

Concomitant SARS-CoV-2 infection and severe neurologic involvement in a late-preterm neonate

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SARS-CoV-2 is recognized as the cause of the coronavirus disease 2019 (COVID-19) pandemic. COVID-19 is less frequent and severe in children, with few cases reported in newborns.^{1,2}

An 18-day-old girl, born at 35⁺ week of postmenstrual age in another center from a diamniotic monochorionic twin pregnancy through spontaneous delivery, was admitted in the neonatal intensive care unit of S. Croce e Carle Hospital, Cuneo, Italy, because of decreased oral intake, mild respiratory distress, and conjunctivitis. She was discharged home clinically well 5 days after birth from a center where COVID-19 pregnant women were treated. Family history was unremarkable, and her mother was not tested for SARS-CoV-2 infection at delivery. At the time of admission, she was drowsy with mild respiratory distress. Treatment with high-flow nasal cannulas was initiated, but she was subsequently intubated and mechanically ventilated because of impending episodes of apnea. In the following hours, the patient developed sudden signs of encephalopathy: she became lethargic and alert state was not maintained. Primitive reflexes were not elicitable, with general hypotonia, absence of spontaneous movements, and pain response, but pupils were reactive to light. No spontaneous breathing was detected during synchronized mechanical ventilation for 48 consecutive hours in the absence of pharmacologic sedation. At this time, she presented leukopenia (white blood cells 2,770/ μ L) and slightly increased of aspecific inflammatory indices (C-reactive protein 12.6 mg/L, procalcitonin 1.31 ng/mL); the chest x-ray showed no lung infiltration and abdominal overdistention. Urine and blood cultures were negative. SARS-CoV-2 and *Hemophilus influenzae* were detected in the nasopharynx and bronchoalveolar lavage samples by PCR. At this time, all family members, always asymptomatic, were screened for SARS-CoV-2: the mother, 2 brothers, and grandmother resulted positive, whereas the father and the twin brother resulted negative. The CSF examination showed 12 cells/ μ L, with glucose 71 mg/dL, and the microbiological investigation was negative, including SARS-CoV-2 research. Broad-spectrum empirical antimicrobial therapy was started. Supportive treatment including oxygen supplementation and the maintenance of water-electrolyte and acid-base homeostasis was continued. Intravenous caffeine was administered as respiratory analeptic. Serial transfontanelar ultrasounds performed from day 1 to day 3 showed no pathologic images. An EEG showed cortical depression without seizures. After 48 hours, the patient became more reactive with a rapid clinical improvement. Spontaneous antigravity movements, primitive reflexes, and initial spontaneous breathing during assisted ventilation were observed. On day 4, she was extubated. Vital signs were within the normal range, and she breathed spontaneously. MRI showed no abnormalities on conventional sequences (T1 and T2 weighted) and no restricted-diffusion abnormalities on the diffusion-weighted image and apparent diffusion coefficient map.

In this 18-day-old late-preterm neonate, severe neurologic impairment occurred in the presence of SARS-CoV-2 infection and of mild symptoms attributable to COVID-19 (conjunctivitis and mild respiratory distress). CSF and MRI were normal, and SARS-CoV-2 was detected only in the respiratory tract, together with *H. influenzae*. This pathogen can be a cause of sepsis and meningitis in newborns,³ but in our patient, clinical and imaging features were completely normal, and the pathogen was not detected both in the blood and CSF. Bacterial and SARS-CoV-2 coinfections have been described in pediatrics, without any worsening of the clinical

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picture.^{1,2,4} Therefore, because no other reliable cause of the clinical picture was observed, a strong suspicion of an association between the encephalopathy and SARS-CoV-2 infection still remains.

Few data are available for SARS-CoV-2 infection in neonates, and the clinical pictures described in the literature are mainly respiratory or gastrointestinal disease associated with fever,^{1,2,4} with rare neurologic manifestations, including lethargy reported also in neonates. Nothing similar to was observed in our patient is described.^{1,2,4} Neurologic manifestations have been observed in adults with COVID-19 that could play a role in the respiratory failure of these patients.^{5,6} It is known that the brainstem of late-preterm infants (34–36⁺ weeks of postmenstrual age) is less mature than that of a full-term infant⁷ and that in preterm newborns, brain stem maturation is not linear, as well as that of upper airway and lung volume control, laryngeal reflexes, chemical control of breathing, and sleep mechanisms.⁷ Therefore, it is possible that the cortical depression observed at the EEG was due to hypersomnia related to a possible, transient involvement of the ascending reticular substance at the brainstem level. Considering the described neurotropism of SARS-CoV-2, it is conceivable that a (late)-preterm infant could be at risk of neurologic involvement with respiratory failure of central origin, even several days after birth. This should be kept in mind by the neonatologists in an era of SARS-CoV-2 pandemic.

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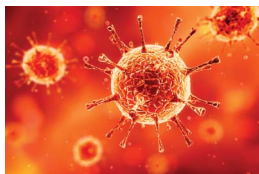
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Andrea Sannia, MD, PhD	Neonatal Intensive Care Unit, S. Croce e Carle Hospital, Cuneo, Italy	Patient evaluation, clinical data analysis and pathophysiologic interpretation, and paper revision

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