

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

Sara Signa, MD\*, Noemi Brolatti, MD\*, Chiara Trincianti, MD, Domenico Tortora, MD, Carolina Saffioti, MD, Eddi Di Marco, MD, Maura Acquila, PhD, Elisabetta Amadori, MD, Chiara Fiorillo, MD, PhD, Erica Ricci, MD, Pasquale Striano, MD, PhD, Elio Castagnola, MD, PhD, and Maria Stella Vari, MD, PhD

## Correspondence

Dr. Vari  
mariastellavari@gaslini.org

*Neurology: Clinical Practice* October 2022 vol. 12 no. 5 e124–e128 doi:10.1212/CPJ.000000000200076

## 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–aquaporin-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.

## MORE ONLINE

### COVID-19 Resources

For the latest articles, invited commentaries, and blogs from physicians around the world

[NPub.org/COVID19](https://www.npub.org/COVID19)

## 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

\*These authors contributed equally to this work as first authors.

UOC Malattie Infettive (S.S., C.S., E.R., E.C.), IRCCS Istituto Giannina Gaslini; COVID Hospital (S.S., E.R.), IRCCS Istituto Giannina Gaslini; UOC Neurologia Pediatrica e Malattie Muscolari (N.B., E.A., C.F., P.S., M.S.V.), IRCCS Istituto Giannina Gaslini; Dipartimento di Neuroscienze (C.T., C.F., P.S.), Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili (DINOIMI), Università di Genova; UOC Neuroradiologia (D.T.), IRCCS Istituto Giannina Gaslini; and UOC Laboratorio Analisi (E.D.M., M.A.), IRCCS Istituto Giannina Gaslini, Genoa, Italy.

Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at [Neurology.org/cp](https://www.neurology.org/cp).

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-aquaporin-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  $\geq 1$ ) and immunoglobulin G 31.9 AU/mL (positive if  $\geq 1,1$ ).

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

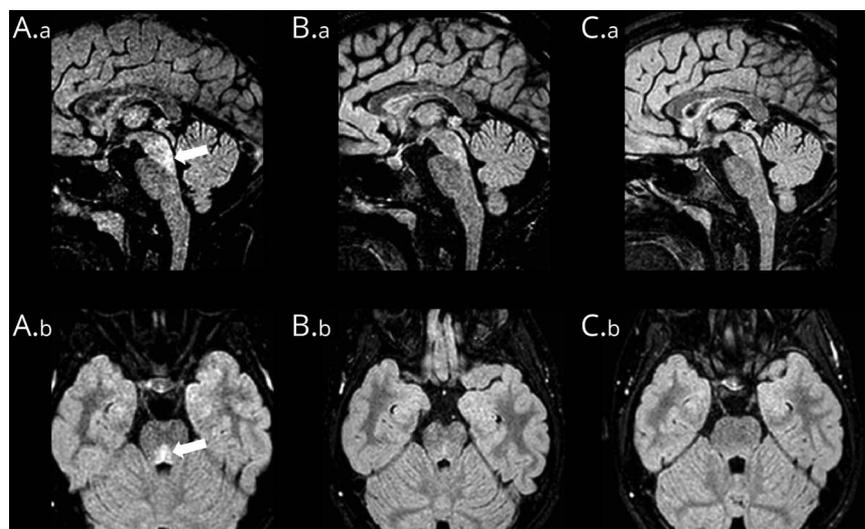
month showed a significant reduction of signal changes in the midbrain (Figure, B.a. and B.b.). Steroid therapy was progressively tapered and finally stopped after further 2 months. At the 4-month follow-up, neurologic examination and neuroimaging were normal (Figure, C.a. and C.b.).

## Discussion

Neurologic manifestations of SARS-CoV-2 may arise because of the direct invasion, parainfectious, or postinfectious immune mechanisms<sup>1,2</sup> with central nervous system (CNS) inflammatory disorders, which include encephalitis, myelitis, and meningitis, more frequently reported among patients younger than 19 years.<sup>3</sup> In children, neurologic symptoms have been observed in 22% of cases in an American cohort,<sup>4</sup> most of them being transient and with a good outcome. In a UK study,<sup>5</sup> 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.<sup>6</sup> 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,<sup>7</sup> whereas splenic 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
<b>SARS-CoV-2</b>	Positive	Positive	—	Negative	Negative
<b>Measles</b>	Negative	Positive	—	—	—
<b>Rubella</b>	Negative	Positive	—	—	—
<b>VZV</b>	Negative	Positive	—	—	Negative
<b>HSV1</b>	Negative	Positive	—	—	Negative
<b>HSV2</b>	Negative	Negative	—	—	Negative
<b>CMV</b>	Negative	Positive	Negative	—	Negative
<b>HHV6</b>	—	—	Negative	—	Negative
<b>HHV7</b>	—	—	—	—	Negative
<b>EBV</b>	Negative	Positive	Low positive	—	Negative
<b>Adenovirus</b>	—	—	—	Negative	Negative
<b>Influenza virus A/B</b>	—	—	—	Negative	—
<b>Human metapneumovirus</b>	—	—	—	Negative	—
<b>Parainfluenza virus 1/2/3/4</b>	—	—	—	Negative	—
<b>Rhinovirus</b>	—	—	—	Negative	—
<b>RSV</b>	—	—	—	Negative	—
<b>Parechovirus</b>	—	—	—	—	Negative
<b>Enterovirus</b>	—	—	—	—	Negative
<b>Mumps virus</b>	—	—	—	—	Negative
<b>Parvovirus B19</b>	—	—	—	—	Negative
<b>Bordetella pertussis</b>	—	—	—	Negative	—
<b>Chlamydia pneumoniae</b>	—	—	—	Negative	—
<b>Haemophilus influenzae</b>	—	—	—	Negative	—
<b>Legionella pneumophila</b>	—	—	—	Negative	—
<b>Mycoplasma pneumoniae</b>	—	—	Negative	Negative	Negative
<b>Streptococcus pneumoniae</b>	—	—	—	Negative	—
<b>Group A <math>\beta</math>-Hemolytic streptococcus</b>	—	—	—	Negative	—
<b>Toxoplasma gondii</b>	Negative	Negative	—	—	—
<b>Borrelia burgdorferi</b>	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.<sup>1</sup> 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 mid-brain 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.<sup>1,2</sup> Although less frequently compared with adults, neurologic manifestations have been reported<sup>3</sup> 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
<b>Pressure</b>	Not available	Not available
<b>Color</b>	Clear	0–0
<b>Protein</b>	30.3	20–40
<b>Glucose mg/dL</b>	67	40–60 mg/dL
<b>Cells</b>	9	0
<b>Type of cells</b>	Mononucleated	
<b>Isoelectrofocusing</b>	Negative	
<b>Anti-MOG antibodies</b>	Absent	
<b>Anti-aquaporin-4 antibodies</b>	Absent	
<b>Anti-NMDA antibodies</b>	Absent	
<b>Malignant cells</b>	Absent	

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

## Study Funding

The authors report no targeted funding.

## Disclosure

The authors report no disclosures relevant to the manuscript. Full disclosure form information provided by the authors is available with the full text of this article at [Neurology.org/cp](https://www.neurology.org/cp).

## Publication History

Received by *Neurology: Clinical Practice* April 14, 2022. Accepted in final form July 28, 2022. Submitted and externally peer reviewed. The handling editor was Editor Luca Bartolini, MD.

## Appendix Authors

Name	Location	Contribution
<b>Sara Signa, MD</b>	UOC Malattie Infettive, IRCCS Istituto Giannina Gaslini, Genoa, Italy; COVID Hospital, IRCCS Istituto Giannina Gaslini, Genoa, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
<b>Noemi Brolatti, MD</b>	UOC Neurologia Pediatrica e Malattie Muscolari, IRCCS Istituto Giannina Gaslini, Genoa, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design
<b>Chiara Trincianti, MD</b>	Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili (DINOEMI), Università di Genova, Genoa, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data

## Appendix (continued)

Name	Location	Contribution
<b>Domenico Tortora, MD</b>	UOC Neuroradiologia, IRCCS Istituto Giannina Gaslini, Genoa, Italy	Major role in the acquisition of data; analysis or interpretation of data
<b>Carolina Saffioti, MD</b>	UOC Malattie Infettive, IRCCS Istituto Giannina Gaslini, Genoa, Italy	Analysis or interpretation of data
<b>Eddi Di Marco, MD</b>	UOC Laboratorio Analisi, IRCCS Istituto Giannina Gaslini, Genoa, Italy	Major role in the acquisition of data; analysis or interpretation of data
<b>Maura Aquila, PhD</b>	UOC Laboratorio Analisi, IRCCS Istituto Giannina Gaslini, Genoa, Italy	Analysis or interpretation of data
<b>Elisabetta Amadori, MD</b>	UOC Neurologia Pediatrica e Malattie Muscolari, IRCCS Istituto Giannina Gaslini, Genoa, Italy	Analysis or interpretation of data
<b>Chiara Fiorillo, MD, PhD</b>	UOC Neurologia Pediatrica e Malattie Muscolari, IRCCS Istituto Giannina Gaslini, Genoa, Italy; Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili (DINOEMI), Università di Genova, Genoa, Italy	Analysis or interpretation of data
<b>Erica Ricci, MD</b>	UOC Malattie Infettive, IRCCS Istituto Giannina Gaslini, Genoa, Italy; COVID Hospital, IRCCS Istituto Giannina Gaslini, Genoa, Italy	Major role in the acquisition of data
<b>Pasquale Striano, MD, PhD</b>	UOC Neurologia Pediatrica e Malattie Muscolari, IRCCS Istituto Giannina Gaslini, Genoa, Italy; Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili (DINOEMI), Università di Genova, Genoa, Italy	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design
<b>Elio Castagnola, MD, PhD</b>	UOC Malattie Infettive, IRCCS Istituto Giannina Gaslini, Genoa, Italy	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design
<b>Maria Stella Vari, MD, PhD</b>	UOC Neurologia Pediatrica e Malattie Muscolari, IRCCS Istituto Giannina Gaslini, Genoa, Italy	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design

## References

1. Ellul MA, Benjamin L, Singh B, et al. Neurological associations of COVID-19. *Lancet Neurol*. 2020;19(9):767-783.
2. Paterson RW, Brown RL, Benjamin L, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain*. 2020;143(10):3104-3120.
3. Sullivan BN, Fischer T. Age-associated neurological complications of COVID-19: a systematic review and meta-analysis. *Front Aging Neurosci*. 2021;13:653694.

4. Larovere KL, Riggs BJ, Poussaint TY, et al. Neurologic involvement in children and adolescents hospitalized in the United States for COVID-19 or multisystem inflammatory syndrome. *JAMA Neurol.* 2021;78(5):536-547.
5. Ray STJ, Abdel-Mannan O, Sa M, et al. Neurological manifestations of SARS-CoV-2 infection in hospitalised children and adolescents in the UK: a prospective national cohort study. *Lancet Child Adolesc Heal.* 2021;5(9):631-641.
6. O'Loughlin L, Alvarez Toledo N, Budrie L, Waechter R, Rayner J. A systematic review of severe neurological manifestations in pediatric patients with coexisting SARS-CoV-2 infection. *Neurol Int.* 2021;13(3):410-427.
7. Lindan CE, Mankad K, Ram D, et al. Neuroimaging manifestations in children with SARS-CoV-2 infection: a multinational, multicentre collaborative study. *Lancet Child Adolesc Heal.* 2021;5(3):167-177.

# Neurology® Clinical Practice

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

Sara Signa, Noemi Brolatti, Chiara Trincianti, et al.

*Neurol Clin Pract* 2022;12:e124-e128 Published Online before print August 31, 2022

DOI 10.1212/CPJ.0000000000200076

**This information is current as of August 31, 2022**

<b>Updated Information &amp; Services</b>	including high resolution figures, can be found at: <a href="http://cp.neurology.org/content/12/5/e124.full.html">http://cp.neurology.org/content/12/5/e124.full.html</a>
<b>References</b>	This article cites 7 articles, 0 of which you can access for free at: <a href="http://cp.neurology.org/content/12/5/e124.full.html##ref-list-1">http://cp.neurology.org/content/12/5/e124.full.html##ref-list-1</a>
<b>Permissions &amp; Licensing</b>	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://cp.neurology.org/misc/about.xhtml#permissions">http://cp.neurology.org/misc/about.xhtml#permissions</a>
<b>Reprints</b>	Information about ordering reprints can be found online: <a href="http://cp.neurology.org/misc/addir.xhtml#reprintsus">http://cp.neurology.org/misc/addir.xhtml#reprintsus</a>

*Neurol Clin Pract* is an official journal of the American Academy of Neurology. Published continuously since 2011, it is now a bimonthly with 6 issues per year. Copyright © 2022 American Academy of Neurology. All rights reserved. Print ISSN: 2163-0402. Online ISSN: 2163-0933.

