COVID-19 and neurologic manifestations: a synthesis from the child neurologist’s corner

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Received: 13 December 2021 / Accepted: 29 March 2022 / Published online: 27 April 2022
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Abstract

Background Since December 2019, the SARS-CoV-2 virus has been a global health issue. The main clinical presentation of this virus is a flu-like disease; however, patients with diverse neurologic manifestations have also been reported. In this review, we attempt to summarize, discuss and update the knowledge of the neurologic manifestations in the pediatric population affected by SARS-CoV-2 infection and the pandemic’s effects in children with neurologic diseases.

Data sources This review analyzes studies found on the PubMed database using the following keywords: Neurologic manifestations COVID-19, Neurological COVID-19, coronavirus, SARS-CoV-2, pediatric COVID-19, COVID-19 in children, MIS-C, Pediatric Inflammatory Multisystem Syndrome, Guillain Barré Syndrome, Stroke, ADEM, and Anti-NMDA encephalitis. All studies cited were published between 2004 and 2022, and represent the most relevant articles in the field. The World Health Organization COVID-19 online dashboard was assessed to obtain updated epidemiological data.

Results The most common neurologic symptoms in the pediatric population are headache, seizures, encephalopathy, and muscle weakness. These can be present during COVID-19 or weeks after recovering from it. Children who presented with multi-system inflammatory syndrome had a higher incidence of neurologic manifestations, which conferred a greater risk of morbidity and mortality. Several neuro-pathophysiological mechanisms have been proposed, including direct virus invasion, hyper-inflammatory reactions, multi-systemic failure, prothrombotic states, and immune-mediated processes. On the other hand, the COVID-19 pandemic has affected patients with neurologic diseases, making it challenging to access controls, treatment, and therapies.

Conclusions Various neurologic manifestations have been associated with children’s SARS-CoV-2 infection. It is important to identify and give them proper and opportune treatment because they can be potentially grave and life-threatening; some can lead to long-lasting sequelae. Different neuro-pathophysiological mechanisms have been proposed, however, a causal relationship between SARS-CoV-2 infection and neurologic manifestations remains to be proven. Patients with neurologic diseases are especially affected by COVID-19, not only by the disease itself but also by its complications and pandemic management measures.

Keywords Coronavirus COVID-19 Neurologic · Pediatric · SARS-CoV-2 · MIS-C

Introduction

Since December 2019, the SARS-CoV-2 virus has infected more than 250 million people and has caused over five million deaths [1]. Despite remarkable scientific and medical efforts to battle the pandemic and after multiple publications, COVID-19 is still a challenge for many health systems worldwide. The most frequent clinical presentation is a flu-like disease that can progress to severe pneumonia, respiratory distress, shock, and even death [2]. Multiple systems may be targeted with involvement of the nervous system being of special relevance. Several publications have demonstrated various neurologic symptoms and diseases associated with SARS-CoV-2 infection, mainly in the adult population. Symptoms ranging from headache or hyposmia to severe complications, such as stroke and Guillain–Barré

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syndrome (GBS), have been reported [3–7]. Interestingly, it is now known that patients recovering from the infection can manifest long-lasting cognitive impairments, as part of a persistent syndrome known as “long COVID” [8–12].

Epidemiological evidence shows that COVID-19 is less common and presents milder symptoms in the pediatric population [13–17]. Despite this, some children can develop multi-system inflammatory syndrome in children (MIS-C), a rare but severe and life-threatening complication, similar to Kawasaki disease and probably result from a hyper-inflammatory state that usually occurs weeks after the infection [18–21]. Most MIS-C patients require hospitalization and pediatric intensive care unit (PICU) admission [20–24], and a significant proportion of them present with neurologic manifestations [19, 21, 25, 26].

The pandemic has affected many patients with chronic diseases [27, 28]. Changes in the opportunity of care and treatments, the implementation of teledmedicine, quarantines, and homeschooling, also have had an impact on pediatric patients with neurologic diseases [29–31].

This review aims to summarize, discuss, and update the knowledge of the neurologic manifestations in the pediatric population affected by SARS-CoV-2 infection and MIS-C, and the pandemic’s effects in children with neurologic diseases.

**Neurologic manifestations associated with SARS-CoV-2 infection in children**

The neurologic features associated with SARS-CoV-2 infection in children are diverse and more common than previously suspected. In a systematic review published by Panda et al., 16.7% of 3707 patients presented with mild and non-specific neurologic manifestations. Only 1% had severe neurologic complications, such as encephalopathy, seizures, and meningeal signs. Other manifestations, such as intracranial hemorrhage, cranial nerve palsy, GBS, and vision problems, were even less frequent [32].

Sandoval et al. reported hospitalized children with neurologic manifestations associated with SARS-CoV-2 infection. Of 90 patients, 13 (14.4%) presented with new-onset neurologic symptoms. Central nervous system (CNS) symptoms were headache (61%), seizures (15.3%), encephalopathy (15.3%), and pyramidal signs (7.6%). Peripheral nervous system symptoms were muscle weakness (61.5%), hypoesthesia (23%), ageusia (15.3%), and anosmia (7.6%). It is noteworthy that in this series, 47% of MIS-C patients presented with neurologic manifestations that resolved as the systemic compromise subsided [25].

LaRovere et al. published findings from 1695 pediatric patients’ medical records hospitalized for MIS-C or COVID-19; 365 (22%) patients had neurologic involvement. Among them, 12% presented a severe and life-threatening neurologic condition, 26% of them died, and 40% survived with neurologic sequelae. The authors stated that the presence of neurologic symptoms in pediatric patients with severe COVID-19 conferred a greater risk of mortality. In this publication, about 35% of the patients who met MIS-C criteria had neurologic involvement. Moreover, 47% of the patients with life-threatening neurologic conditions presented with MIS-C [19]. Sa et al. reported 75 patients with MIS-C, nine (12%) of whom presented the following neurologic manifestations: altered consciousness, behavioral changes, focal neurologic deficits, persistent headache, hallucinations, hypersomnia, and new-onset focal seizures [33]. Some specific neurologic diagnoses and symptoms are mentioned repeatedly in different studies and deserve a more in-depth explanation.

**Guillain–Barré syndrome**

GBS is a varied group of immune-mediated polyneuropathies and is considered a classical neurologic post-infectious disease. The typical GBS presents with distal paresthesia, rapidly progressive ascending bilateral weakness of the extremities, and diminished or abolished tendon reflexes. GBS is frequently associated with dysautonomia and pain. *Campylobacter jejuni* is the primary pathogen associated with GBS. Others are *M. pneumoniae*, *Influenza* and *Zika* viruses. The estimated global incidence of GBS is between 0.8 and 1.9 cases per 100,000 inhabitants/year [34].

The first GBS case after COVID-19 was reported in January 2020 [35]. Since then, the number of published reports has grown exponentially. Palaiodimou et al. analyzed 18 observational studies, with a total of 136,746 COVID-19 patients, estimating an incidence of 15 GBS cases per 100,000 SARS-CoV-2 infections [36]. Comparing this relative incidence with other viruses, GBS related to SARS-CoV-2 infection was higher than influenza (7.3 cases per 100,000 infected) [37] and lower than Zika virus (20 cases per 100,000 infected) [38]. COVID-19 patients had an increased risk of demyelinating GBS, and the clinical outcomes were comparable to historical GBS controls. More studies are still needed to prove causality between COVID-19 and GBS, but the temporal association and the large number of reported cases suggest a strong correlation [36].

**Stroke**

Stroke is a neurologic syndrome characterized by focal deficits secondary to infarction or cerebral hemorrhage [39]. Known risk factors for this cerebrovascular disease include infections and inflammatory diseases, principally causing a secondary focal cerebral arteriopathy [40]. Other viruses have been associated with an increased incidence of stroke in children, including influenza and the varicella-zoster virus.
An increased risk for stroke in COVID-19 patients has been demonstrated, especially in the subgroups that required intensive treatment unit admission and in patients with encephalopathy [6, 40, 42]. In adults, COVID-19-related stroke has a reported incidence up to 7.5 times higher than influenza [43]. Even though most strokes secondary to COVID-19 have been reported in adults (0.9–2.0%) [40], there have also been reports of children presenting with predominantly ischemic stroke [7, 40, 44, 45]. In a systematic review of severe neurologic manifestations coexisting with SARS-CoV-2 infection in children by O’Loughlin et al., the most common neurologic manifestation was cerebrovascular disease (38 cases) including ischemic and hemorrhagic strokes, venous thrombosis, and cerebral arteriopathy [41]. Nonetheless, the incidence of pediatric stroke has not changed since the beginning of the pandemic, and most of the cases published so far had other risk factors for stroke. It seems that the infection by SARS-CoV-2 could be a contributing factor but not the causative one [40].

**Encephalitis, encephalopathy and seizures**

During Middle East respiratory syndrome (MERS) and Severe acute respiratory syndrome (SARS) previous outbreaks, a few encephalitis cases were reported [46]. Because SARS-CoV-2 has a similar viral structure, it could cause encephalitis. The proven presence of SARS-CoV-2 in cerebrospinal fluid (CSF) or brain tissue samples has been reported only in isolated cases [47–50]. Therefore, most encephalitis cases are probably due to an immune-mediated mechanism and not by direct invasion of the CNS [51]. Cases of anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis associated with SARS-CoV-2 infection have been reported across all ages and with various clinical manifestations, such as psychosis and status epilepticus [50, 52–57]. The pathogenesis of anti-NMDAR encephalitis associated with SARS-CoV-2 infection is presumed to be an antigen-mimicking mechanism, similar to other pathogens like herpes simplex virus, Toxoplasma gondii, and Epstein–Barr virus [58, 59].

About 15–25% of hospitalized pediatric patients with COVID-19 or MIS-C presented encephalopathy of variable severity [19, 25, 60]. Encephalopathy can be secondary to the systemic alterations commonly found in these patients, such as severe inflammation, hypoxia, metabolic or electrolyte disturbances, and multi-organ failure. These factors can produce loss of awareness, confusion, delirium, sleep-wake disorders, lethargy, irritability, and electroencephalographic alterations. Almost all the cases described worldwide had normal CSF analyses [61]. Interestingly, some of these patients had transient signal alterations on brain MRI studies at the corpus callosum splenium [19, 62]. Based on previous reports in patients with influenza and Kawasaki disease, the probable underlying mechanism is a focal intramyelin edema secondary to systemic inflammation. These neuroimaging findings were transient and were observed in patients presenting with fever, shock, and rash [62–65]. Patients presenting with encephalopathy, especially the ones with severe COVID-19 or MIS-C had increased mortality and worse outcomes. In this regard, there have also been reports of children presenting with encephalopathy as a sign of acute, and sometimes fatal, cerebral edema associated with COVID-19 [19, 41, 66, 67].

Seizures are a moderately frequent neurologic manifestation that occurs in approximately 20%–30% of hospitalized children with SARS-CoV-2 infection and neurologic symptoms [19, 32, 60]. About 70% of seizures occurred in patients with severe COVID-19 [32]. Most seizures occurred with fever or were symptomatic secondary to other acute conditions, making it difficult to assess if the seizures could be related to CNS involvement. In less severe cases, Kurd et al. reported an incidence of 6% of seizures (including cases of status epilepticus) as the main or initial symptom of COVID-19 of varieded severity (even respiratory asymptomatic) in children presenting to the emergency department, especially in those with prior neurologic diseases and older than 5 years old [68].

**Acute disseminated encephalomyelitis (ADEM)**

ADEM is a demyelinating immune-mediated disease that primarily affects children and usually develops weeks to months after a febrile infection. ADEM often has an acute onset and presents with encephalopathy (from behavioral changes to loss of consciousness), which can be associated with headache, fever, seizures, optic neuritis, ataxia, myelitis, and cranial nerve palsies [69]. Several cases resembling ADEM related to COVID-19 were reported, during the pandemic, curiously mostly in adults [70–74]. Possibly because of the higher COVID-19 incidence in adults, or that the increase of adult ADEM cases, usually rare, were simply more appealing to be published, leading us to believe that de ADEM cases in children could be underreported. In a multi-centric collaborative study, Lindan et al. described 16 children with ADEM-like neuroimaging findings related to SARS-CoV-2 infection. These cases had myelitis, neuritis, anti-NMDAR encephalitis, and antiMOG antibody presence on CSF samples, which reinforcing the possible association of COVID-19 and immune-mediated neurologic diseases [75]. In other reports, some of the ADEM cases developed hemorrhagic and necrotizing complications conferring on them extreme severity and even fatal outcomes in several cases [76–81]. The proposed mechanism of pathogenesis is
an autoimmune response due to a cross reaction by molecular mimicry with SARS-CoV-2 antigens [82].

**Muscle involvement**

The current literature contains many case reports of pediatric patients who presented with various symptoms that note muscle involvement, including myalgia, fatigue, and muscle weakness [4, 19, 25, 50, 62]. Furthermore, elevated creatine kinase titers have also been reported, and it is known that ACE2 is also expressed in skeletal muscle, suggesting that SARS-CoV-2 could cause viral myositis or rhabdomyolysis [83–85]. In addition, severe COVID-19 patients could develop critically ill myopathy owing to prolonged hospitalization, multiple-organ failure, mechanical ventilation, and use of corticosteroids or neuromuscular blockers [86, 87].

**Long COVID**

Long COVID syndrome is a new medical term referring to the persistence of symptoms after acute COVID-19. This syndrome includes post-acute COVID-19 (ongoing symptoms 4 to 12 weeks after the initial symptoms) and post-COVID-19 syndrome (lasting longer than 12 weeks) [11]. There are growing evidences of this syndrome in adults; however, in children, the information is limited. The neurologic manifestations described are cognitive complaints denominated as “brain fog” consisting mainly of attention and short-term and working memory disturbances (executive brain functions alterations), headache, numbness or tingling, dysgeusia, anosmia, myalgia, dizziness, pain, blurred vision, and tinnitus. Other non-neurologic symptoms have been reported, such as hair loss, fatigue, cough, shortness of breath, anxiety/depression, chest pain, night sweats, and palpitations [8, 10, 88]. 13%–52.7% of the children who have recovered from COVID-19 report at least one persisting symptom [10, 89]. The pathophysiological mechanisms of long COVID are not yet clear, but a diminished antibody activation, prolonged inflammatory response to the infection, or a re-infection have been proposed. It is important that this syndrome is recognized, managed, and rehabilitated on time, to offer a better quality of life to COVID-19 survivors [12, 90].

**Temporal relation between SARS-CoV-2 infection and neurologic involvement**

The diverse neurologic manifestations previously mentioned can develop at different times in relation to the infection. Some of these symptoms occur during COVID-19, and others appear a few weeks after the patient has recovered from it (Table 1).

### Neuro-pathophysiological mechanisms

The pathophysiology of the neurologic manifestations associated with SARS-CoV-2 is still under study. There are various hypotheses, some with more support than others, as listed below (Fig. 1).

#### Direct viral invasion

SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) and the transmembrane serine protease 2 (TMPRSS2) as receptors to bind to cells and to infect them. ACE2 is present in various CNS’ cells, and some glial cells express TMPRSS2 [65, 91–93]. Thus, it is plausible that SARS-CoV-2 could infect the CNS passing through a dysfunctional blood–brain barrier (BBB), or by the cranial nerves in a transsynaptic way [5, 65, 93]. However, most of SARS-CoV-2’s PCR performed in CSF and brain tissue yielded negative [61, 94]. Lewis et al. conducted a systematic review of CSF studies of 304 patients with confirmed COVID-19 and neurologic symptoms, and only a 6% positivity rate was found in this review [61]. This low detection rate could be because this mechanism has a lower relative incidence, or that the detection method is not sensitive enough.

#### Table 1 Main neurologic manifestations according to temporal presentations

| Time of Onset                | Manifestations                                                                 |
|------------------------------|-------------------------------------------------------------------------------|
| During COVID-19 or active infection | Headache, Anosmia-hyposmia, Ageusia-hypogeusia, Myalgia, Muscular weakness-Fatigue, Seizures, Febrile Seizures, Encephalopathy, Meningoencephalitis, Myositis, Stroke |
| Post-COVID-19 (weeks to months after) | Autoimmune Encephalitis, GBS, Polyneuropathy, ADEM, Executive brain functions alteration (Long COVID)\textsuperscript{a} |

\textsuperscript{a}Mainly reported in adults

**GBS** Guillain–Barré syndrome, **ADEM** acute disseminated encephalomyelitis
Immune system dysregulation

SARS-CoV-2 can induce a hyper-inflammatory state, primarily through cytokine storm and macrophagic activation. This immune dysregulation is associated with high levels of inflammatory biomarkers, such as C-reactive protein, erythrocyte sedimentation rate, fibrinogen, d-dimer, ferritin, interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α) and procalcitonin [15, 65], and could be the pathophysiological basis of MIS-C and other immune-mediated complications of COVID-19. The hyper-inflammatory state can cause non-specific neurologic symptoms, including headache and muscular weakness. The exacerbation of the immune system may also generate BBB disruption. Together, both processes would allow the entry of the virus, immune cells, cytokines, and antibodies to the nervous system [5, 15, 93, 95, 96]. This theory could explain symptoms like encephalopathy and reports of immune-mediated diseases like anti-NMDAR encephalitis or ADEM, or GBS [96].

Prothrombotic state

COVID-19 is associated with an increased generalized risk of thrombotic complications, especially in critically ill patients [97]. The immune dysregulation brought principally by IL-6 and TNF-α can lead to a prothrombotic state and endothelial dysfunction. This could produce vasculitis and vascular disruption, affecting the basement membrane and causing activation of the clotting cascade [65, 93, 97]. Together, these factors could explain the occurrence of ischemic events, such as stroke, in patients with SARS-CoV-2 infection [6].

Multi-systemic failure

Patients with moderate to severe COVID-19 have a higher risk of kidney and liver dysfunction, associated with metabolic and electrolyte disturbances. They frequently present with hypoxia, fever, and hypotension. All of these factors may cause diverse
neurologic symptoms, such as seizures and encephalopathy [5, 95, 98–102].

**Impact of COVID-19 and pandemic management measures on patients with known neurologic diseases**

The pandemic has affected patients with chronic diseases, making it challenging to access controls, treatment, and therapies. Furthermore, in-hospital care and procedures have been postponed owing to the greater need for beds for COVID-19 patients [27, 28]. Pediatric patients with neurologic diseases are not the exception. Here we emphasize the impact of COVID-19 and its pandemic in some of these diseases.

**Epilepsy**

The current pandemic has changed how pediatric epilepsy teams study, control, and treat patients with epilepsy. In many hospitals, telemedicine has replaced in-person evaluations [103], and the number of electroencephalograms performed has been reduced as well as neuroimaging availability. Secondly, the use of corticosteroids in infantile spasms syndrome and the performance of epilepsy surgery programs have been delayed. Patients and their caregivers also have been avoiding attending healthcare centers, emergency units, and pharmacies for fear of getting infected. In many cases they might have chosen to self-medicate or cease their treatment. Together, these situations put patients with epilepsy at long-term risk of not achieving seizure control [30, 104, 105].

Evidence shows that a greater risk of getting COVID-19 is not associated with epilepsy itself but with its comorbidities and other associated factors (for example, presenting chronic diseases or being in nursing homes). It has been proposed that, as with other viral diseases, SARS-CoV-2 infection can cause an increase in seizure frequency. In addition, emotional stress is also known to worsen seizure burden. Patients with epilepsy have a slightly increased morbidity and mortality associated with COVID-19 [106]. While symptomatic seizures have been proven to appear in patients with COVID-19, the incidence of epilepsy as a long-term complication is still unknown. Prolonged follow-up is needed to clarify this point [107].

**Cerebral palsy and neuromuscular diseases**

Patients with cerebral palsy (CP) and neuromuscular diseases (NMD) have also been affected during the pandemic. Cities’ restrictive lockdowns and hospitals reaching their total capacity have limited access to therapies and procedures of these patients [108, 109]. In addition, these patients are more susceptible to severe respiratory infections and to increased PICU admission than the general population [98]. Fear of SARS-CoV-2 infection, particularly in parents, may have caused them to refrain from going to the hospital with their children. It is important to note that various diseases, such as Duchenne’s muscular dystrophy, spinal muscular atrophy, and multiple sclerosis, are treated with corticosteroids and immuno-suppressants, which are likely associated with a greater risk of severe infections [31, 98].

Down syndrome (DS) is associated with a diminished immune response, which increases the risk of having a more severe SARS-CoV-2 infection [110]. According to Emes et al., patients with DS and advanced age, obesity, or epilepsy had a higher hospitalization rate. Mortality rates in children with DS and COVID-19 were lower (0–6.7%) than in adults with DS (12%) [111]. On the other hand, it is more difficult for children with DS to comply with preventive measures, such as the use of a mask, physical distancing [112].

**Attention deficit and hyperactivity disorder, autism spectrum disorder, and intellectual disability**

The lifestyle changes secondary to the pandemic have affected the entire population, especially children with neurodevelopmental disorders and intellectual disabilities. The difficulties in expressing their feelings and accepting changes in their routines could produce psychological stress that would exacerbate symptoms and even lead to loss of acquired skills and learnings [98]. In addition, adapting schools into online learning modalities and homeschooling education has been hard to implement in children with neurodevelopmental disorders owing to their rigid thinking and their difficulties in maintaining focus. Home learning also interferes with improving social skills by reducing children’s social interactions [113–115].

**Conclusions**

Although infrequent, numerous neurologic manifestations have been associated with children’s SARS-CoV-2 infection in the last year. These manifestations can be present during COVID-19 or weeks after recovering from it. It is important to identify and give them proper and opportune treatment because they can be potentially grave and life-threatening; some can lead to long-lasting sequelae and can alter quality of life. Various neuro-pathophysiological mechanisms have been proposed, such as direct virus invasion, hyper-inflammatory reactions, associated multi-systemic failure,
prothrombotic states, and immune-mediated processes. However, a causal relationship between SARS-CoV-2 infection and neurologic manifestations remains to be proven.

Patients with neurologic diseases are especially affected by COVID-19, not only by the disease itself but also by its complications and pandemic management measures. We want to counsel the medical communities who care for this group of children that evaluation of this matter in all its domains is needed to give better care for our patients. It remains to be seen whether this neurologic involvement could cause neurologic sequelae or neurodevelopmental alterations. It is still unknown if the ongoing vaccination in the pediatric population could reduce the incidence of the neurologic manifestations found thus far.

Acknowledgements We would like to thank Enzo Pérez, Ph.D., Department of Anatomy and Cell Biology, Western University of Ontario for his contributions to this review.

Author contributions CV: conceptualization, methodology, data collection and formal analysis, writing original draft. GM: data collection and formal analysis, writing original draft, writing and formal analysis, writing original draft, writing review and editing. NS: data collection and formal analysis, writing original draft. KJ: writing original draft, writing review and editing, visualization and figure creation. FS: conceptualization (lead), methodology, writing original draft, writing review and editing, project administration and supervision.

Funding Not applicable.

Data availability All relevant data are within the paper and its supporting information.

Code availability Not applicable.

Declarations

Ethical approval Not applicable.

Conflict of interest No financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

References

1. World Health Organization. WHO COVID-19 Dashboard. (2020). https://covid19.who.int/. Accessed 14 Nov 2021.
2. Rajapakse N, Dixit D. Human and novel coronavirus infections in children: a review. Paediatr Int Child Health. 2021;41:36–55.
3. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. Lancet Neurol. 2020;19:767–83.
4. Paterson RW, Brown RL, Benjamin L, Nortley R, Wiethoff S, Bharucha T, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain. 2020;143:3104–20.
5. Schober ME, Pavia AT, Bohnsack JF, Robertson CL, Wainwright MS, Roa JD, et al. Neurologic manifestations of COVID-19 in children: emerging pathophysiologic insights. Pediatr Crit Care Med. 2021;22:655–61.
6. Taquet M, Geddes JR, Hussain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. The Lancet Psychiatry. 2021;8:416–27.
7. Kléneberg NN, Knauss S, Gülke E, Pinnischmidt HO, Jakob CEM, Lingor P, et al. Neurological symptoms and complications in predominantly hospitalized COVID-19 patients – results of the European multinational LEOSS registry. Eur J Neurol. 2021;28:3925–37.
8. Graham EL, Clark JR, Orban ZS, Lim PH, Szymanski AL, Taylor C, et al. Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized Covid-19 “long haulers.” Ann Clin Transl Neurol. 2021;8:1073–85.
9. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. Sci Rep. 2021;11:16144.
10. Radtke T, Ulyte A, Puhna MA, Kriemler S. Long-term symptoms after SARS-CoV-2 infection in children and adolescents. JAMA. 2021;32:869–71.
11. Yan Z, Yang M, Lai C-L. Long COVID-19 syndrome: a comprehensive review of its effect on various organ systems and recommendation on rehabilitation plans. Biomedicines. 2021;9:966.
12. Outhoff K. Sick and tired of COVID-19: long haulers and post viral (fatigue) syndromes. South African Gen Pract. 2020;1:132–3.
13. Cui X, Zhao Z, Zhang T, Guo W, Guo W, Zheng J, et al. A systematic review and meta-analysis of children with coronavirus disease 2019 (COVID-19). J Med Virol. 2021;93:1057–69.
14. Ranabothu S, Onteddu S, Nalleballe K, Dandu V, Veerapaneni K, Veerapanidiyan A. Spectrum of COVID-19 in children. Acta Paediatr. 2020;109:1899–900.
15. Stafstrom CE, Jantzie LL. COVID-19: Neurological considerations in neonates and children. Children. 2020;7:133.
16. García-Vera C, Castejón-Ramírez S, Lain Miranda E, Hernández Abadía R, García Ventura M, Borque Navarro E, et al. COVID-19 in children: clinical and epidemiological spectrum in the community. Eur J Pediatr. 2022;181:1235–42.
17. Moreira A, Chorath K, Rajasekaran K, Burmeister F, Ahmed M, Moreira A. Demographic predictors of hospitalization and mortality in US children with COVID-19. Eur J Pediatr. 2021;180:1659–63.
18. Radia T, Williams N, Agrawal P, Harman K, Weale J, Cook J, et al. Multi-system inflammatory syndrome in children and adolescents (MIS-C): a systematic review of clinical features and presentation. Paediatr Respir Rev. 2021;38:51–7.
19. LaRovere KL, Riggs BJ, Poussaint TY, Young CC, Newhams MM, Maamari M, et al. Neurologic Involvement in children and adolescents hospitalized in the United States for COVID-19 or multisystem inflammatory syndrome. JAMA Neurol. 2021;78:536–47.
20. Hoste L, Van Paemel R, Haerwynck F. Multisystem inflammatory syndrome in children related to COVID-19: a systematic review. Eur J Pediatr. 2021;180:2019–34.
21. Bordet J, Perrier S, Olexa C, Gerout A-C, Billaud P, Bonnemains L. Paediatric multisystem inflammatory syndrome associated with COVID-19: filling the gap between myocarditis and Kawasaki? Eur J Pediatr. 2021;180:877–84.
22. Torres JP, Izquierdo G, Acuña M, Pavez D, Reyes F, Fritis A, et al. Multisystem inflammatory syndrome in children (MIS-C):
report of the clinical and epidemiological characteristics of cases in Santiago de Chile during the SARS-CoV-2 pandemic. Int J Infect Dis. 2020;100:75–81.

23. Pignatelli R, Antona CV, Rivera IR, Zenteno PA, Acosta YT, Tagarro A, Cobos-Carrascosa E, Villaverde S, Sanz-Santacuefemia F-J, Grasa C, Soriano-Aranedes A, et al. Clinical spectrum of COVID-19 and risk factors associated with severity in Spanish children. Eur J Pediatr. 2021;180:2879–88.

24. Tagarro A, Cobos-Carrascosa E, Villaverde S, Sanz-Santacuefemia F-J, Grasa C, Soriano-Aranedes A, et al. Clinical spectrum of COVID-19 and risk factors associated with severity in Spanish children. Eur J Pediatr. 2021;181:1105–15.

25. Sandofal F, Julio K, Méndez G, Valderas C, Echeverría AC, Perinetti MJ, et al. Neurologic features associated with SARS-CoV-2 infection in children: a case series report. J Child Neurol. 2021;36:853–66.

26. Nepal G, Shrestha GS, Rehrig JH, Gajurel BP, Ojha R, Agrawal L, et al. Neurological manifestations of COVID-19 associated multi-system inflammatory syndrome in children: a systematic review and meta-analysis. J Nepal Health Res Counc. 2021;19:10–8.

27. Chudasama YV, Gillies CL, Zaccardi F, Coles B, Davies MJ, Kendzerska T, Zhu DT, Gershon AS, Edwards JD, Peixoto C, Wirrell EC, Grinspan ZM, Knupp KG, Jiang Y, Hammeed B, Panda PK, Sharawat IK, Panda P, Natarajan V, Bhakat R, Dawood MA, Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American heart association/American stroke association. Stroke. 2013;44:2064–89.

28. Beslow LA, Linds AB, Fox CK, Kossorotoff M, Zuñiga Zambrano YC, Hernández-Chávez M, et al. Pediatric ischemic stroke: an infrequent complication of SARS-CoV-2. Ann Neurol. 2021;89:657–65.

29. 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;13:410–27.

30. Khosravi B, Moradveis B, Abedini M, Behzadi S, Karimi A. Stroke in a child with SARS-CoV-2 infection: a case report. eNeurologicalsci. 2021;23:100345.

31. Yaghi S, Ishida K, Torres J, Mac Gory B, Raz E, Humbert K, et al. SARS-CoV-2 and stroke in a New York healthcare system. Stroke. 2020;51:2002–11.

32. Nannoni S, de Groot R, Bell S, Markus HS. Stroke in COVID-19: a systematic review and meta-analysis. Int J Stroke. 2021;16:137–49.

33. Sweid A, Hammoud B, Bekelis K, Missios S, Tjomakaris SI, Gooch MR, et al. Cerebral ischemic and hemorrhagic complications of coronavirus disease 2019. Int J Stroke. 2020;15:733–42.

34. Alshebri MS, Alshouimi RA, Alhumidi HA, Alshaya AH, Alshebri MS, Alshouimi RA, Alhumidi HA, Alshaya AH. Neurological complications of SARS-CoV, MERS-CoV, and COVID-19. SN Compr Clin Med. 2020;2:2037–47.

35. Huang YH, Jiang D, Huang JT. SARS-CoV-2 detected in cerebrospinal fluid by PCR in a case of COVID-19 encephalitis. Brain Behav Immun. 2020:87:149.

36. Paniz-Mondolfi A, Bryce C, Grimes Z, Gordon RE, Reidy J, Ledinsky J, et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). J Med Virol. 2020;92:699–702.

37. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-CoV-2. Int J Infect Dis. 2020;94:55–8.

38. Sánchez-Morales AE, Urrutia-Osorio M, Camacho-Mendoza E, Rosales-Pedraza G, Dávila-Maldonado L, González-Duarte A, et al. Neurological manifestations temporally associated with SARS-CoV-2 infection in pediatric patients in Mexico. Child’s Nerv Syst. 2021;37:2305–12.

39. Abenza Abildúa MJ, Atienza S, Carvalho Monteiro G, Erro Aguirre ME, Imaz Aguayo L, Freire Alvarez E, et al. Encefalopatías y encefalitis durante la infección aguda por SARS-CoV2. Registro de la Sociedad Española de Neurología SEN COVID-19. Neuroligía. 2021;36:127–34.

40. Burr T, Barton C, Doll E, Lakhotia A, Sweeney M. N-methyl-D-aspartate receptor encephalitis associated with COVID-19 infection in a toddler. Pediatr Neurol. 2021;14:75–6.

41. Sarigecili E, Arslan I, Ucar HK, Celik U. Pediatric anti-NMDA receptor encephalitis associated with COVID-19. Childs Nerv Syst. 2021;37:3919–22.

42. Panariello A, Bassetti R, Radice A, Rossotti R, Puoti M, Corradin M, et al. Anti-NMDA receptor encephalitis in a psychiatric Covid-19 patient: a case report. Brain Behav Immun. 2020;87:179–81.

43. Zandifar A, Baddrfam R, COVID-19 and anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis: are we facing an increase in the prevalence of autoimmune encephalitis? J Med Virol. 2021;93:1913–4.

44. McHattie AW, Coobergh J, Khan F, Morgante F, Palilalia as a prominent feature of anti-NMDA receptor encephalitis in a woman with COVID-19. J Neurol. 2021;268:3995–7.
57. Monti G, Giovannini G, Marudi A, Bedin R, Melegari A, Simone AM, et al. Anti-NMDA receptor encephalitis presenting as new onset refractory status epilepticus in COVID-19. Seizure. 2020;81:18–20.
58. Hou R, Wu J, He D, Yan Y, Li L. Anti-N-methyl-d-aspartate receptor encephalitis associated with reactivated Epstein-Barr virus infection in pediatric patients. Medicine (Baltimore). 2019;98:e15726.
59. Nosadini M, Mohammad SS, Corazza F, Ruga EM, Kothur K, Perirlingo G, et al. Herpes simplex virus-induced anti-N-methyl-d-aspartate receptor encephalitis: a systematic literature review with analysis of 43 cases. Dev Med Child Neurol. 2017;59:796–805.
60. Ray STJ, Abdel-Mannan O, Sa M, Fuller C, Wood GK, Pysden K, 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;5:631–41.
61. Lewis A, Frontera J, Placantonakis DG, Lighter J, Galetta S, Balcer L, et al. Cerebrospinal fluid in COVID-19: a systematic review of the literature. J Neurol Sci. 2021;421:117316.
62. Abdel-Mannan O, Eyme R, Löbel U, Bamford A, Eltze C, Tada H, Takanashi J, Barkovich AJ, Oba H, Maeda M, Tatsuki H, et al. Neuroimaging. 2017;27:549–61.
63. Lin JE, Asfour A, Sewell TB, Hooe B, Pryce P, Earley C, et al. Neurological involvement associated with COVID-19. Neurosci Lett. 2021;743:135567.
64. Fragozo DC, Marx C, Dutra BG, da Silva CJ, da Silva PM, Martins Maia Junior AC, et al. COVID-19 as a cause of acute neonatal encephalitis and cerebral cytotoxic edema. Pediatr Infect Dis. 2021;40:e270-1.
65. Chen T-H. Neurological involvement associated with COVID-19 in children. J Neurol Sci. 2020;418:117096.
66. Kurud M, Hashavya S, Benenson S, Gilboa T. Seizures as the main presenting manifestation of acute SARS-CoV-2 infection in children. Seizure. 2021;92:89–93.
67. Pohl D, Alper G, Van Haren K, Kornberg AJ, Lucchinetti CF, Balcer L, et al. Cerebrospinal fluid in COVID-19: a systematic synthesis of worldwide cases. J Neuroimmunol. 2021;359:577674.
68. Saud A, Naveen R, Aggarwal R, Gupta L. COVID-19 and myositis: what we know so far. Curr Rheumatol Rep. 2021;23:63.
69. Singh B, Kaur P, Mechina A, Maroules M. Rhabdomyolysis in COVID-19 infection in children. J Neurol Sci. 2020;418:117096.
70. Suh J, Amato AA. Neuromuscular complications of coronavirus disease-19. Curr Opin Neurol. 2021;34:669–74.
71. Buonsenso D, Munblit D, De Rose C, Sinatti D, Ricchiuto A, Rubino F, et al. Critical illness myopathy after COVID-19. Int J Infect Dis. 2020;99:276–8.
72. Kayim Yildiz O, Yildiz B, Avci O, Hasbek M, Kanat S. Clinical, neurophysiological and neuroimaging findings of critical illness myopathy after COVID-19. Curr. 2021;13:e13807.
73. Crook H, Raza S, Nowell J, Edsow P. Long covid—mechanisms, risks factors, and management. BMJ. 2021;374: n1648.
74. Bagnato S, Boccagni C, Marino G, Prestandreca D, Agostino T, Rubino F, et al. Critical illness myopathy after COVID-19. Acta Paediatr. 2021;110:2208–11.
75. Al-Jahdhami I, Al-Naamani K, Al-Mawali A. The post-acute COVID-19 syndrome (Long COVID). Oman Med J. 2021;36:1–2.
invasion of SARS-CoV-2: a critical systematic review. Eur J Neurol. 2021;28:3856–65.

95. Maury A, Lyoubi A, Peiffer-Smadja N, de Broucker T, Meppiel E. Neurological manifestations associated with SARS-CoV-2 and other coronaviruses: a narrative review for clinicians. Rev Neurol (Paris). 2021;177:51–64.

96. Franke C, Ferse C, Kreye J, Reinecke SM, Sanchez-Sendin E, Rocco A, et al. High frequency of cerebrospinal fluid autoantibodies in COVID-19 patients with neurological symptoms. Brain Behav Immun. 2021;93:415–9.

97. Smadja DM, Mentzer SJ, Fontenay M, Laffan MA, Ackermann M, Helms J, et al. COVID-19 is a systemic vascular hemopathy: insight for mechanistic and clinical aspects. Angiogenesis. 2021;24:755–88.

98. Boronat S. Neurologic care of COVID-19 in children. Front Neurol. 2021;11:1–8.

99. Kanberg N, Ashton NJ, Andersson L-M, Yilmaz A, Lindh M, Nilsson S, et al. Neurochemical evidence of astrocytic and neuronal injury commonly found in COVID-19. Neurology. 2020;95:1754–9.

100. Hennon TR, Penque MD, Abdul-Aziz R, Alibrahim OS, McGreevy MB, Prout AJ, et al. COVID-19 associated multisystem inflammatory syndrome in children (MIS-C) guidelines: a Western new York approach. Prog Pediatr Cardiol. 2020;57:101232.

101. Solomon IH, Normandin E, Bhattacharyya S, Mukerji SS, Keller K, Ali AS, et al. Neuropathological features of Covid-19. N Engl J Med. 2020;383:989–92.

102. Thakur KT, Miller EH, Glendinning MD, Al-Dalahmah O, Banu MA, Boehme AK, et al. COVID-19 neuropathology at Columbia university irving medical center/New York presbyterian hospital. Brain. 2021;144:706–708.

103. Brigo F, Bonavita S, Leocani L, Tedeschi G, Lavorgna L. Telerehabilitation and the challenge of epilepsy management at the time of COVID-19 pandemic. Epilepsy Behav. 2020;110:107164.

104. Kuroda N. Epilepsy and COVID-19: Updated evidence and narrative review. Epilepsy Behav. 2021;116:107785.

105. Cui S, Zhang C, Wang S, Zhang X, Wang L, Zhang L, et al. Experiences and attitudes of elementary school students and their parents toward online learning in China during the COVID-19 pandemic: questionnaire study. J Med Internet Res. 2021;23:e24496.

106. Zhang J, Shuai L, Yu H, Wang Z, Qiu M, Lu L, et al. Acute stress, behavioural symptoms and mood states among school-age children with attention-deficit/hyperactive disorder during the COVID-19 outbreak. Asian J Psychiatr. 2020;51:102077.

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