CLINICAL/SCIENTIFIC NOTE

Pediatric SARS-CoV-2–Related Diplopia and Mesencephalic Abnormalities

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Abstract

Objective

This case report describes a patient with mesencephalic MRI signal abnormality and diplopia, possibly associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Methods

We describe a boy with binocular diplopia and nystagmus. The pattern of serology positivity and negative direct research of SARS-CoV-2 RNA in our patient allowed us to consider novel coronavirus as the trigger of possible immune-mediated phenomena against the central nervous system.

Results

During hospitalization, blood tests revealed a recent SARS-CoV-2 infection. MRI revealed hyperintensity of the mesencephalic tegmentum and periaqueductal region, consistent with an inflammatory lesion of the midbrain tegmentum. Viral and bacterial molecular screening on cerebrospinal fluid and isoelectrofocusing analysis, anti–myelin oligodendrocyte glycoprotein, anti–aquaporine-4, and anti–N-methyl-d-aspartate antibodies were negative. The patient was treated with steroids and immunoglobulin therapy with complete remission of neurologic symptoms.

Discussion

This report expands the spectrum of pediatric COVID-19–associated neurologic symptoms and highlights a possible isolated neurologic COVID-19–related symptom.

PRACTICAL IMPLICATIONS

Consider idiopathic intracranial hypertension in the differential diagnosis for patients undergoing hormonal therapy presenting with headaches and transient visual obscurations.

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Case

A previously healthy, not vaccinated against SARS-CoV-2, 14-year-old adolescent boy presented with a 2-day history of binocular diplopia, particularly evident for distant vision, without any other neurologic symptom. At admission, a nasopharyngeal swab real-time PCR (RT-PCR) for detection of SARS-CoV-2 was negative. The boy reported persisting binocular diplopia at a distance primary position and lateral gaze bilaterally. Spontaneous nystagmus more right beating than left beating was present, whereas no ocular movement abnormality or ocular alignment defect was noticed. Pupils were isocyclic, isochoric, and normally reactive to light; no photophobia was recorded. Physical examination was otherwise normal. The boy was alert and oriented, denying weakness, headache, vomiting, or dizziness. Fundus examination

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was normal. Brain MRI revealed hyperintensity of the mesencephalic tegmentum and periaqueductal region on fluid attenuated inversion recovery and T2-weighted images, with no diffusion restriction or contrast enhancement (Figure, A.a. and A.b.).

Spinal MRI was normal. Routine blood tests were normal, including inflammatory markers (erythrocyte sedimentation rate, c-reactive protein), thyroid function, and autoantibodies (antinuclear antibodies—ANA, anti-cardiolipin and anti–B2-glycoprotein antibodies). The results of infectious diseases detection tests are reported in Table 1.

CSF analysis showed increased glycorrhachia and pleocytosis; 9 cells were present, mostly mononucleated. No malignant cell was detected (Table 2).

CSF viral and bacterial molecular screening, as well as isoelectric focusing assay, anti–myelin oligodendrocyte glycoprotein, anti–aquaporine-4 and anti–N-methyl-d-aspartate antibodies, were negative. SARS-CoV-2 PCR experimentally tested on CSF was not detected (Table 1).

SARS-CoV-2 serology, using Snibe 2019-Novel Coronavirus (nCoV) Kit Ab, on MAGLUMI 800 (Snibe Co), a fully automated chemiluminescence immunoassay analyzer, showed immunoglobulin M 1.834 AU/mL (positive if ≥1) and immunoglobulin G 31.9 AU/mL (positive if ≥1,1).

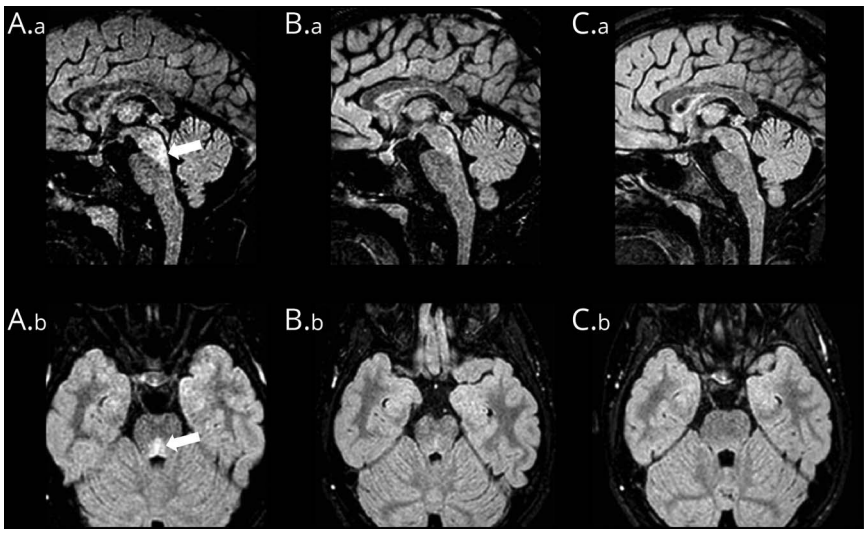
Then, methylprednisolone pulses (30 mg/kg/d) were started and administered for 3 days, with a subsequent shift to oral prednisone (1 mg/kg/d) on the fourth day together with a course of intravenous immunoglobulin (400 mg/kg/d) for 5 days. Gradual improvement of nystagmus and diplopia with complete resolution in a few days was observed. MRI follow-up after 1 month showed a significant reduction of signal changes in the midbrain (Figure, B.a. and B.b.). Steroid therapy was progressively tapered and finally stopped after further 2 months. At the 4-month follow-up, neurologic examination and neuroimaging were normal (Figure, C.a. and C.b.).

Discussion

Neurologic manifestations of SARS-CoV-2 may arise because of the direct invasion, parainfectious, or postinfectious immune mechanisms[1,2] with central nervous system (CNS) inflammatory disorders, which include encephalitis, myelitis, and meningitis, more frequently reported among patients younger than 19 years.[3] In children, neurologic symptoms have been observed in 22% of cases in an American cohort,[4] most of them being transient and with a good outcome. In a UK study,[5] the incidence of these manifestations reached 3.8 cases per 100 hospitalized pediatric patients. In another study, almost half of the pediatric patients were diagnosed with pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2.[6] Among neuroimaging observations, the most common were postinfectious immune-mediated acute disseminated encephalomyelitis-like changes, myelitis, and neural enhancement that could occur in the absence of corresponding neurologic symptoms,[7] whereas splenial lesion and myositis seemed to be more common in patients with MIS-C.

This boy presented with nystagmus and diplopia consistent with a fascicular lesion involving the medial and anterior portions of the midbrain tegmentum and temporally related to SARS-CoV-2 infection. Despite striking imaging findings, neurologic symptoms were mild and promptly resolved with immunosuppressive therapy. The pattern of positive SARS-CoV-2 serology and the negative direct research of

Figure Brain MRI Findings at the Onset and Follow-up



Sagittal (A.a) and axial (A.b) fluid attenuated inversion recovery (FLAIR) images at admission showing hyperintensity of the midbrain tegmentum (arrows) consistent with an inflammatory lesion. Sagittal (B.a) and axial (B.b) FLAIR images after 1 month showed a reduction of midbrain lesions. Sagittal (C.a) and axial (C.b) FLAIR images acquired after 4 months showed complete resolution of signal changes.

Table 1 Infectious Diseases' Detection Tests

Pathogen	IgM	IgG	Blood PCR	Throat swab PCR	CSF-PCR
SARS-CoV-2	Positive	Positive	—	Negative	Negative
Measles	Negative	Positive	—	—	—
Rubella	Negative	Positive	—	—	—
VZV	Negative	Positive	—	—	Negative
HSV1	Negative	Positive	—	—	Negative
HSV2	Negative	Negative	—	—	Negative
CMV	Negative	Positive	Negative	—	Negative
HHV6	—	—	Negative	—	Negative
HHV7	—	—	—	—	Negative
EBV	Negative	Positive	Low positive	—	Negative
Adenovirus	—	—	—	Negative	Negative
Influenza virus A/B	—	—	—	Negative	—
Human metapneumovirus	—	—	—	Negative	—
Parainfluenza virus 1/2/3/4	—	—	—	Negative	—
Rhinovirus	—	—	—	Negative	—
RSV	—	—	—	Negative	—
Parechovirus	—	—	—	—	Negative
Enterovirus	—	—	—	—	Negative
Mumps virus	—	—	—	—	Negative
Parvovirus B19	—	—	—	—	Negative
Bordetella pertussis	—	—	—	Negative	—
Chlamydia pneumoniae	—	—	—	Negative	—
Haemophilus influenzae	—	—	—	Negative	—
Legionella pneumophila	—	—	—	Negative	—
Mycoplasma pneumoniae	—	—	Negative	Negative	Negative
Streptococcus pneumoniae	—	—	—	Negative	—
Group A β-Hemolytic streptococcus	—	—	—	Negative	—
Toxoplasma gondii	Negative	Negative	—	—	—
Borrelia burgdorferi	Negative	Negative	—	—	—

Abbreviations: CMV = cytomegalovirus; EBV = Epstein-Barr virus; HSV = herpes virus; IgG = immunoglobulin G; IgM = immunoglobulin M; SARS-CoV-2 = severe acute respiratory syndrome coronavirus; VZV = varicella zoster virus.

SARS-CoV-2 RNA suggested that coronavirus was the trigger of possible immune-mediated phenomena against CNS, as reported for SARS-CoV-2 and other coronaviruses.[1] This hypothesis was further supported by the exclusion of other common etiologies and the favorable response to immunomodulation. This report expands the spectrum of pediatric COVID-19–associated neurologic manifestations and suggests a COVID-19–related inflammatory lesion of the midbrain tegmentum.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been found to be related to neurologic manifestations, possibly because of a direct invasion, parainfectious, or postinfectious immune mechanisms.[1,2] Although less frequently compared with adults, neurologic manifestations have been reported[3] in children also, ranging from cerebrovascular disease to peripheral nervous system involvement. Neurologic symptoms may also occur in patients with multisystem inflammatory syndrome (MIS-C).

Table 2 Cerebrospinal Fluid Investigations

CSF analysis	Results	Range
Pressure	Not available	Not available
Color	Clear	0–0
Protein	30.3	20–40
Glucose mg/dL	67	40–60 mg/dL
Cells	9	0
Type of cells	Mononucleated	
Isolectrofocusing	Negative	
Anti-MOG antibodies	Absent	
Anti–aquaporine-4 antibodies	Absent	
Anti-NMDA antibodies	Absent	
Malignant cells	Absent	

Abbreviations: MOG = myelin oligodendrocyte glycoprotein; NMDA = N-methyl-d-aspartate.

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