



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

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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 telemedicine, 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%), hypo/areflexia (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

[41]. 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 varied 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

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) ^a

^aMainly reported in adults *GBS* Guillain–Barré syndrome, *ADEM* acute disseminated encephalomyelitis

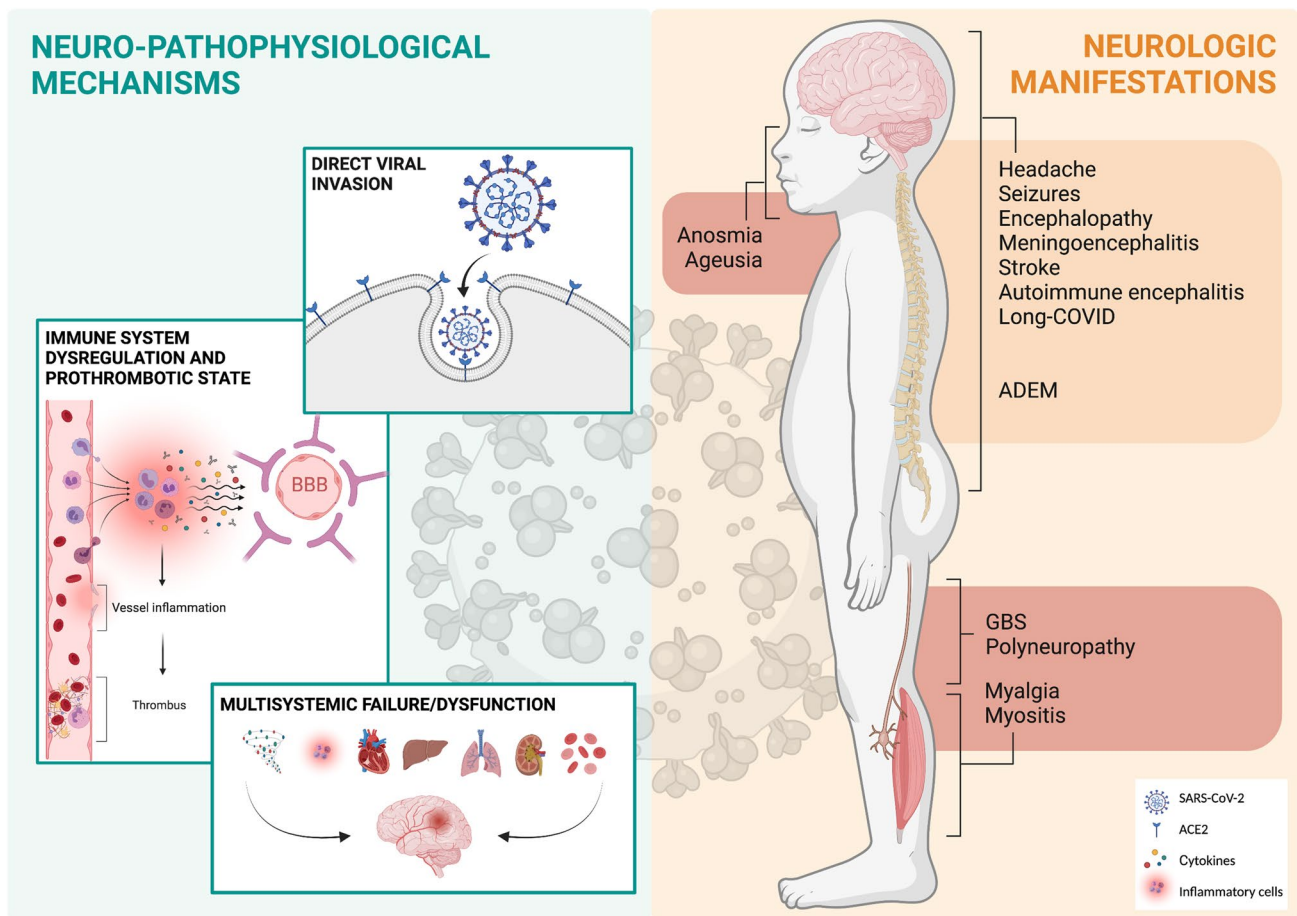


Fig. 1 Main neurologic manifestations associated with SARS-CoV-2 infection in children and possible neuro-pathophysiological mechanisms. ACE2 angiotensin-converting enzyme 2, BBB blood-brain barrier. Created with BioRender.com (reprint copyright obtained)

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.

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