Acute encephalopathy in a neonate associated with infection by SARS-CoV-2

Margarita Tretjakova, Patricia Leroy, Christophe Barrea

University Hospital of Liège, Department of Paediatric Neurology, Liège, Belgium

margo.tretjakova@gmail.com

Keywords

Epilepsy ; punctuate white matter lesions ; SARS-CoV-2 ; meningo-encephalitis ; neonatal seizures.

Abstract

We present the case of a 5-day-old patient who was admitted to the emergency department with initially unilateral and then generalised seizures and lethargy. Cerebral MRI had shown diffusion-restricted symmetrical fronto-parietal lesions consistent with viral encephalitis due to SARS-COV-2. The control MRI showed signs of necrosis with the appearance of cavitation, predominantly on the left side. Neurological follow-up was performed at 1, 3 and 6 months of age and showed no significant neurodevelopmental delay.

Introduction

Our lives have been significantly affected by the SARS-COV-2 (known as COVID-19) pandemic since early 2020. This virus can cause a variety of disease symptoms ranging from asymptomatic carriers to a multisystem inflammatory syndrome in different age groups. Children appear to be less affected by this virus, often showing milder or no symptoms. However, an increasing number of cases have been reported in the literature describing severe disease, particularly neurological, such as lethargy, irritability, hypotonia, apnoea and seizures in young toddlers (1). We present a case of a neonate affected by COVID-19 with seizures due to encephalopathic white matter lesions.

Case report

The patient was a female born at 39 weeks by caesarean section for breech presentation. There were no other complications. The pregnancy was uneventful, except for controlled maternal hyperthyroidism. The Apgar scores were 9 and 10 at 1 and 5 minutes of life, respectively, and her birth measurements were within the normal range for her gestational age.

The patient was admitted to the emergency department because of abnormal movements and lethargy. In the emergency department, she had two further episodes of clonic movements, which started on the left side and then became generalised. There was no association with fever.

Initial blood tests were normal: normoglycaemia, mild leukopenia with 4340 WBC per microlitre, no other abnormalities in the haemogram, negative C-reactive protein, normal electrolytes, liver, and renal function, and basic coagulation tests showing no abnormalities. Empirical treatment with intravenous cefotaxime, amoxicillin, and acyclovir was started to cover the possibility of neonatal sepsis or herpes simplex virus encephalitis. After negative results of blood, urine and CSF cultures, antibiotics and antiviral treatment were discontinued. The seizures were initially controlled with intravenous phenobarbital and midazolam and then successfully managed with levetiracetam. She had no further convulsions.

On the day of admission, a CT-scan of the brain showed no abnormalities. However, a brain magnetic resonance imaging (MRI) scan showed symmetrical fronto-parietal signal abnormalities and restricted diffusion, predominantly on the fronto-polar cortex, precentral and central gyrus, anterior and posterior commissures of the corpus callosum, and postero-lateral regions of the thalami (Figure 1). These findings were consistent with neonatal encephalopathy.

A complete metabolic analysis, including blood, urine, and CSF amino acid levels, organic acid levels, and acylcarnitine profile, was performed to rule out a metabolic cause. All the results were normal. In addition, rapid exome sequencing revealed no significant pathological genetic mutations.

Analysis of cerebrospinal fluid (CSF) collected on days 1 and 3 showed normal cytology and normal glucose and protein levels (885 mg/L). A nasal swab tested positive for SARS-CoV-2 by reverse transcriptase polymerase chain reaction (rt-PCR). No other virus was found in her nasal swab, and we were able to rule out rhinovirus, enterovirus, influenza A&B, parainfluenza 1, 2, 3, 4, coronavirus (non-covid-19), cytomegalovirus (CMV). CMV was also tested by PCR on urine and CSF with negative results.

The patient's father had recently tested positive for SARS-COV-2 following mild respiratory symptoms. Her mother was asymptomatic, but her nasal swab tested positive for SARS-COV-2. The PCR SARS-COV-2 test on the CSF was negative. To exclude other viral causes, we tested the CSF for various neurotropic viruses such as herpes simplex virus types 1&2, enteroviruses, varicella-zoster virus, parechovirus, human herpesvirus 6 and CMV, all of which were negative. The patient had no respiratory symptoms related to her SARS-COV-2 infection, and two chest radiographs taken during her hospitalisation showed no specific abnormalities. Based on these findings, our presumptive diagnosis was viral encephalopathy probably due to SARS-COV-2, as this was the only virus detected.

Follow-up brain MRIs at 10 days (Figure 2) and 6 weeks (Figure 3) showed more defined lesions, reduced inflammation, and the appearance of cavitary zones. Spectroscopic analysis confirmed neuronal loss, supporting providing further evidence of a specific necrotizing encephalitis, with SARS-COV-2 being the only etiological factor detected.

Neurological follow-up at 1, 3, and 6 months of age showed no significant neurodevelopmental delay.

Discussion

There are many causes of neonatal encephalopathy, often related to acute brain injury during the perinatal period (2). The lesions described in this case did not correspond to the classic haemorrhagic or ischaemic lesions. Other aetiologies such as genetic or metabolic syndromes were ruled excluded by laboratory investigations. After excluding all other causes, including metabolic, genetic, haemorrhagic, thrombotic, and other bacterial and viral infections, it was concluded that the encephalopathy was due to SARS-COV-2 infection, which is now known to cause early neurological damage

Figure 1: Day 0. From left to right: cerebral MRI in T1, FLAIR, and diffusion-weighted image. Diffusion-weighted image shows a symmetrical restricted diffusion (hyperintensity of b-1000 and decrease of apparent diffusion coefficient) in the fronto-parietal regions, predominantly on the fronto-polar cortex, precentral and central gyrus, anterior and posterior commissures of corpus callosum, and the postero-lateral regions of thalami. It is associated with discreet flair hyperintensity in the same region. Also a discreet bilateral contrast enhancement in fronto-parietal leptomeninges is present.

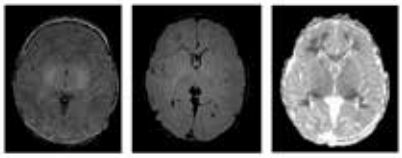


Figure 2: Day 10. From left to right: cerebral MRI in T1, FLAIR, and diffusion-weighted image. The first image shows hyperintense lesions in the white matter, especially in the frontal and the parietal regions. The frontal white matter shows signs of necrosis. Diffusion - restricted lesions are found in the corpus callosum.

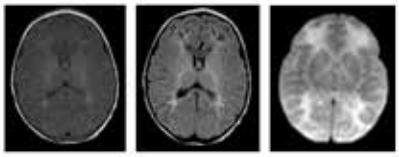
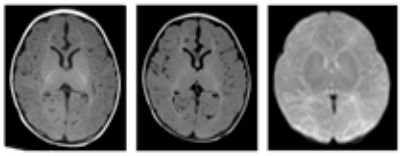


Figure 3: Week 6. From left to right: cerebral MRI in T1, FLAIR, and diffusion-weighted image. This MRI shows the regression of the diffusion restricted lesions, followed by the appearance of white matter lesions in the frontal cortex with the appearance of cavitation, predominantly on the left side.



in neonates (1). We emphasise on the fact that this diagnosis remains presumptive, as it is a diagnosis of exclusion.

Similar neurological lesions have been described in other viral encephalopathies, often associated with rotaviruses or enteroviruses (3, 4). Three similar cases associated with SARS-COV-2 infection have been (5-7). All cases had white matter lesions with restricted diffusion particularly in the corpus callosum and periventricular white matter. Our case, as well as a case described by Fragoso in 2022, showed cytotoxic white matter lesions transitioning into cavities. None of the described cases presented with respiratory symptoms. Of these cases, only one patient was treated with corticoids, in contrast to our patient (5).

The exact mechanism of these neurological lesions remains unclear. In none of these cases was SARS-COV-2 directly detected in the CSF. According to the International Encephalitis Consortium, the CSF pleocytosis is supportive, but not a necessary criterion for encephalitis, particularly in young infants. The major diagnostic criterion is an altered mental status lasting more than 24 hours without an alternative cause as evidence of neurological dysfunction. In addition, at least two additional minor criteria must be present, namely: fever ≥38°C within 72 hours, seizures, new focal neurological findings, CSF pleocytosis (≥5 white blood cells/μL), neuroimaging with brain parenchymal changes, or an electroencephalogram consistent with encephalitis (8). Young infants are more prone to have infectious encephalitis without pleocytosis, for example with enterovirus or parechovirus infections (8). Some authors suggest that central nervous system lesions may result from the virus accessing the central nervous system (CNS) directly or via an excessive cytokine release mechanism (1). The cytokine storm syndrome typically manifests as persistent fever, cytopenia, a high erythrocyte sedimentation rate, increased fibrinogen, and hyperferritinemia (5). However, our patient did not have any of these abnormalities. Studies conducted by Lindan have shown that the most commonly observed neuroimaging manifestation in children, not only neonates, is similar in appearance to ADEM (acute disseminated encephalomyelitis), with patchy or confluent areas of T2 hyperintensity in the grey and white matter, with or without reduced diffusion or enhancement (9).

We would like to emphasize that neurological symptoms due to SARS-CoV-2 represent a non-negligible proportion of affected neonates. A review of the literature on SARS-CoV-2 in neonates (both term and preterm) by Moraes et al in 2022 analysed data from a total of 87 neonates (1). Of these, 23% were asymptomatic. Those with symptoms usually had respiratory symptoms (57.5%) such as respiratory distress, tachypnoea, cough, and coryza. A total of 26.4% had fever. Neurological symptoms were observed in 26.4% of neonates, with lethargy being the most common (9.2%). Gastrointestinal symptoms such as vomiting, feeding intolerance and abdominal distension were seen in 21.8% of patients.

The long-term prognosis of affected children remains uncertain. The neurodevelopment of our patient seems to be completely normal at the age of 3 and 6 months of age, but it should be noted that the prefrontal regions become functional much later. Some other authors conducted a case-control study of newborns diagnosed with SARS-CoV-2 in Wuhan, China (10). A total of five newborns with SARS-CoV-2 were included. Despite a significant difference in the Hammersmith neonatal neurological examination score between infected and non-infected groups at the time of initial evaluation, there was no significant difference in neurobehaviour at 9 months of age. Larger studies with longer follow-up are needed to fully understand the impact of early-onset SARS-CoV-2 encephalitis.

Conclusion

Although our diagnosis is by exclusion and remains presumptive, it is important to consider SARS-CoV-2 infection in neonates presenting with atypical symptoms such as seizures, even in the absenceof respiratory distress. Imaging findings were also non-specific, although they are characteristic of viral encephalitis. Therefore, paediatricians should be aware of these possibilities and test for SARS-CoV-2 in patients with seizures and no other systemic involvement.

Conflict of interest

The authors have no conflict of interest to declare.

REFERENCES

1. de Moraes FM, de Souza J, Alves LP, de Siqueira MFR, Dos Santos APA, de Carvalho Berardo MM, et al. SARS-CoV-2 Infection and Possible Neonatal Neurological Outcomes: A Literature Review. Viruses. 2022;14(5).
2. Vasudevan C, Levene M. Epidemiology and aetiology of neonatal seizures. Semin Fetal Neonatal Med. 2013;18(4):185-91.
3. Kim M, Hwang JY, Lee YJ, Kim YW, Byun SY, Lee YJ, et al. Clinical and Imaging Findings of Neonatal Seizures Presenting as Diffuse Cerebral White Matter Abnormality on Diffusion-Weighted Imaging without any Structural or Metabolic Etiology. Taehan Yongsang Uihakhoe Chi. 2020;81(6):1412-23.
4. Yeom JS, Park JS, Kim YS, Kim RB, Choi DS, Chung JY, et al. Neonatal seizures and white matter injury: Role of rotavirus infection and probiotics. Brain Dev. 2019;41(1):19-28.
5. Fragoso DC, Marx C, Dutra BG, da Silva CJ, da Silva PM, Martins Maia Junior AC, et al. COVID-19 as a Cause of Acute Neonatal Encephalitis and Cerebral Cytotoxic Edema. Pediatr Infect Dis J. 2021;40(7):e270-e1.
6. Yildiz H, Yarci E, Bozdemir SE, Ozdinc Kizilay N, Mengi S, Beskardesler N, et al. COVID-19-Associated Cerebral White Matter Injury in a Newborn Infant With Afebrile Seizure. Pediatr Infect Dis J. 2021;40(7):e268-e9.
7. Martin PJ, Felker M, Radhakrishnan R. MR Imaging Findings in a Neonate With COVID -19-Associated Encephalitis. Pediatr Neurol. 2021;119:48-9.
8. Messacar K, Fischer M, Dominguez SR, Tyler KL, Abzug MJ. Encephalitis in US Children. Infect Dis Clin North Am. 2018;32(1):145-62.
9. Lindan CE, Mankad K, Ram D, Kociolek LK, Silvera VM, Boddaert N, et al. Neuroimaging manifestations in children with SARS-CoV-2 infection: a multinational, multicentre collaborative study. Lancet Child Adolesc Health. 2021;5(3):167-77.
10. Yan K, Xiao FF, Jiang YW, Xiao TT, Zhang DJ, Yuan WH, et al. Effects of SARS-CoV-2 infection on neuroimaging and neurobehavior in neonates. World J Pediatr. 2021;17(2):171-9.