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Case Report

The case of fatal acute hemorrhagic necrotizing encephalitis in a two-month-old boy with Covid-19.

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ABSTRACT

SARS-CoV-2 infection in healthy children is usually benign. However, severe, life-threatening cases have previously been reported, notably in infants. We must be aware that data on the natural history of COVID-19 are still full of gaps, especially as far as the pediatric population is concerned. Therefore, it is important to describe rare manifestations of SARS-CoV-2 acute infection in children. Here we present the case of acute hemorrhagic necrotizing encephalitis (AHNE) in a previously healthy, 2-month-old male infant with SARS-CoV-2 infection. After 2 days of fever with signs of respiratory tract infection, neurological manifestations appeared: irritability, nystagmus, agitation then apathy. As a consequence of apnea, he required emergent intubation and was transferred to our PICU. Brain MRI revealed diffuse areas of oedema associated with numerous symmetrical changes with punctate hemorrhages in basal ganglia, thalami, brainstem, and cerebral gray matter. CSF was clear with pleocytosis 484 cells/μl, elevated lactic acid and protein. Despite broad microbiological testing, only SARS-CoV2 was detected in PCR nasal swab. Therefore, acute hemorrhagic necrotizing encephalitis (AHNE) as a result of COVID-19 was the most probable diagnosis. The outcome was unfavorable - brain death was confirmed, life support was withdrawn.

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Introduction

SARS-CoV-2 infection is benign in most pediatric patients (Bailey et al., 2021; He et al., 2020). However, its clinical course in children is highly variable, with many asymptomatic or monosymptomatic cases with anosmia and hypogeusia. Among hospitalized children, fever, chills and gastrointestinal symptoms prevail, whereas cough and respiratory signs are less common (Kim L. 2020). It has been established that the SARS-CoV-2 virus has neuroinvasive properties (Iadecola et al.,

2020; Severo Bem Junior et al., n.d.). Neurologic complications such as malaise, headache and anosmia are common in all age groups, but more severe: dizziness, altered mental status, ischemic strokes, encephalopathy, and encephalitis have also been reported (Severo Bem Junior et al., 2020 Aug). Children with neurological symptoms associated with COVID-19 have been shown to have changes on MR imaging (Abdel-Mannan et al., 2020), but the exact mechanisms of the SARS-CoV-2 neurotropism have not yet been fully elucidated. Here we present a unique case of fatal, fulminant acute hemorrhagic encephalitis in a SARS-CoV-2 infected infant.

Case description

A 2-month-old, term-born, previously healthy boy was admitted to the tertiary university hospital with a history of cough, sneezing, loss of appetite and fever for two days. Both parents were SARS-CoV-2 positive. The patient's PCR nasal swabs also were positive.

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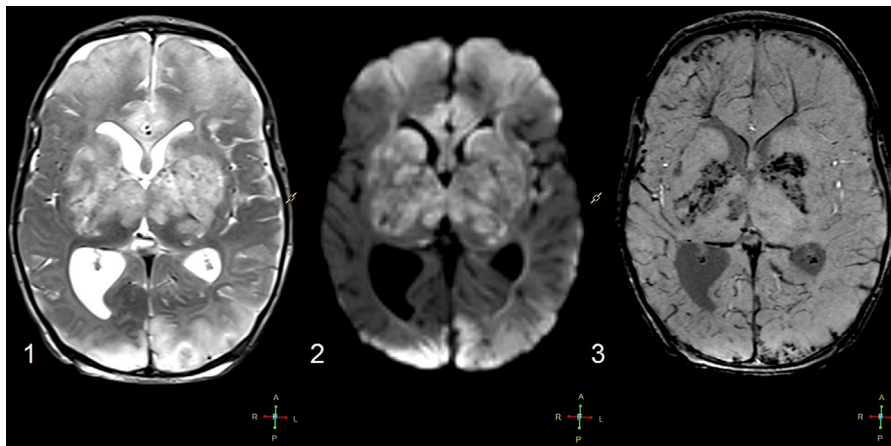


Figure 1. Axial T2W MRI Image - hyperintensity in basal ganglia, thalami, frontal and occipital gray and white matter.

On admission his vital signs were normal, although dehydration was noted.

He was irritable, then apathetic. Nystagmus was observed, neonatal reflexes were normal. His laboratory tests on admission showed leucopenia $1.65 \times 10^3/\mu\text{L}$ with 42% lymphocytes and 52% neutrophils, low Hb 9.3g/dl and PLT $183 \times 10^3/\mu\text{L}$, CRP 7.4 mg/l, PCT 116.76 ng/ml, D-dimers 0.97 (N <0.5), glucose 149 mg/dl. Intravenous rehydration was started. The attempts of lumbar puncture failed. A few hours after admission, the baby had apnea with consequent cardiac arrest. The child's trachea was intubated, and after successful resuscitation, he was transferred to PICU. As anisocoria appeared, a CT scan was obtained. An area of lower density in the left insula was found, so edema or encephalitis was suggested. On cranial ultrasound, meningitis was suspected. Analgesedation with morphine and midazolam was started, and 3% hypertonic saline was administered. The blood cultures, bacterial PCRs, as well as PCRs for common neurotropic viruses were taken. Lumbar puncture was successfully performed. The CSF was clear with pleocytosis 484 cells/ μl , (34.9% mononuclear and 65.1% polynuclear cells), elevated concentration of lactic acid >12 mmol/l (serum lactic acid was approximately 3 mmol/l), extremely high protein - 660.00 mg/dl (N 20-50), positive Pandy's and Nonne-Apelt tests, low glucose <10mg/dl (blood 102 mg/dl) chlorides 138 mmol/l (115-130). CSF meningoencephalitis PCR panel was negative; it was also tested for viral antibodies, including SARS-CoV-2. Antimicrobial therapy was started with cefotaxime, vancomycin, and acyclovir, as herpes meningoencephalitis was considered. Despite treatment, the child's condition quickly deteriorated.

On the second day, he was unconscious, his pupils were fixed and dilated, corneal, and gag reflexes were absent, with absent respiratory drive and motor response to painful stimuli. Global hypotonia and lack of deep reflexes were observed. His anterior fontanelle was remarkably elevated. The MRI (Fig. 1) revealed diffuse areas of edema associated with numerous symmetrical changes with punctate hemorrhages in basal ganglia, thalami, brainstem, and cerebral gray matter.

Figure 1: Axial T2W MRI Image – bilateral symmetrical hyperintensity in basal ganglia, thalami, frontal and occipital gray and white matter. 2: Axial DWI (B = 1000) at the same level as Fig 1 – bright areas of restricted diffusion. 3: Axial SWI – dark spots of numerous acute hemorrhages (deoxyhemoglobin) Fig 2.

It was suggested that Acute Hemorrhagic Necrotizing Encephalitis (AHNE) or Acute Necrotizing Encephalopathy (ANE) triggered by a viral infection should be considered. As ANE may result from genetic mutations, e.g., the RANBP2I gene and mitochondrial disease, genetic (including WES - Whole Exome Sequencing) and metabolic

testing were performed. All the obtained laboratory results were negative, including bacterial cultures, except for repeated positive PCR swabs for SARS-CoV-2. Immunoglobulin treatment was considered, but due to neurologic sequelae, it was not administered. The later course of the disease was unfavorable. The baby showed signs of brain death. After confirming the diagnosis, ventilatory support was switched off Fig 3.

Discussion

Severe neurologic complications of pediatric COVID-19 are rare. They were more commonly observed in MIS-C/PIMS-TS (Multi-system Inflammatory Syndrome in Children/Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2) than the acute infection phase (Feldstein et al., 2021; Siracusa et al., 2021; Singer et al., 2021). They include cerebrovascular events, encephalopathy, acute disseminated encephalomyelitis, meningoencephalitis, Guillain Barre syndrome, and cranial nerve palsies. (Siracusa et al., 2021; Singer et al., 2021). Several mechanisms for SARS-CoV-2 neuroinvasion have been postulated including transsynaptic transfer across infected neurons, entry via the olfactory nerves, infection of vascular endothelium, or leukocyte migration across the blood-brain barrier (BBB), affected by inflammation and dysregulated immune response. (Zubair et al., 2020). The ability of spike proteins on the viral surface to bind to the angiotensin-converting enzyme 2 receptors (ACE-2) makes it a possible way of entry as they are expressed in the human respiratory system: airway epithelia and lung parenchyma, vascular endothelia and brain- in neurons, astrocytes, and oligodendrocytes. Both direct neuroinvasion/neurotropy and indirect mechanisms may play an important role in COVID neuropathology; evidence although rapidly emerging is still limited. In our patient hemorrhagic changes seen on MRI suggest AHNE (acute hemorrhagic encephalitis). We also considered acute necrotizing encephalopathy (ANE). This is a fatal syndrome with the damage of symmetrical subcortical structures of gray matter, including mostly basal ganglia and thalami, usually triggered by a viral infection or less commonly by metabolic errors in genetically susceptible patients. The disorder is characterized by fulminant encephalopathy, coma, and bilateral symmetrical necrotizing parenchymal changes on neuroimaging. Its pathophysiology is unclear, but the immune mechanism is probably involved. Importantly, it is not considered inflammatory encephalitis as there are no signs of inflammation in the CSF (pleocytosis extremely rare) or the brain (Mizuguchi, 1997). The first infantile ANE case was recently reported in association with a previous COVID infection (Lazarte-Rantes et al., 2021). We

excluded ANE because of signs of neuroinflammation: high pleocytosis and protein in CSF and lack of metabolic or genetic abnormalities in WES linked to mutations in RANBP2. Acute hemorrhagic necrotizing encephalitis (AHNE) is not the same entity as acute necrotizing encephalopathy (ANE), however, they are sometimes used interchangeably in the medical literature. In AHNE the mechanism is probably directly related to acute viral infection, so we postulate that AHNE may be the correct diagnosis in our patient. Up to now, cases of Covid-19 related AHNE have been reported in the adult population but not in children. (Ghosh et al., 2020) It is the first, to our knowledge, pediatric acute phase COVID-19 AHNE case. The uncommon finding compared to previously reported COVID meningoencephalitis cases (Lazarte-Rantes et al., 2021; Siracusa et al., 2021) was relatively high CSF cell count (484 cells/ μ l), yet it was within the typical range for viral meningoencephalitis. Also, Lewis et al. report WBC pleocytosis >100 in 8/409 (2%) patients with COVID-related CNS involvement (Lewis et al., 2021). The exact mechanism of COVID-related neurologic injury is not known. Karnik et al. showed that SARS-CoV-2 could enter the nervous system directly and indirectly (Karnik et al., 2021 Jun 5) leading to direct viral neuronal injury, induced cell death, poor cell-to-cell communication, a secondary hyperinflammatory syndrome, para- or post-infectious inflammatory or immune-mediated disorder (Karnik et al., 2021 Jun 5). Neurological complications may also be a consequence of hypoxia, critical illness, and iatrogenic complications. In our case neurological manifestations with concomitant changes on CT imaging were observed early in the course of the disease. This fact may support the idea that they were directly COVID-19 related. We could not identify the SARS-CoV2 in the CSF, but in the recent systematic review of the literature, its presence in CSF was proven only in 2/59 pediatric cases and in 17/303 (6%) of all COVID-19 patients tested (Lewis et al., 2021). As many bacterial and viral pathogens were excluded, and only SARS-CoV2 tested positive, we assume it must have been the cause of AHNE in our case. The fulminant course of the disease leading to brain death in our patient made treatment futile, but early immunomodulatory treatment with intravenous immunoglobulin, plasma exchange, steroids and possibly also interleukin 6 blockade have been effective in some cases. (Finsterer J, 2021, (Finsterer and Scorza, 2021; Koh et al., 2019)

Conclusions

The vast majority of SARS-CoV-2-related neurologic problems concern the adult population. Pediatric COVID-19 is commonly perceived as benign, with most severe cases concerning children with MIS-C/PIMS-TS. Severe neurologic manifestations in children are sporadic and data are sparse. The presented case with the fatal outcome is the first report to our knowledge of AHNE in a previously healthy, SARS-CoV-2 acutely infected infant.

The authors declare no conflict of interest.

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This case report complies ethical standards as we received the parental consent for publication.

Reference

- Abdel-Mannan O, Eyre M, A Löbel UBamford, Ch Eltze, Hameed B, Ch Hemingway, Hachon Y. Neurologic and Radiographic Findings Associated With COVID-19 Infection in Children. *JAMA Neurol* 2020;77(11):1440–5. doi:10.1001/jamaneurol.2020.2687.
- Bailey LC, Razzaghi H, Burrows EK, Bunnell HT, Camacho PEF, Christakis DA, Eckrich D, Kitzmiller M, Lin SM, Magnusen BC, Newland J, Pajor NM, Ranade D, Rao S, Sofela O, Zahner J, Bruno C, Forrest CB. Assessment of 135 794 Pediatric Patients Tested for Severe Acute Respiratory Syndrome Coronavirus 2 Across the United States. *JAMA Pediatr* 2021;175(2):176–84. doi:10.1001/jamapediatrics.2020.5052. PMID: 33226415.
- Feldstein LR, Tenforde MW, Friedman KG, et al. Characteristics and Outcomes of US Children and Adolescents With Multisystem Inflammatory Syndrome in Children (MIC) Compared With Severe Acute COVID-19. *JAMA* 2021;325(11):1074–87. doi:10.1001/jama.2021.2091.
- Finsterer J, Scorza FA. Infectious and immune-mediated central nervous system disease in 48 COVID-19 patients. *J Clin Neurosci* 2021 Aug; 90:140–3. doi:10.1016/j.jocn.2021.05.065.
- Ghosh R, Dubey S, Finsterer J, Chatterjee S, Ray BK. SARS-CoV-2-associated acute hemorrhagic, necrotizing encephalitis (AHNE) presenting with cognitive impairment in a 44-year-old woman without comorbidities: a case report. *Am J Case Rep* 2020;21 10.12659/AJCR.925641.
- He J, Guo Y, Mao R, Zhang J. Proportion of asymptomatic coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *J Med Virol* 2020 jmv.26326. 10.1002/jmv.26326. doi:10.1002/jmv.26326.
- Iadecola C, Anrather J, Kamel H. Effects of COVID-19 on the Nervous System. *Cell* 2020;183(1):16–27 e1, 2020 10 01.
- Karnik M, Beeraka NM, Uthaiyah CA, Nataraj SM, Bettadapura ADS, Aliev G. Madhupantula SV A Review on SARS-CoV-2-Induced Neuroinflammation, Neurodevelopmental Complications, and Recent Updates on the Vaccine Development. *Mol Neurobiol* 2021 Jun 5:1–29. doi:10.1007/s12035-021-02399-6.
- Kim L. Hospitalization Rates and Characteristics of Children Aged <18 Years Hospitalized with Laboratory-Confirmed COVID-19 - COVID-NET, 14 States, March 1–July 25, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69(32):1081–8 10.15585/mmwr.mm6932e3.
- Koh JC, Murugasu A, Krishnappa J, Thomas T. Favorable Outcomes With Early Interleukin 6 Receptor Blockade in Severe Acute Necrotizing Encephalopathy of Childhood. *Pediatric Neurology* 2019. doi:10.1016/j.pediatrneurol.2019.04.009.
- Lazarte-Rantes C, Guevara-Castañón J, Romero L, Guillén-Pinto D Acute Necrotizing Encephalopathy Associated With SARS-CoV-2 Exposure in a Pediatric Patient. *Cureus* 2021;13(5):e15018. doi:10.7759/cureus.15018.
- Lewis A, Frontera F, Placantonakis DG, Lighter J, Galetta S, Balcer L, Melmed KR. Cerebrospinal fluid in COVID-19: A systematic review of the literature. *J Neurol Sci* 2021;421 Published online 2021 Jan 10. doi:10.1016/j.jns.2021.117316.
- Mizuguchi M. Acute necrotizing encephalopathy of childhood: a novel form of acute encephalopathy prevalent in Japan and Taiwan. *Brain Dev* 1997;19:81–92. doi:10.1016/S0387-7604(96)00063-0.
- Severo Bem Junior L, do Rego Aquino PL, Nunes Rabelo N, do Rego Aquino MA, Veiga Silva AC, Ferreira Valença Mota RC, Rocha Cirne de Azevedo Filho H. SARS-CoV-2 and Nervous System - Neurological Manifestations in Patients With COVID-19: A Systematic Review. *J Neurol Res* Aug 2020;10(4):113–21 10.14740/jnr602.
- Singer TG, Evankovich KD, Fisher K, Demmler-Harrison GJ, Risen RG. Coronavirus Infections in the Nervous System of Children: A Scoping Review Making the Case for Long-Term Neurodevelopmental Surveillance *Pediatr Neurol*. 2021; 117: 47–63. Published online 2021 Jan 29. doi: 10.1016/j.pediatrneurol.2021.01.007
- Siracusa L, Cascio A, Giordano S, Medaglia AA, Restivo GA, Pirrone I, Saia GF, Collura F, Colomba C. Neurological complications in pediatric patients with SARS-CoV-2 infection: a systematic review of the literature. *Ital J Pediatr* 2021;2;47(1):123. doi:10.1186/s13052-021-01066-9.
- Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuro-pathogenesis and Neurologic Manifestations of the Coronaviruses in the Age of Coronavirus Disease 2019 A Review. *JAMA Neurol* 2020;17(8):1018–27. doi:10.1001/jamaneurol.2020.2065.