Published Ahead of Print on September 15, 2020 as 10.1212/WNL.0000000000010729

Neurology®
The most widely read and highly cited peer-reviewed neurology journal
The Official Journal of the American Academy of Neurology

AMERICAN ACADEMY OF NEUROLOGY®

Neurology Publish Ahead of Print
DOI: 10.1212/WNL.0000000000010729

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

Paola Di Nicola, MD[1], Simone Ceratto, MD[2], Cristina Dalmazzo, MD[1], Luca Roasio, MD, PhD[3], Elio Castagnola, MD, PhD[4], Andrea Sannia, MD, PhD[1]

1) Neonatal Intensive Care Unit, S.Croce e Carle Hospital, Cuneo, Italy
2) Post-Graduation School of Pediatrics, University of Turin, Torino, Italy
3) Department of Pediatrics, "E. Agnelli" Hospital, Pinerolo, Italy
4) Infectious Diseases Unit, IRCCS Istituto Giannina Gaslini, Genova, Italy

Corresponding Author: Dr Elio Castagnola, MD, PhD, E-mail address: eliocastagnola@gaslini.org

Study Funding: No targeted funding reported.

Disclosure: The authors report no conflicts of interest relevant to the manuscript.

Keywords: SARS-CoV-2, preterm neonate, neurological manifestations

Number of Figures: 0

Number of Tables: 0

SARS-CoV-2 is recognized as the cause of 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-days-old female, born at 35^{+1} weeks of post-menstrual age in another centre 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 centre 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 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 apnoea. 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 absence of pharmacological sedation. At this time, she presented leukopenia (White Blood Cells 2770/μL), 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 *Haemophilus influenzae* were detected in nasopharynx and bronchoalveolar lavage samples by polymerase chain reaction. At this time all family members, always asymptomatic, were screened for SARS-CoV-2: the mother, two brothers and grandmother resulted positive, while the father and the twin brother resulted negative. Cerebrospinal fluid (CSF) examination showed 12 cells/μL, with glucose 71 mg/dl, 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 trans-fontanellar ultrasounds performed from day 1 to day 3 showed no pathological images. An electroencephalogram (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. Magnetic Resonance Imaging (MRI) showed no abnormalities on conventional MRI sequences (T1 and T2-weighted) and no restricted-diffusion abnormalities on Diffusion-Weighed Image and Apparent Diffusion Coefficient map.

In this 18-day old, late preterm neonate severe neurological impairment occurred in presence of SARS-CoV-2 infection and of mild symptoms attributable to COVID-19 (conjunctivitis, 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 [4], but in our patient clinical and imaging features were completely normal and the pathogen was not detected both in blood and CSF. Bacterial and SARS-CoV-2 coinfections have been described in pediatrics, without any worsening of the clinical picture [1-3]. Therefore, since 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 literature are mainly respiratory or gastrointestinal disease associated with fever [1-3], with rare neurological manifestations, including lethargy reported also in neonates. However, nothing similar to was observed in our patient is described [1-3]. Neurological manifestations have been observed in adults with COVID-19 that could play a role in the respiratory failure of these patients [6]. It is known that brainstem of late preterm infants (34 – 36^{+6} weeks of post-menstrual age) is less mature than that of a full-term infant [7], and that in preterm newborns brain stem maturation is not linear, as well as that as 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 brainstem level. Considering the described neurotropism of SARS-CoV-2 is conceivable that a (late) preterm infant could be at risk of neurological involvement with respiratory failure of central origin, even several days after birth. This should be kept in mind by neonatologist in an era of SARS-CoV-2 pandemia.

Appendix 1. Authors' contributions:

Author	Location	Contribution
Paola Di Nicola	Neonatal Intensive Care Unit, S.Croce e Carle Hospital, Cuneo, Italy	patient evaluation and data collection, manuscript preparation
Simone Ceratto	Post-Graduation School of Pediatrics, University of Turin, Torino, Italy	patient evaluation and data collection, manuscript revision
Cristina Dalmazzo	Neonatal Intensive Care Unit, S.Croce e Carle Hospital, Cuneo, Italy	patient evaluation and data collection, manuscript revision
Luca Rosario	Department of Pediatrics, "E. Agnelli" Hospital, Pinerolo, Italy	patient evaluation and data collection, manuscript revision
Elio Castagnola	Infectious Diseases Unit, IRCCS Istituto Giannina Gaslini, Genova, Italy	clinical data analysis and pathophysiological interpretation, paper revision
Andrea Sannia	Neonatal Intensive Care Unit, S.Croce e Carle Hospital, Cuneo, Italy	patient evaluation, clinical data analysis and pathophysiological interpretation, paper revision

REFERENCES

1. Di Nardo M, van Leeuwen, G. Loreti A, Barbieri MA, Guner Y, Locatelli F, Ranieri VM. A literature review of 2019 novel coronavirus (SARS-CoV2) infection in neonates and children. Pediatr Res . 2020 Jul 17. doi: 10.1038/s41390-020-1065-5
2. Deniz M, Tezer H. Vertical transmission of SARS CoV-2: a systematic review. J Matern Fetal Neonatal Med. 2020 Jul 21:1-8. doi: 10.1080/14767058.2020.1793322
3. Castagnoli R, Votto M, Licari A, Brambilla I, Bruno R, Perlini S, Rovida F, Baldanti F, Marseglia GL. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review. AMA Pediatr. 2020 Apr 22. doi: 10.1001/jamapediatrics.2020.1467.
4. Nizet V, Klein JO. Bacterial sepsis and meningitis. pp: 271-271
5. Baig AM. Neurological manifestations in COVID-19 caused by SARS-CoV-2. CNS NeurosciTher. 2020; 26(5):499-501. doi: 10.1111/cns.13372.
6. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol. 2020 Feb 27. doi: 10.1002/jmv.25728.
7. Darnall RA, Ariagno RL, Kinney HC. The late preterm infant and the control of breathing, sleep, and brainstem development: a review. ClinPerinatol. 2006; 33(4):883-914.doi: 10.1016/j.clp.2006.10.004.

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

Paola Di Nicola, Simone Ceratto, Cristina Dalmazzo, et al.

Neurology published online September 15, 2020
DOI 10.1212/WNL.0000000000010729