COVID-19-ASSOCIATED CEREBRAL WHITE MATTER INJURY IN A NEWBORN INFANT WITH AFEBRILE SEIZURE

Harun Yildiz, MD, Erbu Yarci, MD,† Sefika Elmas Bozdemir, MD,‡ Nesrin Ozdinc Kizilay, MD,§ Senay Mengi, MD,§ Naciye Beskardesler, MD,* Gulay Korukluoglu, MD,¶ Andreas Mueller, MD,‖ and Soyhan Bagci, MD‖*

Abstract: Coronavirus disease 2019 (COVID-19) symptoms in newborn infants are incompletely described. We present the first case of neuroradiologic abnormality associated with COVID-19 in a newborn infant with afebrile seizure. This case underlines the possible neurologic involvement of severe acute respiratory syndrome coronavirus 2 in this age group.

Key Words: SARS-CoV-2, COVID-19, newborn, white matter injury, febrile seizure

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From the *Department of Radiology, Dortcelik Children's Hospital; †Department of Neonatology; ‡Department of Pediatric Infectious Diseases; §Department of Pediatrics, Dortcelik Children's Hospital, Bursa; ¶Clinical Microbiology, Virology, National Virology Laboratory, Turkish Public Health Institution, Ankara, Turkey; and ‖Neonatology and Pediatric Intensive Care, Children's Hospital, University of Bonn, Bonn, Germany.

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Address for correspondence: Soyhan Bagci, Neonatology and Pediatric Intensive Care, Children's Hospital, University of Bonn, Sigmund-Freud-Strasse 25, D-53127 Bonn, Germany. E-mail: soyhan.bagci@ukbonn.de.

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may present a wide spectrum of disease states, from asymptomatic infection to a multisystem inflammatory syndrome in all age groups. Initial reports suggested that neonates, infants and young children are more likely to remain asymptomatic or less affected by the disease. Nevertheless, the possibility has been raised that SARS-CoV-2 could invade the brain and cause neurologic disease in children. Recently, several consistent neuroimaging patterns, such as acute disseminated encephalomyelitis-like changes to the brain and restricted diffusion involving the white matter, have been reported as a complication of SARS-CoV-2 infection in children.[1,2] It is known that diffuse white matter abnormality on diffusion-weighted imaging (DWI) can be seen in newborn infants with neonatal seizures in the context of viral infections, such as enterovirus, rotavirus, human parechovirus and astrovirus.[3–6] In this case report, we present a COVID-19-associated bilateral diffusion restriction on DWI involving the white matter in a newborn infant with afebrile seizure.

CASE PRESENTATION

A 4-day-old boy, born full-term by cesarean delivery without complications, was presented to the emergency room. The parents reported atypical movements of the right leg and arm without fever. On admission, he showed normal vital signs/physiologic values for temperature, heart rate, blood pressure, respiratory rate and oxygen saturation.

There were no signs of neurologic deficit or other signs of meningeal irritation. In the emergency department, the atypical movements occurred again. The infant was admitted to the intensive care unit with the diagnosis of afebrile seizure. Initial labs revealed a normal white blood cell count and a normal C-reactive protein. Ampicillin and gentamicin treatment was initiated empirically to cover the possibility of neonatal sepsis. Antibiotic treatment was stopped as the result of blood, stool and urine cultures which were negative. Phenobarbital was administered for the seizures. Cerebrospinal fluid (CSF) presented a normal cell count and protein and glucose content. The first cranial ultrasound (Hitachi HI Vision Preirus) showed a periventricular echogenicity in the periventricular and deep white matter (see Figure, Supplemental Digital Content 1; http://links.lww.com/INF/E360). Therefore, a cranial MRI (1.5-T system, GE Optima) was performed. DWI (b-value = 1000 s/mm^2) revealed symmetrical restricted diffusion in the periventricular white matter, subcortical white matter, corpus callosum, internal capsule, optic radiation and posterior thalami. Reduced apparent diffusion coefficient values were found in these areas of increased DWI signal intensity. Signal changes in the same area of the white matter were not evident on T1- and T2-weighted images. Two days later, both the brain MRI and cranial ultrasound were repeated. It was observed that the radiologic findings became more pronounced (Fig. 1). The radiologic pattern was found to be consistent with neonatal viral encephalopathy. Due to the ongoing pandemic, a nasopharyngeal swab was performed and tested for the SARS-CoV-2 virus via reverse transcriptase-polymerase chain reaction (RT-PCR) and returned positive on days 4 and 11.

The nasopharyngeal swab samples from the patient's mother, grandfather and grandmother were also positive for SARS-CoV-2. CSF culture was negative. To rule out other viral causes, we tested common neurotropic viruses including herpes simplex 1 and 2, enteroviruses (echovirus, coxsackievirus and poliovirus), mumps and varicella-zoster virus in CSF and rotavirus in stool, which all turned out to be negative. SARS-CoV-2 in CSF was also negative. A nasopharyngeal swab sample was inoculated in cell culture (for SARS-CoV-2) which grew positive for SARS-CoV-2.

Although the patient showed no sign of rotavirus infection, antigen testing in stool was performed twice with negative results. On day 15, a nasopharyngeal swab for SARS-CoV-2 PCR was negative. Cranial ultrasound and brain MRI on day 15 revealed that the patient had recovered and no longer exhibited the previous neuroradiologic findings. Throughout his hospitalization, he did not show any notable respiratory symptoms. The patient was discharged on day 16 without any neurologic deficit.

DISCUSSION

Abnormal neuroimaging findings have been previously reported in neonates with viral infections, such as rotavirus, human parechovirus and enterovirus.[5,6] To the best of our knowledge, this is the first case documenting diffuse and symmetric restricted diffusion involving the cerebral white matter, corpus callosum, internal capsule, optic radiation and posterior thalami associated with SARS-CoV-2 in a newborn infant with afebrile seizure.

Since the first reports of atypical pneumonia caused by SARS-CoV-2 in Wuhan in December 2019, a growing number of epidemiologic clinical studies, as well as case series, have reported various COVID-19-associated neurologic manifestations affecting the central and peripheral nervous systems both in children and adults.[2,7] The neuro-radiologic studies in adults with SARS-CoV-2 infection demonstrated a wide range of structural changes in the brain such as acute infarcts, restricted diffusion, intracranial hemorrhage, leukoencephalopathy, global hypoxic injury, meningitis and encephalitis.[8] Similarly, SARS-CoV-2-associated severe CNS injury, although less frequent than in adults, was also previously reported in healthy children. In a large case study, Lindan et al[2] identified different recognizable patterns of the brain, cranial

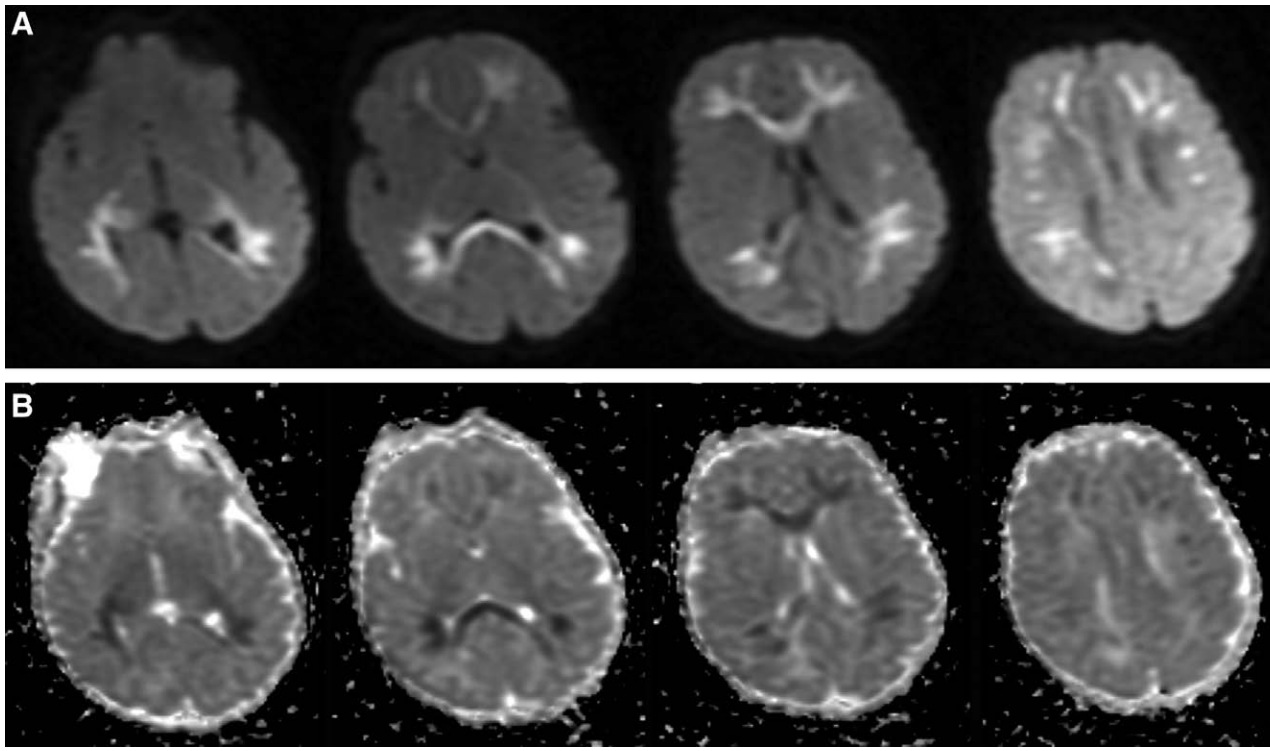

FIGURE 1. Diffusion-weighted imaging (a) and apparent diffusion coefficient map (b) show restricted diffusion in the periventricular white matter, subcortical white matter, corpus callosum, internal capsule, optic radiation and posterior thalami.

nerve and spinal cord involvement, including multifocal T2 bright lesions in brain white matter, vasculitic patterns with ischemic lesions, enhancing neuritis or polyradiculitis, venous thrombosis, splenial lesions of the corpus callosum, longitudinally extensive myelitis and myositis. By contrast, there are only a few case reports on SARS-CoV-2-associated mild neurologic manifestations such as hypotonia, encephalopathy, or encephalitis with seizures in newborn infants.[9] Our patient was also presented with afebrile seizure without any other symptoms, which improved without further neurologic deterioration. The exact pathophysiology of neurologic manifestations of COVID-19 disease in neonates and children remains to be fully elucidated. Such as other respiratory viruses and enterovirus, potential mechanisms of CNS involvement in COVID-19 might be associated with a direct neurotropic or neuroinvasive effect of SARS-CoV-2, a secondary effect of the systemic inflammatory responses triggered by SARS-CoV-2, post-viral triggered the autoimmune response, hypercoagulability and metabolic, or hypoxic injury.[10] Our case had no systemic inflammation or any hypoxic events and SARS-CoV-2 PCR in CSF was negative. Whether restricted diffusion in white matter may result from any immune response remains unclear.

CONCLUSIONS

We reported a novel case of symmetrical restricted diffusion in the brain of a newborn infant with afebrile seizure due to SARS-CoV-2. The clinical spectrum of SARS-CoV-2 in newborn infants and children is still poorly understood and is continually evolving. We think that pediatricians should be aware of the possible neurologic involvement of SARS-CoV-2 in this age group and advise the use of current neuroimaging techniques to broaden knowledge of the neurologic manifestation of SARS-CoV-2, even if patients only show mild neurologic symptoms.

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