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Editor's Choice

INVITED REVIEW

Neurological effects of COVID-19 in infants and children

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Abstract

Neurological manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in children are becoming increasingly apparent as the coronavirus disease (COVID-19) pandemic continues. While children manifest relatively milder features of the disease, accumulating evidence warrants concern that COVID-19 exacts both acute- and long-term effects on the developing central and peripheral nervous systems. This review focuses on the relatively underinvestigated topic of the effects of SARS-CoV-2 on the brain in infancy and childhood, concluding that clinicians should be attentive to both the acute effects and long-term consequences of COVID-19 from a neurological perspective.

The ongoing coronavirus disease (COVID-19) pandemic, caused by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to cause unprecedented disease with medical, social, and economic challenges across the globe. As of 4th February 2022, more than 388 million cases have been confirmed worldwide, with over 5.7 million deaths (https://coronavirus.jhu.edu/map.html). The pandemic is proving to be dynamic, with new challenges arising as new viral variants emerge. The number of vaccinated adults, while increasing, is insufficient to achieve herd immunity. A higher percentage of cases is now being reported in adolescents, children, and infants, especially with the currently predominant Omicron variant (98.3% of all new cases in the USA for the week ending 8th January 2022; https://covid.cdc.gov/covid-data-tracker). For much of the past 2 years, children accounted for only a few percent of cases, less than 5% in most areas, but some recent reports cited the pediatric age group as accounting for 15% or more of confirmed cases.[1–3] Fortunately, the severity of the illness in children is often relatively mild, but children can contract severe disease and can transmit the disease to others. Hospitalization rates for children are below 2% (although rising) and the mortality rate is under 1%.[4] Among newborns- to 17-year-olds, the hospital admission rate per 100 000 population was 0.19 on 30th November 2021 and 1.2 on 11th January 2022 (https://covid.cdc.gov/covid-data-tracker). Pediatric case numbers are expanding for many reasons, among them that more children are being tested, although the number of pediatric cases is likely to be underestimated because mildly symptomatic or asymptomatic children may not undergo testing.[5] New variants of the virus may affect different age groups differently. Children with underlying medical comorbidities, including neurological disease, are at higher risk for severe COVID-19 manifestations.

While COVID-19 predominantly affects the pulmonary system, it is now abundantly clear that this is a multisystem disease with manifestations and sequelae that involve multiple organ systems. Neurological manifestations were initially thought to be quite rare; however, over time they have become increasingly recognized in both adults[6–13] and children.[14–24] The reported neurological symptoms are wide-ranging, from non-specific to specific, across the lifespan. A meta-analysis of COVID-19 in children noted that 16.7% of 3707 patients reviewed had non-specific neurological symptoms (headache, myalgia, fatigue), with other (specific) neurological deficits being much less prevalent (approximately 1% with encephalopathy, seizures, or meningeal signs).[25] Other reviews found a similar spectrum of

Abbreviations: ADEM, Acute disseminated encephalomyelitis; CSF, Cerebrospinal fluid; MIS-C, Multisystem inflammatory syndrome of children; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.

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nervous system disorders and rates of involvement, with severely ill children manifesting greater neurological morbidity.[19] Children with multisystem inflammatory syndrome of children (MIS-C) (also called pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2), considered to be a postinfectious hyperinflammatory condition related to SARS-CoV-2 infection, is also associated with a high frequency of neurological adjuncts (including status epilepticus, focal deficits, headache, hallucinations, and encephalopathy), ranging from 12% to 50%, depending on illness severity and inclusion criteria.[21,26–29] Based on the increasing number of SARS-CoV-2 infections and their severity in children, neurological manifestations cannot be ignored in the diagnosis, treatment, and management of this subpopulation.[30,31]

This review considers current data regarding the neurological adjuncts of COVID-19 in children, with an emphasis on infants (defined as the first year of life in this review). While potential neurological impairments should be considered at any age, the particular vulnerability of infants to the disease has not been discussed extensively and the biological complexities of the developing central and peripheral nervous systems warrant focused consideration. Four topics are discussed, updating a previous comprehensive review:[14] the possibility of vertical transmission of the virus from mother to fetus; neurological manifestations in infants and children; potential mechanisms of neurological involvement in the developing brain; and dynamic aspects of COVID-19 in the pediatric age group, such as the role of vaccines, virus variants, and long-term neurological and neuropsychiatric effects. Clearly, any conclusions stated in this review may need revision over time given the constantly changing landscape of COVID-19.

What this paper adds

- Vertical transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from mother to fetus is extremely rare.
- Similar but milder neurological dysfunction occurs in infants and children compared with adults.
- There is no definitive evidence that SARS-CoV-2 invades the central nervous system.
- Long-term neurological and psychiatric effects of coronavirus disease are emerging.
- No data are yet available on variant-specific neurological effects of SARS-CoV-2.

VERTICAL TRANSMISSION

Even in the early stages of the pandemic, SARS-CoV-2 rarely affected neonates and lack of maternal vertical transmission was widely reported. That observation has largely held over the past 2 years. While a few case reports implicated transplacental or vertical transmission,[32,33] suggesting proof of principle, recent case series continue to document its rarity.[34–41] This situation is completely unlike that of strongly neurotropic viruses such as Zika virus.[42] Neonates testing positive for SARS-CoV-2 soon after delivery are most likely to have been infected during parturition or postpartum and were usually asymptomatic or presented with mild-to-moderate medical complications, mainly fever, gastrointestinal problems, or respiratory distress.[43,44] Although community acquisition of SARS-CoV-2 after birth is the most likely scenario, this issue is controversial and the possibility of vertical transmission cannot be dismissed.[45] This is an important question because of the known neurodevelopmental impact of ascending infections in the maternal–fetal axis.[46] In any case, treatment of affected neonates is largely supportive and long-term outcomes are uncertain, although most neonates with documented SARS-CoV-2 infection have mild disease and survive. Important remaining questions about the consequences of maternal COVID-19 infection include the effects of infection in the first and second trimesters (most reports have focused on third trimester infections), the role of COVID-19 in preterm birth, and the long-term neurodevelopmental consequences of exposure to SARS-CoV-2 even in the absence of overt postnatal infection. Some of the outstanding questions about COVID-19 and neonates are posed in Table 1.

NEUROLOGICAL MANIFESTATIONS IN INFANTS AND CHILDREN

Overview

Neurological manifestations of COVID-19 are diverse across the lifespan (Table 2). These can be divided into nonspecific (e.g. headache, myalgia, fatigue, somnolence) and specific (encephalopathy, stroke, seizures, meningeal signs). Outcomes can now be categorized into acute, post-acute, and long-term.

Until recently, our understanding of neurological involvement in COVID-19 has been based mainly on case reports and anecdotes. The initial and most highly cited report of neurological manifestations of SARS-CoV-2 described 214 hospitalized adult patients, 36.4% of whom manifested a variety of neurological symptoms such as dizziness, headache, altered consciousness, acute cerebrovascular disease, and ataxia, with a higher proportion of impairments occurring in more severely ill patients.[6] That paper drew attention to the neurological adjuncts of COVID-19 and subsequent reports have relied heavily on its assumptions. However, those patients were severely ill and do not reflect the full disease spectrum, especially in children. Subsequent case series and reviews have elucidated some of these early conclusions[17] but many knowledge gaps remain, in part due to the variability of study methodologies and many other confounding factors.[47]

TABLE 1 Clinical questions related to COVID-19 during pregnancy and birth

Clinical question	Comments (and selected studies)
Is pregnancy a risk factor for COVID-19?	Controversial but possible; related to immune factors during pregnancy[117–119]
Does maternal COVID-19 increase the risk for preterm birth?	Reported[41]
Have complications during labor been reported?	Generally manageable with optimal obstetric care[120,121]
Is vertical transmission a feature?	Extremely rare[39,40]
Is there a risk of perinatal infection?	Mostly postnatal exposure[35]
Is SARS-CoV-2 transmitted via breast milk?	Unlikely[34,122–124]
Does COVID-19 have an impact in pregnant mothers on neurodevelopment in the offspring?	Uncertain; requires considerable further study[102,103]

Abbreviations: COVID-19, coronavirus disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Among newborn infants with COVID-19 who exhibit neurological features, clinical manifestations are quite varied and can involve the entire neuraxis, affecting the central nervous system (CNS), the peripheral nervous system, or both. Some neonatal series described no neurological concerns.[43,48] When neurological symptoms are present in neonates, they often include irritability and lethargy, which are non-specific and do not address the localization of the disease process or its mechanism. In one febrile term infant, born to a mother with COVID-19, rectal and nasopharyngeal swabs were positive for SARS-CoV-2. Lethargy, 'hyperexcitability', and a high-pitched cry began about 24 hours after birth leading the authors to conclude that the cause was encephalitis, although the cerebrospinal fluid (CSF) did not show the SARS-CoV-2 virus or viral RNA and cranial ultrasonography was normal.[49] In other case reports, two newborn infants, aged 3 weeks and 6 weeks, presented with suspected seizures in the context of respiratory symptoms and had positive polymerase chain reaction with reverse transcription for SARS-CoV-2 in the blood and nasopharynx but not in the CSF.[50,51]

Larger data-based clinical series are now appearing, providing expanded information about COVID-19 in young children. A large, registry-based series of hospitalized children and adolescents with COVID-19 or MIS-C described neurological involvement in 365 of 1695 patients (22%) from 52 sites.[29] The 22% of patients with neurological involvement were more likely to have had underlying neurological conditions compared with those without previous neurological disease, but many previously healthy children were also affected. Neurological problems (such as encephalitis, encephalopathy, stroke, and acute disseminated encephalomyelitis [ADEM]) were transient in most children (88%) but 43 of the 365 children (12%) developed 'life-threating' neurological conditions (e.g. severe encephalopathy or CNS infection, fulminant cerebral edema); of those 43 children, 11 died and 17 had new neurological sequelae at the time of hospital discharge. Among the 616 children (36%) who met the criteria for MIS-C, a similar number presented with and without neurological symptoms (approximately 35% each). From the data provided, it is not possible to discern how many of the reported patients were neonates or infants but most were beyond infancy and the interquartile age range was 2 years 5 months to 15 years 4 months. Three of the 43 children with life-threatening neurological involvement were infants; one infant presented with each of the following: severe encephalopathy, CNS infection/ADEM, and status epilepticus/severe cerebral edema (culminating in death). The long-term neurological consequences in this cohort are not yet known.

A prospective national cohort in the UK included 1334 children with COVID-19, 51 (3.8%) of whom had neurological abnormalities at presentation.[20] About half of the children met the criteria for MIS-C. Those without MIS-C had a high prevalence of status epilepticus (26%), encephalitis (18.5%), or Guillain–Barré syndrome (18.5%), while those with MIS-C more often had multiple CNS abnormalities, including findings seen in the non-MIS-C group plus a higher prevalence of peripheral nervous system disorders (40%), encephalopathy, and behavioral dysfunction. Furthermore, children severely ill with MIS-C more often required intensive care. Despite some of the differences in presenting symptoms, the authors concluded that children in both the MIS-C and non-MIS-C groups fared rather well, although approximately one-third in each group had some disability at hospital discharge. Of the 51 children studied, the youngest were 12 months and 13 months of age; both had ADEM/encephalitis, one had a 'favorable' outcome and the other's gait regressed from walking to crawling at the time of the follow-up assessment (at hospital discharge). Another outcome study from the UK assessed 46 children with MIS-C at 6 weeks and 6 months after hospital admission.[52] The authors found complete resolution of inflammatory markers and symptoms at the 6-month assessment, and, using the Expanded Disability Status Scale, there was minimal motor function impairment. However, the children demonstrated significant emotional difficulties and muscle fatigue, attesting to long-lasting post-acute manifestations. According to Centers for Disease Control and Prevention data, infants under 1 year of age comprise about 4% of patients with MIS-C.[53] The course and severity of infants with MIS-C was milder than that of older children with MIS-C; in a report of 85 such infants, the outcome was favorable. Significantly fewer infants

required intensive care (33% compared with 58% among older children) and only one infant died.[53]

A radiological case series involving 38 children with COVID-19 and encephalopathy was collated from 10 countries.[54] A wide range of imaging findings was described, the most common being ADEM-like changes, myelitis, and neural enhancement, especially cranial nerves (V–VIII, XII, sometimes correlating with clinical signs, such as facial paralysis or ophthalmoplegia). This study covered the age range from 0 to 18 years; only two patients were infants and both had the 'classic' acute pulmonary symptoms of COVID-19. Interestingly, both of these infants had seizures among their presenting signs, both had ADEM radiological features on brain magnetic resonance imaging (MRI), and both had good outcomes (no persisting neurological problems at hospital discharge, although long-term outcomes were not reported). Overall, most of the brain MRI findings in the 38 reported children resembled immune-mediated parainfectious patterns: 42% of patients had ADEM-like changes, 37% had evidence of neuritis, and 21% had myelitis. Most patients did well, even those with profound radiological abnormalities. However, 4 of the 38 children, all previously healthy, developed fatal 'atypical' coinfections (two had tuberculous granulomas, one each had Fusobacterium necrophorium/Streptococcus constellatus or methicillin-resistant Staphylococcus aureus). In children with MIS-C, lesions of the splenium of the corpus callosum or myositis were seen commonly. As the largest pediatric neuroradiological series to date, the most useful aspect of this study is its documentation of a wide spectrum of radiographic abnormalities, with careful case correlation and clinical categorization. Notably, these cases were highly selected for more severely affected children and the neuroimaging findings may not be representative of COVID-19 in the overall pediatric population. Indeed, in a small series of 20 SARS-CoV-2-positive children presenting with acute neurological findings, only two had abnormal neuroimaging findings.[55]

Selected specific neurological impairments

Neurological impairments in infants and children with COVID-19 are diverse, as inferred from the cases studies and series described earlier. In this section of the review, three specific neurological conditions that may accompany COVID-19 – stroke, seizures, and anosmia/ageusia – are discussed, acknowledging that these do not represent the full spectrum of impairments (the cited reviews provide more details).

Stroke

Compared with adults, ischemic strokes are very rare in children with COVID-19 (8 of 971 patients, 0.82% from 61 international sites).[56] In that study, 34 neonates with acute ischemic stroke underwent testing for SARS-CoV-2; only one neonate (2.9%) tested positive for SARS-CoV-2 and that child's stroke was considered to be 'possibly' causally related to the infection. None of 33 neonates with cerebral sinovenous thrombosis tested positive. Therefore, cerebrovascular disease is an uncommon association with COVID-19 in pediatric data accumulated to date, although studies with longer baseline periods and outcome time points are needed.[57] By comparison, there is concern among adult patients that strokes are more common, especially in younger adults, thought to be possibly related to vascular endothelial damage or hyperinflammation.[58]

Seizures

Perhaps somewhat surprisingly, seizures, either new onset or exacerbations in patients with established epilepsy, were not commonly encountered (or reported) for much of the early pandemic.[59] Initial adult studies cited an incidence of about 2%, barely above the population prevalence of 0.5% to 1%.[6] Many subsequent series found similar numbers, including a meta-analysis of 145 721 patients with COVID-19 that yielded a prevalence of 1%.[13] Low seizure occurrences were also documented in early pediatric series (0.7% of children in one study[24] and 3.1% of severely ill children in another study[25]). If SARS-CoV-2 was truly causing hyperexcitable neuronal network dysfunction leading to seizures, a much higher incidence of symptomatic seizures would be predicted, especially in cases of encephalitis. That being said, recent reports have cited cases of seizures, even status epilepticus, at many ages, although prospective studies are still lacking.[19,60] It is not known with certainty whether seizures may be more common or severe in infants than in older children but it is striking that among case reports of infants, seizures or status epilepticus are often described.[29,50,51,54,61,62] An apropos example is an 8-month-old infant with confirmed SARS-CoV-2 who developed status epilepticus in the context of fever but without encephalitic symptoms.[61] A longitudinal study of 32 patients with COVID-19 presenting with seizures included three infants with a wide spectrum of presumed etiologies (hypocalcemia, fever, encephalitis); one child had preexisting epilepsy and none of the children had further seizures in the 2 months after presentation.[62] These and other case reports[50,51] underscore the limited generalizability of such small series in making conclusions about a multifactorial disorder such as epilepsy. In larger cohort studies and meta-analyses, approximately 13% to 30% of patients hospitalized with COVID-19 had symptomatic seizures or status epilepticus; however, in those reports, little clinical detail was provided. Those percentages are likely to be high because these cohorts had severe illness.[20,25,29] Kurd et al. reported that 11 of 175 (6.2%) children with acute COVID-19 presented with seizures in the context of mild or no respiratory symptoms. Six of these children had previous epilepsy and five children presented with status epilepticus (not all of those with status epilepticus had a previous diagnosis of epilepsy).[63] Seizures were easily controlled in

TABLE 2 Neurological manifestations of COVID-19

Selected neurological signs	Children and adults	Relevance to infants
Peripheral nervous system		
Anosmia/ageusia	Occurs frequently in adults; often not asked of children	Unknown since infants cannot report
Demyelinating disease (e.g. Guillain–Barré syndrome)	Occurs but controversial as to whether incidence is increased	Possible
Central nervous system		
Cerebrovascular disease	Concern for hypercoagulable state or vasculopathy; younger adults may be at higher risk	No causation proven
Encephalitis	Rare	Rare (some possible cases)
Mental status changes (somnolence, encephalopathy)	More common in adults; can present in children	Can present in infants
Seizures	Variable, usually in acutely ill patients	Some suggestive case reports; outcomes favorable
Headache	Common in children and adults	Unknown since infants cannot report

Abbreviation: COVID-19, coronavirus disease.

TABLE 3 Possible mechanisms of neurological involvement in COVID-19

Hypothesized mechanism	Comments
Direct virus neuroinvasion	Minimal evidence of viral presence in the brain or cerebrospinal fluid, both pathological or viral markers
Neural propagation	
Hematogenous spread	
Vascular endothelial injury	Blood–brain barrier dysfunction
	Virus, leukocyte, or immune cell entry
	Endotheliitis
	Coagulopathy
Immune hyperinflammatory/autoimmune injury	Excessive release of proinflammatory cytokines, chemokines, interleukins
Infectious	
Postinfectious	
Systemic factors	Secondary hypoxic injury Critical illness effects Sedatives and other medications

Abbreviation: COVID-19, coronavirus disease.

all of the children, even those with status epilepticus, and follow-up ranging from 1 week to 17 weeks showed good outcomes. Of note, only one of the patients was aged under 1 year. If verified, the findings by Kurd et al. would suggest a higher rate of new seizures and seizure exacerbations related to COVID-19 than appreciated before now. Some cases of COVID-19-associated seizures may be febrile seizures, while others warrant investigation for encephalitis, which is very rare in infants and children with COVID-19.[64]

Among children with preexisting epilepsy, there is no good evidence that seizures will exacerbate. For children with infantile spasms, consensus guidelines recommended specific care precautions during the acute pandemic, with emphasis on telemedicine evaluations and follow-up to minimize potential exposures in infants whose immune responses might be reduced due to adrenocorticotropic hormone or corticosteroid treatment.[65] Overall, the question as to whether patients with preexisting epilepsy have poorer seizure control secondary to COVID-19 remains controversial, with most authorities concluding that decreased access to medical services, medications, and routine surveillance plays a pivotal role.[66,67] Regardless of seizure etiology, prognosis appears to be more favorable in children than adults with COVID-19.

Anosmia/ageusia

Impairment of smell (anosmia) or taste (ageusia) is often reported by adult patients with COVID-19, especially early on in the course of the disease. The number of adults reporting smell dysfunction in available studies ranges from 14%

to 85%.[13,68,69] Fortunately, these deficits are usually transient and resolve over weeks to months. Only a few reports have focused on anosmia/ageusia in children, finding deficits ranging 2-3%[3,24] up to 15%[70] possibly because younger children were not often asked about this symptom, at least early in the pandemic.[71] Since anosmia can occur in the absence of respiratory or systemic symptoms, it behooves clinicians to seek this information from children. Controversy has arisen as to the cause of anosmia. Nasal congestion, which often impairs the sense of smell in upper respiratory infections, is not usually a prominent component of COVID-19, so the possibility of olfactory neuron damage or viral transmission to the brain via the olfactory epithelium/olfactory bulb has been suggested. To date, the bulk of histological, ultrastructural, and molecular data favors inflammation not neuroinvasion as the predominant mechanism of anosmia (see the section on 'Selected specific neurological impairments').[69]

NEURAL MECHANISMS

Hypotheses about the neuronal mechanisms operative in COVID-19, outlined in Table 3, include direct neuroinvasion of SARS-CoV-2, spread of the virus hematogenously via the immature or injured blood–brain barrier, vascular endothelial injury, and cytokine/autoimmune effects. Another potential 'mechanism' by which COVID-19 incites neurological dysfunction is non-specific – the consequence of severe systemic illness; for example, concurrent hypoxia-ischemia, abnormal blood pressure regulation and cardiac function, and other concomitants of critical illness, may contribute to the neuropathology.

Numerous reviews have speculated on whether (and how) the SARS-CoV-2 virus might enter the brain and exert pathological effects;[9,72–79] unfortunately, data supporting most of these postulated mechanisms are scarce. It is quite possible that multiple mechanisms coexist. These hypotheses require rigorous evaluation in the laboratory and clinic. It is critical to decipher which (if any) of these mechanisms plays a predominant role in COVID-19 neuropathology to devise targeted therapies.[80]

Direct neuroinvasion

There are two main ways by which the virus might enter the brain 'directly': neural and hematogenous/vascular/endothelial.

Neural

Many authors attribute neurological signs and symptoms to the 'neuroinvasive' properties of SARS-CoV-2. Distinction must be made between neuroinvasion (the virus can enter the nervous system), neurotropism (the virus can infect nerve cells once in the brain), and neurovirulence (the virus is capable of causing neurological disease).[81] To date, the neuroinvasiveness of SARS-CoV-2 has not been proven definitively. The SARS-CoV-2 virus or its RNA by polymerase chain reaction with reverse transcription has almost never been recovered from the CSF, even in most cases with severe neurological involvement and encephalitic symptoms.[82] Previous demonstrations that other coronaviruses (severe acute respiratory syndrome, Middle East respiratory syndrome) were found in neural tissue is intriguing but does not comprise proof that SARS-CoV-2 is likewise neuroinvasive. Yet, because COVID-19 is unquestionably associated with neurological signs and symptoms, there must be some mechanism(s) by which the virus, either directly or indirectly, incites neurological damage.

The olfactory epithelium is often purported to be an entry point for direct viral invasion and subsequent retrograde transynaptic propagation. Olfactory receptor neurons traverse the olfactory epithelium, form the olfactory nerve, and then reach the brain parenchyma. Several other viruses have been shown to enter the CNS in this manner (e.g. influenza A, herpesvirus, poliovirus, and others).[81,83] While SARS-CoV-2 localizes within supporting ('sustentacular') cells of the olfactory epithelium, it does not appear to have a predilection for neurons.[84] No evidence has yet supported this attractive but unproven route, at any age. The many failures to demonstrate virus or its RNA in CSF, even in cases of presumed encephalitis, support that position. Perhaps CSF samples were obtained at suboptimal time points or the tests to detect the presence of SARS-CoV-2 in CSF were not sufficiently sensitive.[9,18] Extensive neuropathological studies (of adults) revealed that viral RNA or protein are not detected consistently in autopsied brains, whereas most brains had activated microglia, microglial nodules, or neuronophagia, implicating systemic inflammation rather than direct viral invasion as the more likely mechanism.[85–88] A recently published autopsy on a 14-month-old infant who succumbed to COVID-19 pneumonitis reported severe cortical atrophy and neuronal loss.[89] SARS-CoV-2 staining was documented in the epithelium of the choroid plexus and in the ventricular ependymal cells, but not the brain parenchyma. The timing and extent of the child's CNS involvement was beyond that expected for an acute SARS-CoV-2 infection and the authors concluded that blood–brain barrier disruption provided a potential route for viral invasion, although unequivocal neuroinvasion was not demonstrated.

Hematogenous, vascular, and endothelial

Another potential route for the virus to enter the CNS is through the bloodstream (hematogenous), gaining access to the brain by infecting the endothelial cells of the blood–brain barrier or epithelial cells of the choroid plexus blood–CSF barrier. The blood–brain barrier is essential for the transport of molecules into the brain and the exclusion of pathogens and overall maintenance of cerebral homeostasis.[90] The blood–brain barrier consists of several

cell types and proteins, each with its own maturational profile – astrocyte foot processes, pericytes, tight junction proteins, and extracellular matrix – providing structural and functional support. Virus attachment to angiotensin-converting enzyme type 2 receptors at the blood–brain barrier might facilitate entry of the virus into the CNS with subsequent endothelial damage and edema.[91] While the blood–brain barrier is structurally complete at birth, it is not mature physiologically for several months.[92] In a SARS-CoV-2 infection, the blood–brain barrier may be dysfunctional, disrupted either by the inflammatory response or the virus itself, allowing transmission of the virus or activated immune cells from the circulation into the CNS.[93] The release of inflammatory cytokines by activated glia and neural mast cells can exacerbate the inflammation.[91] A prothrombotic, inflammatory state is purported to accompany SARS-CoV-2 infection, inciting endothelial damage and predisposing to thrombotic or hemorrhagic stroke. The angiotensin-converting enzyme type 2 receptor depletion seen in COVID-19 enhances this possibility by altering the stability of the renin–angiotensin system.[94]

Hyperinflammatory response

SARS-CoV-2 invades a variety of epithelial cells via attachment of the virus spike protein to epithelial angiotensin-converting enzyme type 2 receptors; the virus spike protein is then cleaved by the transmembrane protease serine 2. Viral RNA enters the cell and replicates rapidly, translating viral proteins and inducing an extensive host immune response.[77] While this immune response may be adaptive, attacking and inactivating the virus, it can also be maladaptive and cause hyperinflammation with excessive secretion of cytokines (cytokine storm) that can cause endothelial and cellular damage.[91,95] Cytokine elevations have been correlated with COVID-19 severity and neurological dysfunction in both adults and children.[96,97] Specifically, interleukins such as interleukin-6, tumor necrosis factor-α, and the chemokine (C-X-C motif) ligands CXCL8 and CXCL10 have been implicated in the SARS-CoV-2 response. The role of these molecules in infant neurological dysfunction is to be elucidated.

The presence of angiotensin-converting enzyme type 2 receptors on neural tissue (neurons, glia), although at low levels, led to the hypothesis that these receptors are necessary and sufficient for brain entry of the virus; however, other receptor systems might also be involved. For example, using cultured pediatric cortical neurons (HCN-2 cells), in which SARS-CoV-2 can replicate, it was shown that other receptors (e.g. Toll-like receptors) mediate nuclear factor kappa-light-chain-enhancer of activated B cells activation and increased cytokine and chemokine release.[98] Moreover, dysfunction of mitochondrial and mammalian target of rapamycin (mechanistic target of rapamycin) pathways may play a role in SARS-CoV-2 pathogenesis since these signaling pathways modulate both CNS viral invasion and the immune response to viruses.[99]

Taken together, the predominant evidence favors immune dysregulation/hyperinflammation as the primary mechanism of neurological dysfunction in COVID-19, although more research is necessary to evaluate this and the other potential mechanisms.

ROLE OF THE BRAIN DEVELOPMENTAL STAGE

When discussing the effect of SARS-CoV-2 in causing neurological disease in infants and young children, it is critical to consider the specific stage of brain development at which the infection occurs; this correlation has rarely been addressed in the literature. That is, SARS-CoV-2 infection during specific critical periods of brain development may have different consequences on brain function acutely and chronically.

The newborn and infant brain undergoes rapid developmental changes. While the brain's basic structure and form are already established in infancy, numerous processes continue to undergo development: myelination is quite immature, synaptic organization is ongoing, the blood–brain barrier is not fully functional,[92] and the immune system is undergoing age-related changes.[100] SARS-CoV-2 is a superimposed acute stressor on these multiple fundamental developmental processes and little is known currently about the effect of the virus on myelination, ion channel function, synaptic activity, behavioral plasticity, and other critical aspects of infant brain development. Human and animal studies will hopefully shed light on these questions.[101]

Long-term consequences

Neurodevelopment

As just discussed, the potential effects of COVID-19 on brain development are just beginning to be appreciated and studied. In a pilot study, nine children born to mothers with COVID-19 and nine age-matched controls were compared neurodevelopmentally at 8 to 10 months of age using the Ages and Stages Questionnaire, Third Edition.[102] While children (none of whom developed COVID-19 disease postnatally) born to mothers with COVID-19 had lower Ages and Stages Questionnaire, Third Edition scores across multiple domains (communication, gross motor function, problem-solving, and personal-social), only deficits in fine motor performance reached statistical significance. A recent, larger study compared 114 infants exposed to SARS-CoV-2 in utero with 141 infants not exposed to SARS-CoV-2 but also born during the pandemic.[103] There were no differences on the Ages and Stages Questionnaire, Third Edition at 6 months of age as a function of infection status, timing during gestation, or severity

of maternal illness. However, when these groups were compared with historical controls born before the pandemic, both groups born during the pandemic had significantly decreased gross motor, fine motor, and personal-social Ages and Stages Questionnaire, Third Edition scores. Acknowledging the confounding factors inherent in both of these preliminary studies, the data suggest that fetuses exposed to SARS-CoV-2 in utero may be at risk for exhibiting neurodevelopmental deficits long after birth. Of course, these findings must be examined over longer time periods, by a variety of other developmental tests, and in larger populations of children. Nevertheless, they represent the type of neurodevelopmental study that is needed for longitudinal assessment of children who are exposed to SARS-CoV-2 prenatally or postnatally.

Long COVID-19

Assessment of neurological involvement in COVID-19 was not initially a priority because pulmonary compromise represented the major morbidity. Now that the pandemic is persisting, more people are surviving and long-term sequelae are becoming obvious. The symptoms of so-called 'long COVID-19' are especially concerning because they might not become apparent or maximal for weeks or months (or longer) after the resolution of the acute infection. Symptoms of long COVID-19 are disproportionately neurological and psychiatric in nature, including headache, malaise, joint and muscle pain, anxiety, depression, altered cognition ('brain fog'), and sleep disturbances.[104–106] Addressing these long-term sequelae is critical for quality of life in patients who have survived acute COVID-19 and will require allocation of appropriate resources and services. Special clinics are being developed to diagnose and treat both children and adults with long COVID-19 and such clinics will provide essential long-term data regarding prognosis, neurological and beyond.[107–109]

Some of the lingering post-COVID-19 symptoms may be related to consequences of the infection itself, to altered immune function, or to other biological factors. It is also possible that some children reporting those symptoms have suffered the manifold psychological stressors of the pandemic itself and that their symptoms may not directly relate to the biological aspects of the disease. These topics are being investigated currently but data in infants regarding post-COVID-19 neurological sequelae are not yet available. Nevertheless, the neurodevelopmental implications of COVID-19 at any age are essential to consider.[110,111] Stressors such as family separation or quarantine, isolation, school closures, and economic and psychological pressures can affect a child at any age and can manifest with a variety of psychiatric disorders, particularly anxiety and depression.[31] All of these issues are likely impacted by socioeconomic factors. In addition to COVID-19-associated neuropsychiatric long-term effects, concern about acceleration or exacerbation of neurodegenerative disorders has been raised in adults;[112] obviously such very long-term sequelae are currently unknown for infants and young children.

UNANSWERED QUESTIONS AND FUTURE DIRECTIONS

Unanswered questions abound regarding COVID-19, especially its neurological and neuropsychiatric outcomes in children. A few relevant future directions are discussed briefly here.

Data quality and quantity

Data accumulated as the pandemic continues stresses the need to acknowledge that some initial assumptions about COVID-19 may have been inaccurate. Specifically, the disease obviously involves multiple organ systems and entails long-term as well as acute pathology. Data are becoming more robust as larger studies reduce reliance on anecdotal reports and small case series. Yet, there are still relatively few large prospective series, especially in children. There is considerable variability between reports in terms of degree and methods of investigation, quality of neurological assessment, and the number and type of neurological investigations performed.[9,47] There is inconsistency in defining study populations and variability in tests for the virus (availability, reliability). Moreover, local and regional differences in symptom classification and data collection contribute to interstudy variability. Several attempts to standardize these confounders are underway by establishing national and international consortia, which should provide a clearer picture over time.[113] Much more pediatric data are needed from neuroimaging, neuropathological, and ancillary studies (e.g. CSF, electrophysiology).

Vaccines

The availability of vaccines has had a major impact on limiting disease severity and severe consequences but is not achieving the hoped-for amelioration of the disease due to an inadequate number of persons immunized, time-limited or incomplete protection, and the emergence of new variants. Vaccines have recently become available to 5 to 12-year-old children; whether (or which) children even younger should be vaccinated is controversial.[114] There are no data as yet on the effectiveness of vaccination on emerging virus variants. Hopefully, vaccine technology and dissemination will continue to reduce case occurrence and severity while minimizing vaccine complications.[115]

Virus variants

The Delta and Omicron variants of SARS-CoV-2 have proven to be more contagious than the original Alpha version and Omicron is responsible for much of the worldwide infection surge since December 2021. There are no data as to whether the Delta and Omicron variants are more or less

likely to produce neurological morbidity. While extremely contagious and transmissible, the Omicron variant typically exerts mainly mild signs and symptoms in children.[116]

Disease mechanisms

As discussed in detail earlier, numerous reviews have speculated on the potential mechanisms by which SARS-CoV-2 could affect neurological function, yet data supporting any of these mechanisms are scarce. Whether alternative mechanisms also play a role, including brain-immune system interplay, and whether neurological mechanisms alter respiratory control in very ill patients need to be determined. Also unclear is whether different mechanisms predominate at different ages. Much more basic research is necessary to elucidate COVID-19 and MIS-C pathogenesis and hopefully lead to targeted therapies. To summarize, the pathogenesis of neuro-COVID-19 in children (and adults) remains unclear.

CONCLUSIONS

The new coronavirus, SARS-CoV-2, can affect CNS and peripheral nervous system function in both children and adults, although symptoms are usually less severe at younger ages. Much more research is needed on the role of brain development in COVID-19 manifestations and outcomes. At any age, neurological involvement can be specific or non-specific and involve decreased taste/smell, headache, myalgia, confusion/encephalopathy, strokes, seizures, and a variety of other symptoms. The long-term consequences of both the virus infection itself and secondary effects of quarantine, isolation, family illness, and other stressors mandate that clinicians should monitor chronic symptoms and maintain a high degree of vigilance over time and in an age-specific manner. As the COVID-19 pandemic continues and evolves, continuing and new/emerging challenges face the healthcare system. COVID-19 cases are clearly increasing now with the Omicron variant. With more cases and potentially more severe presentations, neurological problems will likely become even more prominent in the pediatric age range and warrant careful surveillance for long-term adverse developmental outcomes. Healthcare providers who focus on neurological disease will be ever more crucial in the upcoming years as the world learns to cope with new and ongoing brain dysfunction related to SARS-CoV-2.

CONFLICT OF INTEREST

The author declares no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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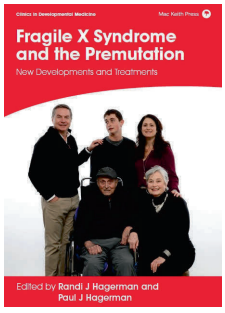
Fragile X Syndrome and the Premutation

New Developments and Treatments

Clinics in Developmental Medicine

Randi J Hagerman and Paul J Hagerman



Offers clinicians and families a multidisciplinary approach in order to provide the best possible care for patients with Fragile X. Unique features of the book include what to do when an infant or toddler is first diagnosed, the impact on the family and an international perspective on how different cultures perceive the syndrome.

"This book is an essential addition to the existing literature, offering a wealth of information on all clinical and molecular aspects of the Fragile X syndrome mutation in one place."
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