Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Neurological involvement associated with COVID-19 infection in children

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Dear Editor,

We read with great interest the recently published articles regarding neurological involvement associated with COVID-19 infection by Asadi-Pooya et al. and Roman et al. [1,2]. Compared with adult patients, children account for only 1–5% of COVID-19 (SARS-CoV-2) cases, of which more than 80% are asymptomatic or mild cases [3]. SARS-CoV-2 may have neuroinvasive potential because 36% of adult patients are reported to have a variety of neurological manifestations, including headache, dizziness, acute cerebrovascular events, and changes in mental status. [4]. However, another study of 171 Chinese children with COVID-19 infection did not report neurological involvement [5]. According to the latest data from Western countries, non-specific headaches were the only reported neurological symptoms, accounting for 4–28% of COVID-19 infected children [3].

Of note, recent reports described emerging cases diagnosed with multisystem inflammation syndrome in children (MIS-C) related to COVID-19 infection, which share common characteristics with toxic shock syndrome and incomplete Kawasaki disease. [6]. When reviewing 187 children from the six latest reports of MIS-C cases, we found that these children had an unexpectedly high incidence (34%) of neurological involvement [6–11]. Compared with Kawasaki disease shock syndrome (KDSS), which shares several clinical features and severity with MIS-C, the neurological manifestations of KDSS have been found in as high as 54% of the affected children [12]. The high incidence of neurological complications in children with MIS-C Kawasaki-like disease remains unclear; nevertheless, the mechanism might be different from the thromboembolic mechanism of the cerebrovascular system observed frequently in adult COVID-19 patients.

In these MIS-C cases, 46% and 92% of children were reported positive COVID-19 reverse transcription polymerase chain reaction (RT-PCR) and serum antibody (IgG and/or IgM), respectively. This evidence suggests that while MIS-C occurred, most children might not have an active COVID-19 infection (Table 1). Of the 187 children, 64 had varying degrees of neurological symptoms, most of which were headaches, positive meningeal signs (meningism), and altered mental status. However, although their symptoms strongly implied the need to rule out the possibility of meningoencephalitis associated with COVID-19, only eight patients underwent cerebrospinal fluid (CSF) study, and one of them had received a brain computed tomography (CT). In the CSF results, five children showed non-specific pleocytosis, suggesting a diagnosis of aseptic meningitis, but SARS-CoV-2 was not detected in RT-PCR. Brain CT showed cerebral edema suggesting a neuroinflammatory reaction in one case [6]. Accordingly, the clinicolaboratory and neurological characteristics of MIS-C patients strongly suggest a post-infectious immune response, similar to the mechanism of COVID-19-related autoimmune meningoencephalitis recently reported in adult COVID-19 patients [13]. Autoimmune meningoencephalitis may occur at all ages, but in some cases, it mainly affects children and young adults. It is imperative to investigate whether children may have similar neurological complications related to COVID-19 infection. Correspondingly, all children with MIS-C had increased inflammatory acute-phase reactants in their serum, including C-reactive protein, calcitonin, ferritin, or interleukin 6, which suggests a dysregulated immune response after infection with COVID-19. Brain magnetic resonance imaging (MRI) is essential for the diagnosis of meningoencephalitis; however, there are no MRI reports of these MIS-C cases complicated with neurological involvement.

The pathophysiological characteristics of SARS-CoV-2 associated meningoencephalitis are still under investigation but may be related to possible causes. One of the plausible causes is neuronal cell edema secondary to neuroinflammatory injury. Such immune-mediated neuronal damage may be due to cytokine storm syndrome induced by the overreaction of monocytes, macrophages, and T cells after SARS-CoV-2 infection. Further release of interleukins-6 (IL-6) might aggravate damage to neuronal cells. Moreover, the pathomechanism may be related to acute necrotizing encephalopathy, a parainfectious disease predominantly described in the pediatric population, which has been reported in an adult case with COVID-19-induced cytokine storm syndrome [2]. Direct invasion of COVID-19 virus to CNS system or metabolic encephalopathy associated with severe hypoxia caused by severe respiratory compromise has also been reported in adult cases [2]. Given no positive findings of SARS-CoV-2 RT-PCR in CSF and relatively mild lung involvement in these cases, it seems unlikely to cause MIS-C-related encephalopathy.

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Table 1
Demography, clinical characteristics, and outcome of COVID-19-related neurological involvement in MIS-C cases.

Case series	Case number	Age (median)/ Gender, n	Cases with neurological involvement, n (%)	Neurological manifestations, n (%)	Neurological investigations and findings, (n)	Positive SARS-CoV-2 RT-PCR, n (%)	Positive SARS-CoV-2 Ab, n (%)	Serum acute inflammatory markers (Median)	Treatment for MIS-C, n (%)	Outcome
Verdoni 2020	10	7.5 yrs.*; Male: 7	4 (40%)	Meningism: 4 (40%)	EEG: slow wave pattern (2) CSF study: normal (1)	Nasal swab: 2 (20%) CSF: 0	8 (80%)	CRP: 240 mg/L*; ESR: 72 mm/h*; Ferritin: 1176 ng/mL*	IVIG: 10 (100%); Steroid: 8 (80%)	Full Recovery without neurological sequelae: 10 (100%)
Toubiana 2020	21	7.9 yrs.; Male: 9	6 (29%)	Headaches, confusion or meningism: 5 (29%)	CSF study: Normal (2); pleocytosis (1)	Nasal swab: 8 (38%)	19 (90%)	CRP: 253 mg/L; PCT: 22.5 ng/mL; IL-6: 170 pg/mL	IVIG: 21 (100%); Steroid: 10 (48%)	Full Recovery without neurological sequelae: 21 (100%)
Belhadjer 2020	35	10 yrs.; Male: 18	11 (31%)	Meningism: 11 (31%)	CSF: aseptic meningitis (1) Brain CT: cerebral edema suggesting neuroinflammatory changes (1)	Nasal swab: 12 (34%) Fecal specimens: 2 (6%)	30 (86%)	CRP: 241 mg/L; PCT: 36 ng/mL; IL-6: 135 pg/mL	IVIG: 25 (71%); Steroid: 12 (34%)	Full Recovery without neurological sequelae: 35 (100%)
Chiotos 2020	6	8.5 yrs.; Male: 2	4 (67%)	Headache: 1 (17%); Meningism: 1 (17%); Altered mentality: 2 (33%)	No described	Nasal swab: 3 (50%)	5 (83%)	CRP: 223 mg/L*; PCT: 49 ng/mL*; Ferritin: 1015 ng/mL*	IVIG: 6 (100%); Steroid: 6 (100%)	Full Recovery without neurological sequelae: 6 (100%)
Pouletty 2020	16	10 yrs.; Male:8	9 (56%)	Headache: 6 (38%); Meningism: 3 (19%)	CSF: aseptic meningitis (3)	Nasal swab: 9 (56%) Fecal specimens: 2 (13%)	7/8 (88%)	CRP: 207 mg/L; PCT: 12.6 ng/mL; IL-6: 270 pg/mL; Ferritin: 1067 ng/mL	IVIG: 15 (94%) Steroid: 4 (25%)	Full Recovery without neurological sequelae: 16 (100%)
Dufort 2020	99	0–5 yrs.: 31%; 6–12 yrs.: 42%; 13–20 yrs.: 26%; Mal4: 53	30 (30%)	Headache: 29 (29%); Altered mentality: 2 (2%)	No described	Nasal swab: 50/98 (51%)	76/77 (99%)	CRP: 219 mg/L; PCT: 6.2 ng/mL; IL-6: 116.3 pg/mL; Ferritin: 522 ng/mL	IVIG: 69 (70%) Steroid: 63 (64%)	Full Recovery without neurological sequelae: 97 (98%)

MIS-C: multisystem inflammatory syndrome in children; RT-PCR: reverse transcription polymerase chain reaction; Ab: antibodies; EEG: electroencephalogram; CSF: cerebrospinal fluid; CT: computed tomography; CRP: C-reactive protein (reference value: < 6 mg/mL); ESR: erythrocyte sedimentation rate (reference value: < 20 mm/h); PCT: procalcitonin (reference value: < 2 ng/mL); IL-6: interleukine 6 (reference value: < 8.5 pg/mL); IVIG: intravenous immunoglobulin.
Reference value of ferritin: < 78.8 ng/mL
*Data are presented in mean value.

Treatment with plasma exchange or intravenous immunoglobulins (IVIG) has been reported of potential benefit for several neuroinflammatory crises. In an adult case-series study, plasmapheresis was found useful in COVID-19 patients with autoimmune meningoencephalitis [13]. The therapeutic effect of plasmapheresis in children with MIS-C associated encephalopathy is unclear. However, it should be cautious that children appear to be at higher risk for plasmapheresis-related complications, including hemodynamic instability, allergic reactions, and electrolyte imbalance [14]. Interestingly, most MIS-C cases treated with the standard treatment regimen for Kawasaki disease (IVIG and/or steroids) recovered uneventfully without neurological sequelae. In conclusion, further investigations on the pediatric COVID-19 population, including the extensive brain MRI examination, CSF study, and children-specific therapies, are encouraged to decipher this emerging neurological complication.

Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article.

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