Neurological complications in pediatric patients with SARS-CoV-2 infection: a systematic review of the literature

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Abstract

Objectives: To describe clinical characteristics, laboratory tests, radiological data and outcome of pediatric cases with SARS-CoV-2 infection complicated by neurological involvement.

Study design: A computerized search was conducted using PubMed. An article was considered eligible if it reported data on pediatric patient(s) with neurological involvement related to SARS-CoV-2 infection. We also described a case of an acute disseminated encephalomyelitis (ADEM) in a 5-year-old girl with SARS-CoV-2 infection: this case was also included in the systematic review.

Results: Forty-four articles reporting 59 cases of neurological manifestations in pediatric patients were included in our review. Most (32/59) cases occurred in the course of a multisystem inflammatory syndrome in children (MIS-C). Neurological disorders secondary to cerebrovascular involvement were reported in 10 cases: 4 children with an ischemic stroke, 3 with intracerebral hemorrhage, 1 with a cerebral sinuses venous thrombosis, 1 with a subarachnoid hemorrhage, 1 with multiple diffuse microhemorrhages. Reversible splenial lesions were recognized in 9 cases, benign intracranial hypertension in 4 patients, meningoencephalitis in 4 cases, autoimmune encephalitis in 1 girl, cranial nerves impairment in 2 patients and transverse myelitis in 1 case. Five cases had Guillain-Barré syndrome (GBS) and two, including ours, had ADEM. Radiological investigations were performed in almost all cases (45/60): the most recurrent radiological finding was a signal change in the splenium of the corpus callosum. The presence of SARS-CoV-2 viral nucleic acid in the cerebrospinal fluid was proved only in 2 cases. The outcome was favorable in almost all, except in 5 cases.

Conclusions: Our research highlights the large range of neurological manifestations and their presumed pathogenic pathways associated with SARS-CoV-2 infection in children. Nervous system involvement could be isolated, developing during COVID-19 or after its recovery, or arise in the context of a MIS-C. The most reported neurological manifestations are cerebrovascular accidents, reversible splenial lesions, GBS, benign intracranial hypertension, meningoencephalitis; ADEM is also a possible complication, as we observed in our patient. Further studies are required to investigate all the neurological complications of SARS-CoV-2 infection and their underlying pathogenic mechanism.
Introduction
At the end of December 2019, many cases of atypical pneumonia of unknown origin were described in the city of Wuhan, China. In January 2020 a novel coronavirus, later called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as the responsible of a new disease called coronavirus disease 2019 (COVID-19), declared pandemic by the World Health Organization (WHO) in March 2020.

As regards pediatric COVID-19 cases, unlike the clinical presentation of adult patients, a systematic review showed that the most commonly reported symptoms are fever, cough, pharyngitis and rhinorrhea; other frequent symptoms are headache, myalgia, rash, conjunctivitis, syncopal episodes and gastrointestinal manifestations such as vomiting, diarrhea, abdominal pain and difficulty in feeding [1–3].

In later April 2020, a novel syndrome in children and adolescents, termed multisystem inflammatory syndrome in children (MIS-C), related to SARS-CoV-2 infection was first described: initial reports surfaced in the United Kingdom and Italy [4, 5]. This condition, similar to Kawasaki disease and toxic shock syndrome, is characterized by persistent fever, a multisystem (≥ 2) organ involvement, elevation of inflammatory markers, link to SARS-CoV-2 (verified by polymerase chain reaction, serology or COVID-19 contact) and the exclusion of alternative diagnosis [6].

Regarding neurological involvement in COVID-19, severe neurological manifestations (encephalopathy, meningoencephalitis, stroke, seizure, Guillain-Barré syndrome, acute disseminated encephalomyelitis) have been reported mainly in adults [7, 8], while a few cases have been described in children. Two mechanisms were proposed to explain how SARS-CoV-2 may induce neurological damage: direct viral infection of nervous system through ACE2 receptors and inflammatory injury mediated by cytokines release [9]; in the latter case, neurological manifestations may be part of a MIS-C [10].

We describe here a case of acute disseminate encephalomyelitis (ADEM) related to SARS-CoV-2 infection in a pediatric patient and, with the aim of focus our attention on neurological manifestations of pediatric patients with SARS-CoV-2 infection, we performed a systematic review of the literature contextualizing our new case among all the cases retrieved in our search.

Case report
A 5-year-old girl presented with a 3-day history of fever, neck swelling and erythematous skin rash. In the previous days an antigen rapid swab test for SARS-CoV-2 was performed with a negative result and she was treated with antibiotic and anti-inflammatory therapy.

On physical examination, the child was febrile (body temperature 39°C); the skin was characterized by a maculopapular and not itchy rash on the face, neck, trunk and extremities, with palmpoplantar involvement. A right laterocervical and painful lymphadenopathy, eyelid, hand and foot edema, red and fissuring lips and injected pharynx were present. The abdomen was painful and she complained of diarrhea. Cardiovascular, respiratory and neurological examinations were normal. Vital signs showed oxygen saturation 99%, heart rate 104 bpm, blood pressure 104/60 mmHg.

Blood tests revealed microcytic and hypochromic anemia, leukocytosis with lymphopenia, C-reactive protein (CRP) 20.55 mg/dL (normal value < 0.6), procalcitonin 4.5 ng/mL (normal value < 0.5), fibrinogen 649 mg/dL (normal range 200–400), D-dimer 2653 ng/mL (normal range < 500), ferritin 603 ng/mL (normal range 11–306), hyponatremia and hypoalbuminemia. Chest radiograph and abdomen ultrasound showed no abnormalities, while neck ultrasound revealed different oval-shape nodes with maximum diameter of 1.6 cm. Echocardiogram and electrocardiogram, performed to rule out Kawasaki disease, did not show pathological findings.

Two days after hospital admission, the girl became irritable; neck stiffness, muscular weakness and right Babinski sign were also found. In suspicion of viral encephalitis, she was treated with intravenous (IV) acyclovir 10 mg/kg three times a day. Brain MRI showed two lesions, one in the splenium of the corpus callosum and the other in the subcortical white matter of the left parietal lobe, that exhibit restricted diffusion without contrast enhancement (Figs. 1, 2 and 3).
Electroencephalogram (EEG) disclosed a generalized slowing of background activity. Cerebrospinal fluid (CSF) was tested: samples were acellular, with normal levels of proteins and glucose and no evidence of viral or bacterial infection (Escherichia coli, Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae, Streptococcus agalactiae, Neisseria meningitidis, Lysteria monocytogenes, Adenovirus, Herpes simplex virus 1–2, Varicella Zoster virus, Citomegalovirus, Epstein-Barr virus, Enterovirus) on real-time polymerase chain reaction (RT-PCR). Tests for oligoclonal bands in CSF and serum neuronal autoantibodies (anti-NMDA, anti-VGCK, anti-AMPA) had negative results.

The molecular nasopharyngeal swab test for SARS-CoV-2 detected initially low viral load, while the second specimen was negative. A COVID-19 serology test, performed a week after the hospital admission, revealed IgG positive and IgM within grey-zone limits.

According to multi-organ involvement, neuroradiological findings, laboratory exams with elevated inflammatory parameters, temporal relationship with SARS-CoV-2 infection and exclusion of other causes, a diagnosis of ADEM in a patient with MIS-C was made; she started methylprednisolone 1 mg/kg/day IV and immunoglobulin 0.4 g/kg/day for 5 days IV, with a progressive resolution of the systemic hyperinflammatory state and improvement of neurological symptoms. Brain MRI, performed two weeks after the first one, demonstrated no abnormalities.

**Literature search**

A computerized search was performed using PubMed, combining the terms (neurolog* OR CNS OR nervous OR encephal*) AND (COVID OR SARS-CoV-2 OR coronavirus) AND (baby OR child* OR pediatr*) with English language filter, to identify studies on neurological manifestations in children with SARS-CoV-2 infection, published until December 31, 2020. Furthermore, references within the included articles were scanned for other relevant papers. The following data were evaluated for each case: age, sex, comorbidities, clinical features, radiological and other neurological investigations, laboratory test for confirmation of SARS-CoV-2 infection and outcome; we also assessed if neurological complication occurred in the course of a MIS-C. We excluded articles that reported only aggregate data and that revealed the presence of coinfection with other microbes. The selected articles were reviewed by two independent authors and judged on their relevant contribution to the subject of the study. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines were followed [11].

**Results**

After an extensive search in PubMed, 1000 articles were identified, along with 20 additional records detected through hand-searching (Fig. 4). 1020 records were screened; 963 were excluded after title and abstract screening and 13 were excluded after full-text review. We selected 44 studies for inclusion [5, 12–54], reporting 59 cases of neurological manifestations in pediatric patients with SARS-CoV-2 infection. Most of the articles were single case reports, 10 were case series. Clinical
and radiological features, diagnosis and outcome of 60 patients (including our new case) are systematically reported in Table 1.

There were 35 boys and 25 girls. The median age was 9 years. All children had no comorbidity, except 7 patients with no reported data and 6 patients with underlying conditions: a 3-year-old male with allergy to cow milk [24], a 6-year-old girl with sickle cell disease, complicated by cerebral vasculopathy, who underwent hematopoietic stem cell transplantation [42], a 6-year-old male with history of prematurity, chromosome 17 and 19 deletions, submucosal cleft palate, atrial and ventricular septal defects, immune deficit, hypospadias, asthma, obstructive sleep apnea syndrome and gastrostomy [49], a female with congenital adrenal hyperplasia [5], a male born preterm [52] and a 17-year-old female with Cornelia de Lange syndrome [54]. Four children were under 1 year old: one case of transplacental transmission of SARS-CoV-2 was demonstrated in a neonate born to a mother infected in the last trimester [52].

As regards neurological symptoms, the most commonly reported were headache in 2/3 of cases, altered mental status (from irritability and confusion to lethargy) in 32% of cases, seizure in 14/60 patients, muscular weakness in 14/60 children and meningism in 10/60.

Concerning neurological manifestations, we recognized acute cerebrovascular accidents in 10 children (4 cases of ischemic stroke, 3 cases of intracerebral hemorrhage, a subarachnoid hemorrhage, a case of multiple diffuse microhemorrhages, a cerebral sinus venous thrombosis), reversible splenial lesions in 9 cases, GBS in 5 persons, benign intracranial hypertension or pseudotumor cerebri in 4 patients, meningoencephalitis in 4 cases, autoimmune encephalitis in 1 girl, ADEM in 2 children (including ours),
| Author/Country [Ref.] | Age/sex | Pre-existing medical conditions | Neurological symptoms | Respiratory symptoms | Other symptoms | Diagnosis of MIS-C | NP/CSF/Serology | Radiology and other neurological investigations | Outcome |
|-----------------------|---------|-------------------------------|----------------------|---------------------|----------------|-------------------|----------------|-----------------------------------------------|---------|
| Abdel-Mannan et al./UK [12] | 4 cases | No M 8y | Headache, meningism, confusion, muscular weakness | No | Fever, rash, abdominal pain, emesis, shock | Yes | Pos/Neg/ND | CT: hypodensity of the splenium of the corpus callosum | Improved |
| | | | 9y | No | Headache, confusion, ataxia, dysarthria, muscular weakness | No | Fever, rash, emesis, shock | Yes | Pos/Neg/ND | MRI: signal changes of the genu and splenium of corpus callosum and bilateral centrum semiovale with restricted diffusion | Recovered |
| | | | 15y F | No | Confusion, dysarthria, dysphagia, muscular weakness | Yes | Fever, rash, emesis, shock | Yes | Pos/ND/Pos | MRI: signal changes in the splenium of corpus callosum and bilateral centrum semiovale with restricted diffusion | Improved |
| | | | 15y F | No | Headache, confusion, muscular weakness | Yes | Fever, rash, emesis, shock | Yes | Pos/ND/Pos | MRI: signal change in the splenium of corpus callosum with restricted diffusion | Recovered |
| Abel et al./USA [13] | 3y M | No | Irritability, hypotonia, muscular weakness | Yes | Fever, rash, emesis | Yes | Neg/Neg/Pos | MRI: restricted diffusion in the bilateral lateral thalamic nuclei | Improved, under physiotherapy |
| | | | | | | | | EEG: moderate slow background activity | |
| Asif et al./UK [14] | 18y M | No | Headache, photophobia | No | Fever, cough and myalgia before neurological manifestations | No | Neg/ND/ND (previous diagnosis of COVID-19) | CT venogram: filling defects in the sigmoid and transverse sinuses bilaterally and in the straight and superior sagittal sinuses | Improved |
| | | | | | | | | MRI: normal LP: elevated opening pressure | |
| | | | | | | | | LP: elevated opening pressure | |
| | | | | | | | | MRI: finding consistent with elevated intracranial pressure | Recovered |
| Baccarella et al./US[15]2 cases | 9y M | No | Headache, diplopia, right abducens nerve palsy | No | Fever, abdominal pain | Yes | Neg/Neg/Pos | MRI: normal LP: elevated opening pressure | Recovered |
| | | | | | | | | CT: hyperdensity at basal cisterns, interhemispheric and bilateral Sylvian fissures suggesting of subarachnoid hemorrhage and reduction of white matter density (brain edema) | Died |
| Basirjafari et al./Iran [16] | 9y M | No | Headache, bilateral fixed mydriasis | Yes | Fever, abdominal pain | No | Pos/ND/ND | MRI: hyperintensity in the splenium of corpus callosum with restricted diffusion EEG: slowed background activity | Recovered |
| | | | | | | | | MRI: hyperintensity in the splenium of corpus callosum with restricted diffusion | |
| | | | | | | | | MRI: hyperintensity in the splenium of corpus callosum with restricted diffusion | |
| | | | | | | | | CT: normal | Recovered |
| Bhatta et al./ | 11y | No | Seizure | No | No | No | Pos/NR/ND | | | |
| Siracusa et al. Italian Journal of Pediatrics (2021) 47:123 | | | | | | | | | |

Siracusa et al. Italian Journal of Pediatrics (2021) 47:123
| Author/ Country [Ref.] | Age/ sex | Pre-existing medical conditions | Neurological symptoms | Respiratory symptoms | Other symptoms | Diagnosis of MIS-C | NP/CSF/ Serology SARS-CoV-2 | Radiology and other neurological investigations | Outcome |
|------------------------|----------|--------------------------------|-----------------------|---------------------|---------------|-------------------|------------------------|---------------------------------|---------|
| USA [18] M | 23 m/F | No | Irritability, hyperkinetic movements of head, arm and legs | No | Fever | No | Pos/Neg/Pos | MRI: normal | Recovered |
| Chiotos et al./ US A [20] | 14 y/ F | No | Headache | Yes | Fever, rash, diarrhea | Yes | Neg/ND/Pos | ND | Recovered |
| | 12 y/ M | No | Altered mental status, irritability | Yes | Fever, fissured lips, abdominal pain, diarrhea, shock | Yes | Neg/ND/Pos | ND | Recovered |
| | 5 y/F | No | Altered mental status, irritability, nuchal rigidity | No | Fever, conjunctivitis, shock | Yes | Neg/ND/Pos | ND | Recovered |
| | 5 y/F | No | Irritability, nuchal rigidity | No | Fever, rash, conjunctivitis, fissured lips, swollen hands, emesis, diarrhea, shock | Yes | Pos/ND/Pos | CT: diffuse cerebral edema | Recovered |
| Curtis et al./ India [21] | 8 y/ M | No | Muscular weakness, paralysis and paresthesia of the lower limbs | No | No | No | Pos/Neg/Pos | MRI: enhancement of the posterior nerve roots from T11 to cauda equine | Improved |
| de Miranda Henrique-Henriques-Souza et al./ Brazil [22] | 12 y/ F | No | Headache, muscular weakness, tetraplegia | Yes | Fever, rash | Yes | Pos/Neg/ND | MRI: bilateral and symmetric areas of restricted diffusion involving the subcortical and deep white matter. Extensive cervical myelopathy | Improved |
| De Paulis et al./Brazil [23] | 4 y/F | No | Confusion, lethargy | Yes | Fever, emesis, rash, palpebrae, hands and feet edema, cracked lips, shock | Yes | Neg/Neg/Pos | CT: normal LP: pleiocytosis and elevated protein | Improved |
| Emami et al./ Iran [24] | 2.9 y/M | Allergy to cow milk | Seizure, altered mental status, dysarthria | No | Fever | No | Pos/Neg/Pos | MRI: right occipital mass and intracerebral hemorrhage EEG: generalized slowing (pathology of the mass: normal brain tissue with dilated vessels and haemorrhage) | Recovered |
| Enner et al./ USA [25] | 14 y/ F | No | Seizure and central apnea | Yes | Fever, nasal congestion, myalgia | No | Pos/Neg/ND | MRI: normal EEG: epileptiform abnormalities | Improved |
| Frank et al./ Brazil [26] | 15 y/ M | No | Ascending weakness from the lower to the upper limbs, headache | No | Fever | No | Pos/Neg/Pos | MRI: normal Electroneurography: acute motor axonal neuropathy | Improved, under physiotherapy |
| Gaur et al./ UK [27] | 12 y/ M | NR | Headache, lethargy | No | Fever, diarrhea, conjunctivitis, shock | Yes | Neg/ND/Pos | MRI: hyperintensity in the splenium of corpus callosum with restricted diffusion | Recovered |
| Author/Country [Ref.] | Age/sex | Pre-existing medical conditions | Neurological symptoms | Respiratory symptoms | Other symptoms | Diagnosis of MIS-C | NP/CSF/SeroLOGY SARS-CoV-2 | Radiology and other neurological investigations | Outcome |
|-----------------------|---------|--------------------------------|----------------------|---------------------|---------------|------------------|--------------------------|---------------------------------|---------|
| Gulko et al./USA [28] | 9 y/ M  | NR                             | Lethargy, ataxia, dysarthria | No                  | Fever         | No               | Neg/ND/NDPos bronchoalveolar lavage | MRI: hyperintensity in the splenium of corpus callosum and in the deep cerebral white matter with restricted diffusion | Recovered |
| Kaur et al./Mexico [29] | 13 y/ F | No                             | Headache, muscular weakness, speech difficulty | No                  | No            | No               | Pos/ND/ND | CT: left frontal hypodensity concerning for ischemic infarct. MRI: hyperintensity with restricted diffusion in the left frontal, parietal and temporal lobes stenosis of the left middle cerebral artery | Improved |
| Khalifa et al./ Saudi Arabia [30] | 3 y/ F | No                             | Quadriplegia and paraesthesia | Yes                 | Yes           | Neurogenic respiratory failure | No | MRI: swelling of the cervical spinal cord involving most of the transverse aspect of the spinal cord, extending from the lower medulla to the midthoracic level | Quadriplegia |
| Kim et al./USA [31] | 11 y/ M | No                             | Muscular weakness, hypotonia, paraesthesia in the lower limbs | Yes                 | Yes           | Fever and cough before neurological manifestations | No | MRI: cauda equina nerve root enhancement LP: albuminoctyologic dissociation | Recovered |
| Lin et al./USA [32] | 7 y/ M  | No                             | Headache, emesis | No                  | Yes           | Fever, abdominal pain | Yes | CT: diffuse cerebral edema EEG: generalized voltage attenuation | Died |
| Lin et al./USA [32] | 13 y/ M | No                             | Dizziness, gait instability, auditory hallucinations | Yes                 | Yes           | Fever, diarrhea, emesis, hypotension | Yes | MRI: hyperintensity in the splenium of corpus callosum with restricted diffusion EEG: slow background activity | Recovered |
| Lorenz et al./Germany [33] | 40 w/f  | No                             | Lethargy, hyperexcitability | Yes                 | Yes           | Fever | No | Pos/Neg/ND | US: normal | Recovered |
| Manji et al./Tanzania [34] | 12 y/ M | No                             | Progressive paresis, bilateral facial nerve paresis | Yes                 | Yes           | Fever and cough before neurological manifestations | No | Pos/Neg/ND | ND | Died |
| McAbee et al./USA [35] | 11 y/ M | No                             | Seizure | No                  | Fever         | No               | Pos/Neg/ND | CT: normal EEG: intermittent frontal delta activity LP: pleiocytosis | Recovered |
| Mirzaee et al./Iran [36] | 12 y/ M | No                             | Seizure, dysarthria, hemiparesis | No                  | No            | No               | Pos/Pos/ND | MRI: acute infarction with narrowing of the left middle cerebral artery | Improved, under rehabilitation |
| Moreno-Galanaga et al./Spain [37] | 2 m/ F | No                             | Headache, seizure | No                  | No            | Diarrhea Flu-like symptoms before neurological manifestations | No | MRI: normal LP: normal | Recovered |
| Natarajan et al./India [38] | 13 y/ F | No                             | Headache, irritability, seizure | No                  | Yes           | Fever | No | Pos/Neg/ND | MRI: normal LP: pleiocytosis | Recovered |
| Paybast et al. | 14 y/ NR | No                             | Progressive | No                 | Flu-like symptoms before | No | Pos/Neg/ND | LP: albuminoctyologic dissociation | Improved |
| Author/ Country [Ref.] | Age/sex | Pre-existing medical conditions | Neurological symptoms | Respiratory symptoms | Other symptoms | Diagnosis of MIS-C | NP/CSF/Serology SARS-CoV-2 | Radiology and other neurological investigations | Outcome |
|------------------------|---------|---------------------------------|-----------------------|---------------------|---------------|-------------------|--------------------------|----------------------------------|---------|
| Iran [39] F            |         |                                 | paresthesia, muscular weakness, headache, dizziness | neurological manifestations |               |                   |                          | ND                               | Recovered |
| Raj et al./India [40] | 2 y/ M  | No                              | Seizure               | No                  | Fever, diarrhea, hypotension | Yes              | Pos/Neg/Neg            | ND                               | Recovered |
|                        | 15 m/M  | No                              | Seizure               | No                  | Fever, rash, conjunctivitis, chilblain | Yes              | NR/NR/ NR(COVID-19 contact) | ND                               | Recovered |
| Regev et al./Israel [41]| 16 y/ M| No                              | Headache, nuchal rigidity | No                  | Fever, abdominal pain, rash, conjunctivitis, pharyngitis, shock | Yes              | Pos/ND/Pos             | MRI: multiple low attenuating small lesions in the subcortical white matter, internal and external capsule and in the anterior and posterior part of the corpus callosum, suggesting microhemorrhages | Recovered |
| Roussel et al./France [42]| 6 y/F  | Sickle cell disease, cerebral vasculopathy, HSCT | Impairment of V-VII-IX cranial nerves | Yes               | No                 | No                 | Pos/Neg/ND               | CT: cerebral edema MRI: cranial nerves enhancement (left hypoglossal nerve and bilateral facial nerves) | Improved |
| Saeed et al./Iran [43] | 3 y/ M  | No                              | Seizure               | No                  | Fever, hypotension | Yes              | Pos/Neg/ND               | CT: left side frontoparietal intracerebral hematoma with intraventricular extension CT angiography: pseudoaneurysm of the frontoparietal branch of the left middle cerebral artery | Not improved |
| Savic et al./Kuwait [44]| 13 y/ F| No                              | Altered mental status, right side weakness | No                  | No                 | No                 | Pos/ND/ND               | CT: a right middle cerebral artery infarction, cerebral edema and diffuse contralateral subarachnoid hemorrhage | Died |
| Schupper et al./USA [45]| 5 y/ M | No                              | Right mydriasis       | Yes                 | Fever, abdominal pain, shock | Yes              | NR/NR/Pos               | MRI: normal | Recovered |
| Seth et al./India [46] | 15 y/ M| NR                              | Headache, emesis, photophobia | No                 | Fever before neurological manifestations | No              | Pos/Neg/ND               | LP: elevated opening pressure and pleiocytosis | Recovered |
| Shenker et al./USA [47]| 12 y/ M| NR                              | Seizure               | No                  | Fever, rash, conjunctivitis, neck swelling, cracked lips, hypotension | Yes              | Pos/Neg/ND               | MRI: normal | Recovered |
| Swarz et al./USA [48]  | 9 y/ M  | No                              | Seizure               | No                  | Fever, emesis         | No              | Pos/ND/ND               | EEG: focal epilepsy arising in the central region | Recovered |
| Theophanous            | 6 y/    | Prematurity,                   | Right facial nerve palsy | No                 | No                  | No              | Pos/ND/ND               | EEG: delta activity in the right hemisphere | Recovered |
| Author/Country [Ref.] | Age/sex | Pre-existing conditions | Neurological symptoms | Respiratory symptoms | Other symptoms | Diagnosis of MIS-C | NP/CSF/SARS-CoV-2 | Radiology and other neurological investigations | Outcome |
|-----------------------|---------|-------------------------|-----------------------|----------------------|---------------|-------------------|-------------------|------------------------------------------------|---------|
| et al./USA [49]       | M       | chromosome 17 and 19 deletions, submucosal palate cleft, atrial and ventricular septal defects, agammaglobulinemia with hyper-IgM, hypospadias, asthma, OSAS, gastrosomy | Headache, right hemiplegia, right facial nerve palsy | Yes | Fever, conjunctivitis, emesis | Yes | Pos/Neg/Pos | CT: multifocal hypodensities in the genu and body of corpus callosum, left basal ganglia and bilateral thalami suggestive of infarcts | Improved, under rehabilitation |
| Twari et al./India [50] | 9 y/F    | No                       | Headache, right hemiplegia, right facial nerve palsy | Yes | Fever, conjunctivitis, emesis | Yes | Pos/Neg/Pos | CT angiography: multifocal stenosis of both intracranial internal carotid arteries, right middle cerebral artery, both A2 segments of the anterior cerebral arteries and M2/ M3 segments of both middle cerebral arteries | |
| Verdoni et al./Italy [55] | 7 y/ M  | No                       | Meningism | Yes | Fever, conjunctivitis, changes in lips and oral cavity, diarrhea | Yes | Pos/Neg/Pos | ND | Recovered |
|                        | 7.7 y/F  | No                       | Meningism | No | Fever, conjunctivitis, changes in lips and oral cavity, diarrhea | Yes | Neg/ND/Pos | ND | Recovered |
|                        | 5 y/M    | No                       | Meningism | No | Fever, rash, conjunctivitis hands and feet anomalies | Yes | Neg/ND/Pos | ND | Recovered |
|                        | 5.5 y/M  | No                       | Meningism | No | Fever, rash, conjunctivitis hands and feet anomalies | Yes | Neg/ND/Pos | ND | Recovered |
|                        | 5.5 y/M  | No                       | Drowsiness | Yes | Fever, rash, conjunctivitis hands and feet anomalies, diarrhea | Yes | Neg/ND/Pos | ND | Recovered |
| Verkuil et al./USA [51] | 14 y/ F  | No                       | Headache, right abducens nerve palsy | Yes | Fever, diarrhea, rash, shock | Yes | Neg/ND/Pos | MRI: finding consistent with elevated intracranial pressure, LP: elevated opening pressure | Recovered |
| Vivanti et al./Francea [52] | 3 d/ M  | Prematurity              | Irritability, opisthotonos | No | Feeding difficulty | No | Pos/Neg/ND | MRI: hyperintensity of the periventricular and subcortical frontal and parietal white matter | Improved |
| Yousefi et al./Iran [53] | 9 y/F    | NR                       | Headache, diplopia, photophobia, meningism | No | Fever | No | Neg/Pos/ND | LP: pleocytosis, elevated protein, decreased glucose | Recovered |
Table 1  Reported cases of neurological involvement during SARS-CoV-2 infection in children (Continued)

| Author/ Country [Ref] | Age/ sex | Pre-existing medical conditions | Neurological symptoms | Respiratory symptoms | Other symptoms | Diagnosis of MIS-C | NP/CSF/ Serology SARS-CoV-2 | Radiology and other neurological investigations | Outcome |
|----------------------|----------|---------------------------------|-----------------------|---------------------|---------------|-------------------|--------------------------|---------------------------------|---------|
| Zombori et al./ UK [54] | 17 y/ F | Cornelia de Lange syndrome | Seizure | Yes | Fever | Yes | Pos/ND/ND | MRI: multifocal cortical, cerebellar and thalamic swelling areas EEG: bilateral independent periodic lateralized epileptiform discharges | Improved, under rehabilitation |
| Our case | 5 y/ F | No | Irritability, nuchal rigidity | No | Fever, rash, diarrhea, neck swelling | Yes | Pos/ND/Pos | MRI: two lesions, one in the splenium of the corpus callosum and the other in the subcortical white matter of the left parietal lobe, with restricted diffusion | Recovered |

**Abbreviations:** y years; m months; w weeks; d days; F female; M male; NP nasopharyngeal; CSF cerebrospinal fluid; MRI magnetic resonance imaging; CT computerized tomography; US ultrasound; EEG electroencephalogram; LP lumbar puncture; Pos positive; Neg negative; NR not reported; ND not done; HSCT hematopoietic stem-cell transplantation; OSAS obstructive sleep apnea syndrome

*transplacental transmission of SARS-CoV-2 infection*
cranial nerves impairment in 2 patients and transverse myelitis in 1 case. Furthermore we found one report of severe encephalopathy with bilateral thalamic lesions and one article of fatal cerebral edema.

Fever was recorded in 75% of cases, while respiratory symptoms were present in 23/60 children. Six patients had flu-like symptoms before the onset of neurological complications. More than half of patients (55%) showed neurological complications in the course of a MIS-C, associated with a multisystem organ involvement (especially mucocutaneous, gastrointestinal and cardiac).

Radiological investigations (CT, MRI and/or ultrasound) were performed in almost all cases (45/60): the most recurrent radiological finding was a signal change in the splenium of the corpus callosum (12/60).

The diagnosis of SARS-CoV-2 infection was made according to the presence of SARS-CoV-2 viral nucleic acid in the nasopharyngeal swab in 29 cases and positive serology in 15 children; both nasopharyngeal swab and serology were positive in 11 patients. The presence of SARS-CoV-2 viral nucleic acid in the CSF was proved only in 2 cases (associated with a positive nasopharyngeal swab in 1 case). The outcome was favorable in almost all cases; 5 children died.

**Discussion**

We described a case of ADEM in a pediatric patient with MIS-C related to SARS-CoV-2 infection. The diagnosis of ADEM was established according to the consensus criteria of the International Pediatric Multiple Sclerosis Study Group in 2013: a polyfocal, clinical central nervous system (CNS) event with a presumed inflammatory demyelinating cause; an encephalopathy that cannot be explained by fever; no new clinical and MRI findings emerging 3 months or more after the onset; abnormal brain MRI during the acute phase [55]. The close temporal relationship between encephalopathy and SARS-CoV-2 infection in our patient allowed us to consider the novel coronavirus as the trigger of the immune-mediated response against CNS, as already reported for other human coronavirus [56]. Furthermore our patient fulfilled the criteria for the diagnosis of MIS-C: she presented fever, mucocutaneous involvement, lymphadenopathy, diarrhea and neurological symptoms associated with elevated inflammatory markers and the presence of antibodies against SARS-CoV-2; unfortunately, the search for the novel coronavirus in the CSF was not performed, because a validated test was not available.

As recommended by American College of Rheumatology (ACR) [6], the first-tier agents for MIS-C treatment are IV immunoglobulin (typically 1–2 g/kg) and/or low to high doses of glucocorticoids (from 1 to 2 mg/kg/day to a bolus of 20–30 mg/kg/day for 3 days); acute treatment approach for pediatric ADEM is high-dose IV glucocorticoids for 3 or 5 days (either 10–30 mg/kg/day methylprednisolone or 1 mg/kg/day dexamethasone) followed by an oral steroid tapering or IV immunoglobulin at a total dose of 1–2 g/kg, administered either as a single dose or divided in 5 days (usually 400 mg/kg/day) [57]. Our girl was treated with glucocorticoids and immunoglobulin with a complete recovery; the outcome was favorable.

Afterwards, we have conducted a systematic review of the neurological complications during SARS-CoV-2 infection in pediatrics. Headache, irritability, drowsiness and seizure are the most frequent symptoms, that could be signs of different neurological conditions or neuroimaging abnormal findings: ischemic stroke, cerebral hemorrhage, benign intracranial hypertension, encephalitis, GBS, ADEM, splenial lesions. Furthermore, we observed that neurological investigations, especially radiological examinations, were not performed in all patients, especially in those with mild symptoms; in these cases, it is not clear what neurological condition is associated to SARS-CoV-2 infection.

The clinical observations summarized above suggest that SARS-CoV-2 could be responsible for many neurological manifestations, which can be divided into three different scenarios, related to the presumed pathophysiologic mechanism:

1) Neurological involvement during COVID-19;
2) Neurological involvement that arises after the recovery from COVID-19;
3) Neurological involvement during MIS-C.

The first condition could be caused by direct invasion of CNS by the virus through hematogenous dissemination or neuronal retrograde dissemination. In hematogenous dissemination, the virus can pass to the bloodstream and then enters the brain by either infecting endothelial cells of the blood-brain barrier or epithelial cells of the blood-CSF barrier in the choroid plexus, though the binding between spike protein and ACE2 receptor; furthermore, coronavirus can infect leukocytes, that disseminate towards other tissues and cross the blood-brain barrier to access the CNS (the so-called Trojan horse mechanism) [58]. In neuronal retrograde dissemination, the virus can gain access to CNS though the infection of olfactory neurons, using retrograde axonal transport [58]. This pathophysiological mechanism could explain how SARS-CoV-2 can induce encephalitis and vasculitis leading to cerebrovascular accidents; the detection of the virus in the CSF samples using RT-PCR is an important sign of its neurotropism.

The second condition could be related to a post-infectious immune-mediated mechanism: SARS-CoV-2 might induce an autoimmune response after a latent
period following the infection illness [59], correlated to the hypothesis of “molecular mimicry” between microbial and self-antigens. For example, GBS is characterized by ascending paralysis, occurring after the resolution of COVID-19 symptoms (fever and cough): it is caused by a cross-reaction against gangliosid-components of the peripheral nerves [60].

The third condition, the most recurrent observed in this review, could be explained though indirect mechanism caused by the novel coronavirus: the cytokine storm, characterized by high levels of tumor necrosis factor-alpha (TNF-α), interleukin (IL-1β, IL-6, IL-12, and interferon gamma (INFγ) [59]. The integrity of the blood-brain barrier may be disrupted by cytokine-driven injury without CNS direct invasion by the virus [59]. Moreover, the hyperinflammatory state can lead to a pro-coagulable state: initial vasculitis causes the disruption of vascular integrity, the exposure of thrombogenic basement membrane and, finally, the activation of the clotting cascade [9]. Children with MIS-C exhibit alteration of inflammatory biomarkers (procalcitonin, CRP, fibrinogen, ferritin, D-dimer, IL-6), that suggest a possible involvement of the immune system in the pathogenesis of this syndrome [6]. Many observational studies about clinical characteristics of patients with MIS-C have reported the presence of neurological involvement: children could complain of headache, confusion, altered mental status, stiff neck or meningism [10, 61–65]. In the course of MIS-C, neurological complications, such as ADEM (our case), pseudotumor cerebri [15, 46, 51], cerebral edema [20, 31], seizure [40, 47], cerebral stroke [45, 50] and cytotoxic lesions of the corpus callosum [13, 17, 27, 32] have been described and included in this review. During hyperinflammatory state, the corpus callosum, especially the splenium, is highly vulnerable to excess of cytokines and glutamate release from astrocytes because of its high concentration of cytokines and glutamate receptors: this higher density leads to a tendency of cytotoxic edema of the corpus callosum when cytokine storm occurs [66]. Despite the great variability of neurological manifestations, from mild to severe ones, the prognosis is favorable in the majority of cases.

This systematic review has several limitations due to the quality of the selected studies (all articles are case reports or case series and do not represent the full population) and the potential impact of publication bias.

**Conclusions**

Our research highlights the large range of neurological manifestations and their presumed pathogenic pathways associated with SARS-CoV-2 infection in children. CNS involvement could be isolated, developing during COVID-19 or after its recovery, or arise in the course of a MIS-C. The most reported neurological manifestations are cerebrovascular accidents, reversible splenial lesions, GBS, benign intracranial hypertension, encephalitis, cranial nerves impairment, transverse myelitis; ADEM is also a possible complication, as we observed in our patient. Outcome is good in almost all cases. Further studies are required to investigate all the neurological complications of SARS-CoV-2 infection and their underlying pathogenic mechanism.

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CC, AC, GAR wrote the paper and performed literature search. LS, SG, AAM, GAR, IP, GFS, FC collected clinical data, wrote the paper and revised the manuscript. All authors read and approved the final manuscript.

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**Availability of data and materials**

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**Declarations**

**Ethics approval and consent to participate**

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**Consent for publication**

Parent’s informed written consent was provided.

**Competing interests**

The authors declare that they have no competing interests.

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