xanthochromia and cerebral sinus venous thrombosis, the consequence of the clinical and radiological correlation of overall the MRI findings were consistent with the diagnosis of venous ischemic stroke due to thrombosis with secondary hemorrhage.

Xantochromia, yellow discoloration of the cerebrospinal fluid, can be caused by subarachnoid and intracranial bleeding, increase in cerebrospinal fluid (CSF) protein >150 mg/dl, hyperbilirubinemia, high intake of carotenoids and presence of red blood cells (oxyhemoglobin as a result of lysis of red blood cells) which may persist thereafter for two to four weeks.[6,7] As stated in the report, CSF examination of the patient revealed a slight increase in protein and a normal white blood cell count, both of which were in normal ranges for neonates, there was no history of caretonid intake and the patient's serum biochemistry markers were normal including bilirubin level, so xantochromia was attributed to intraventricular bleeding secondary to thrombosis which probably took place 2-4 weeks age before birth. Another issue mentioned in the letter, it would not be posssible in our center to study the cytokines or chemokines related to SARS-COV2 infection in CSF.

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