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LETTER TO THE EDITOR

Cranial polyneuropathy as the first manifestation of a severe COVID-19 in a child

To the Editor:

Coronavirus disease 2019 (COVID-19) has led to a pandemic in early 2020. The typical clinical syndrome is respiratory distress, leading ultimately to severe viral pneumonia.[1] In children, symptoms are reported to be milder compared to adults.[2,3] In severely ill pediatric cases, the main symptoms are fever, tachypnea, productive cough, expectoration, nausea/vomiting, diarrhea and asthenia.[4] Various neurological symptoms have also been reported in adults and children, consistent with the neurological tropism reported for certain members of the coronavirus family.[5,6]

We herein report a novel neurological presentation associated with COVID-19 in a 6-year-old patient. The patient presented with sickle cell anemia complicated by cerebral vasculopathy. She underwent hematopoietic stem cell transplantation (HSCT) from a matched-related donor following myeloablative conditioning (busulfan, cyclophosphamide, and anti-T-lymphocyte globulin). Graft-versus-host disease prophylaxis included cyclosporin and methotrexate. A historical timeline is presented in the Supporting Information figure.

Various infectious complications occurred around the date of transplant (day 0):

- Asymptomatic Epstein-Barr virus (EBV) replication starting from day −14, treated with one rituximab infusion.
- Severe mucositis, aggravated by concomitant herpes simplex virus-1 (HSV-1) reactivation (oral and pelvic localizations), early after conditioning, treated with high dose acyclovir.
- Forty-eight-hour long febrile neutropenia during HSV-1 reactivation, without other microbial documentation, treated with broad-spectrum antibiotics (piperacillin-tazobactam from day 0 to 20, vancomycine from day 2 to 15, ciprofloxacin from day 2 to 10).

At day 20, neutrophil engraftment was acheived, mucositis/HSV lesions healed, antibiotics were stopped, and acyclovir was switched to prophylactic doses.

At day 21, the patient presented with bilateral facial palsy, left trigeminal hypoesthesia, and voice alteration, followed 24 h later by swallowing impairment. The full clinical picture was limited to impairment of cranial nerves V, VII, and IX, with no evidence for limb sensory-motor deficit or areflexia.

Cerebral magnetic resonance imagery performed a few hours after onset of symptoms demonstrated T2-FLAIR hypersignals of the intracranial and meatal segments of the two facial nerves as well as the left hypoglossal nerve, with T1 gadolinium enhancement. There was no sign of hemorrhage, ischemia, or PRES syndrome (see Figure 1). Cerebrospinal fluid (CSF) examination, performed 18 h after onset of symptoms , found normal protein level 25 mg/dL (reference range 15-60 mg/dL), glucose 66 mg/dL, white blood cells 1/μL (reference range 0-5/μL). CSF Gram stain and culture were negative, as well as polymerase chain reaction (PCR) targeting HSV, varicella, enterovirus, EBV, human Herpesvirus (HHV) 6, HHV8, adenovirus, mycoplasma, Cryptococcus, and toxoplasma nucleic acids. A second CSF examination performed 48 h after onset of symptoms was also found unconclusive. C-reactive protein (CRP) never exceeded 10 mg/L during this neurological phase.

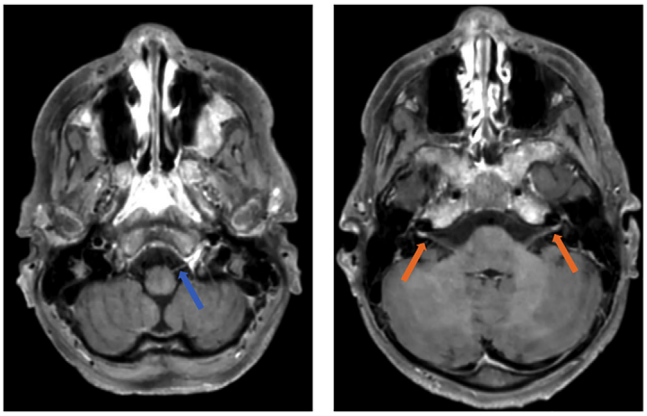

FIGURE 1 Axial slices of brain magnetic resonance imagery (MRI) (T1w TSE SPIR images). Cranial nerves enhancement upon gadolinium injection is shown: blue arrow pointing the hypoglossal nerve (left panel) and the two red arrows pointing the two facial nerves (right panel)

Intravenous immunoglobulin (1 g/kg) was infused at days 22 and 23 without improvement. Fever and respiratory symptoms appeared secondarily at day 25, 4 days after the onset of neurological symptoms, with productive cough and fever up to 40°C. CRP remained normal. Chest computerized tomography scan showed images characteristic of pulmonary COVID-19. SARS-CoV-2 reverse transcriptase-PCR assay was positive in nasopharyngeal swab and blood, not in CSF. No replication of EBV, HSV, CMV, or adenovirus could be documented. Acute respiratory distress syndrome led to transfer to an intensive care unit at day 29.

The patient required protective mechanical ventilation for 17 days, received treatment by remdesevir (10 days), tocilizumab (two infusions), and a second course of intravenous immunoglobulin at

days 51 and 52. Facial diplegia was persistent beyond mechanical ventilation. Significant clinical improvement started around day 60.

This case is the first description of a cranial polyneuropathy in a child infected with SARS-CoV-2. Neurological symptoms during the course of COVID19 have been reported in more than 35% cases in a recent study of 214 adult patients,[7] with three possible presentations: (a) central manifestations including dizziness, headache, ataxia, and seizure, (b) peripheral symptoms, like taste, smell, or vision impairment, and neuropathic pain, and (c) skeletal muscular failure. Of the 214 patients, only five presented isolated peripheral nerve damage. Six cases of Guillain-Barré syndromes (GBS) occurring 5-10 days after onset of COVID-19 were recently described in adults, four of them presenting with facial paresia or diplegia.[8] One case of a 61-year-old was reported with complete GBS preceding typical COVID-19 symptoms.[9] In children, a recent study described neurological signs with COVID-19 affecting both central and peripheral nervous systems, without reported forms of cranial polyneuropathy.[10] Our observation is reminiscent of these reports, with some novel features: only craniofacial nerves were impaired, symptoms were presenting manifestations, and CSF never displayed a classic profile of GBS. The context of a heavily immunocompromised patient and the pre-existing cerebral vasculopathy may explain these discrepancies, even though cranial polyneuropathy is not reported as a classic side effect of HSCT conditioning or sickle cell anemia. Viral co-infections (EBV and HSV) may also have interplayed with SARS-CoV-2 in the pathogenesis of this polyneuropathy, although no concomitant replication could be documented.

In conclusion, peripheral nerve involvement is rarely described in COVID-19. The present report confirms that children can display peripheral neuropathy, reminiscent of GBS or Miller-Fischer syndromes, with concomitant SARS-CoV-2 infection. Neurological symptoms may precede or follow detection of virus replication, as described in a few adult cases. Cranial nerve involvement might predict an aggressive course of the disease, especially in immunocompromised patients.

CONFLICT OF INTEREST

The other authors declare that there is no conflict of interest.

Aphaia Roussel[1]
David Germanaud[2]
Yassine Bouchoucha[1]
Naïm Ouldali[3]
Meryl Vedrenne-Cloquet[4]
Martin Castelle[5]
André Baruchel[1,6]

[1] *Pediatric Hematology-Immunology Department, University Hospital Robert-Debre (APHP), Paris, France*
[2] *Pediatric Neurology Department, University Hospital Robert-Debre (APHP), Paris, France*
[3] *General Pediatric Department and Infectious Diseases, University Hospital Robert-Debre (APHP), Paris, France*
[4] *Pediatric Intensive Care Unit, University Hospital Necker-Enfants-Malades (APHP), Paris, France*
[5] *Hematology-Immunology Department, University Hospital Necker Enfants Malades (APHP), Paris, France*
[6] *University of Paris, UFR Paris-Nord, Paris, France*

Correspondence
Aphaia Roussel, Pediatric Hematology-Immunology Department, University Hospital Robert Debré (APHP), 48 Bd Sérurier, Cedex 19, 75935 Paris, France.
Email: aphaia.roussel@aphp.fr

ORCID

Aphaia Roussel https://orcid.org/0000-0002-9943-2860
David Germanaud https://orcid.org/0000-0001-5055-4624
Yassine Bouchoucha https://orcid.org/0000-0002-9965-6573
Naïm Ouldali https://orcid.org/0000-0003-4996-9640
Meryl Vedrenne-Cloquet https://orcid.org/0000-0002-7177-2273
Martin Castelle https://orcid.org/0000-0001-9087-4411
André Baruchel https://orcid.org/0000-0001-7445-1005

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.