A Comprehensive Review of Neurologic Manifestations of COVID-19 and Management of Pre-existing Neurologic Disorders in Children

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Abstract
Since the first reports of SARS-CoV-2 infection from China, multiple studies have been published regarding the epidemiologic aspects of COVID-19 including clinical manifestations and outcomes. The majority of these studies have focused on respiratory complications. However, recent findings have highlighted the systemic effects of the virus, including its potential impact on the nervous system. Similar to SARS-CoV-1, cellular entry of SARS-CoV-2 depends on the expression of ACE2, a receptor that is abundantly expressed in the nervous system. Neurologic manifestations in adults include cerebrovascular insults, encephalitis or encephalopathy, and neuromuscular disorders. However, the presence of these neurologic findings in the pediatric population is unclear. In this review, the potential neurotropism of SARS-CoV-2, known neurologic manifestations of COVID-19 in children, and management of preexisting pediatric neurologic conditions during the COVID-19 pandemic are discussed.

Keywords
COVID-19, SARS-CoV-2, Children, Neurological, Encephalitis, Neuroimmunology, Pediatric, Treatment

In December 2019, the first cases of the coronavirus disease 2019 (COVID-19) were reported as pneumonia of an unknown etiology in Wuhan, China.1 The causative novel virus was identified as the severe acute respiratory syndrome CoV2 (SARS-CoV-2), which belongs to the broad family of viruses known as corona viruses. It is a positive sense single-stranded RNA (þssRNA) virus, with a single linear RNA segment. And it is the seventh known corona virus to infect people. In addition, it is believed to have zoonotic origins and has close genetic similarity to bat coronaviruses, suggesting it emerged from a bat-borne virus.1,2 Although most coronaviruses are associated with mild symptoms of the common cold, SARS-CoV, MERS-CoV, and now SARS-CoV-2 have the potential to produce severe acute respiratory syndromes leading to fatality in a subset of patients.2 As of August 28, 2020, the World Health Organization has reported 24,257,989 confirmed cases and 827,246 deaths worldwide, affecting 216 different countries.3 With an estimated median R0 of 2.4, SARS-CoV-2 has rapidly spread across multiple countries, threatening the lives and livelihoods of many people across the globe.4 The basic reproduction number (R0) indicates the number of secondary infections from a single case in a susceptible population and is used to estimate the infectious potential of a pathogen.

SARS-CoV-2 is thought to be mainly transmitted by infectious aerosols, and epidemiologic studies have identified the main symptoms associated with the viral infection to be fever, malaise, and dry cough.5,6 Older adults are more susceptible to complications of the disease, and comorbidities such as diabetes and hypertension predict higher severity of cases.7 Although COVID-19 is generally recognized as a respiratory illness, multiple reports have identified neurologic manifestations of COVID-19.8,9 Currently, it is unclear whether SARS-CoV-2 affects the nervous system.
Coronaviruses and the Nervous System

Coronaviruses infect numerous animal species including humans. To date, 7 human coronaviruses have been identified: (HCoV)-229E, HCoV-NL63, HCoV-HKU1, HCoV-OC43, MERS-CoV, SARS-CoV-1, and SARS-CoV-2. Betacoronaviruses SARS-CoV-1, SARS-CoV-2, and MERS-CoV can cause severe infections, whereas others cause mild symptoms. Three human coronaviruses (HCoV-229E, HCoV-OC43, and SARS-CoV-1) have previously been shown to be capable of infecting the nervous system. Using in vitro cell culture models, HCoV-229E and HCoV-OC43 were capable of infecting various cells that make up the nervous tissue including neurons, astrocytes, microglia, and oligodendrocytes. Murine HCoV-OC43 inoculation has also been shown to cause generalized central nervous system infection, demonstrating the neuroinvasive capability of the virus. Similarly, SARS-CoV-1 infection of human and rat neural cells has been demonstrated in vitro. Because SARS-CoV-2 shares large parts of its genome with SARS-CoV-1, it is likely that SARS-CoV-2 is also able to directly spread to the nervous system. A recent study using U251 glioblastoma cell line reported modest replication of SARS-CoV-2, indicating potential neurotropism of the virus. Furthermore, some of the earliest symptoms of SARS-CoV-2 infection include anosmia and ageusia, indicating potential central nervous system involvement. However, SARS-CoV-2 detection in the cerebrospinal fluid has been limited to a single case report.

HCoV-OC43 infections in mouse models have shown that intranasal inoculation of the virus leads to direct virus-mediated injury to neurons, oligodendrocytes, and astrocytes that quickly spread throughout the brain, ultimately resulting in encephalitis and transient flaccid paralysis. Studies in humans have also shown a potential link between HCoV-OC43 infection and multiple sclerosis. Some multiple sclerosis patients have detectable HCoV-OC43 RNA in their cerebrospinal fluid, but more importantly antibodies against HCoV-OC43 have been shown to cross-react with myelin antigens, and thus the viral infection could be postulated as one possible mechanism of multiple sclerosis pathogenesis. SARS-CoV-1 RNA has also been detected in the cerebrospinal fluid of patients infected with the virus. Furthermore, SARS-CoV-1 RNA has been identified directly from autopsied brain tissues. In the mouse model of SARS-CoV-1 infection, heavy brainstem involvement has been reported to be linked to respiratory failure. Similar to HCoV-OC43, SARS-CoV-1 is thought to be transmitted to the central nervous system via an intranasal route. MERS-CoV has been reported to cause neurologic symptoms including seizures, headache, and confusion; however, direct detection of MERS-CoV in cerebrospinal fluid or brain tissue has not been reported.

The tropism of a virus is generally thought to be consistent with the tissue expression of the host receptors identified by the virus. Multiple studies have shown that SARS-CoV-2 cellular entry requires ACE2 expression. ACE2 is also the receptor responsible for SARS-CoV-1 cellular entry. ACE2 expression has been reported in kidney, lung, heart, vasculature, and brain. Brain transcriptomic analyses have shown that ACE2 is expressed in excitatory and inhibitory neurons as well as glia, including astrocytes and oligodendrocytes. Spatial distribution analysis also found high ACE2 expression in the substantia nigra, choroid plexus of the lateral ventricles, and olfactory bulb. When ACE2 mRNA levels were measured during different stages of development in a mouse model, it was shown that brain ACE2 expression peaks in adult mice and steadily increases from early embryonic stage to adulthood. A recent study has also reported that ACE2 expression in the nasal epithelium is age dependent, with lowest expression in younger children. This may suggest that the pediatric population is less susceptible to direct neurologic infection of the SARS-CoV-2 virus, as intranasal is the favored mechanism of central nervous system entry for many viruses.

Neurologic Manifestations of COVID-19 in Children

In the adult population, studies have shown that nervous system involvement was more likely in severe cases than in nonsevere. However, neurologic manifestations have also been reported in patients without the typical features of COVID-19. Headache, dizziness, anosmia, and ageusia are the most commonly reported symptoms, but neurologic manifestation also include acute cerebrovascular disease, impaired consciousness, transverse myelitis, acute hemorrhagic necrotizing encephalopathy, encephalopathic, seizures, ataxia, neuralgia, Guillain-Barre syndrome, and skeletal muscle injury.

In comparison to the adult population, few neurologic complications of COVID-19 have been reported in the pediatric patients. Most manifestations are limited to headaches and loss of taste and/or smell. However, there are case reports describing more severe neurologic complications, including encephalitis, seizure, and cerebrovascular infarct.
One case report from Maimonides Medical Center, Brooklyn, New York, describes a previously healthy 11-year-old who presented with status epilepticus and cerebrospinal fluid evidence of encephalitis after a 2-day history of generalized weakness and no respiratory symptoms. Nasopharyngeal swab confirmed COVID-19 and rhinovirus/enterovirus; however, cerebrospinal fluid polymerase chain reaction (PCR) was negative for the latter, which suggests possible COVID-19 etiology. However, it is unclear whether the patient’s cerebrospinal fluid was positive for SARS-CoV-2. Management of status epilepticus required 4 anticonvulsant therapies, but the child recovered fully after 6 days without further treatment. Dugue et al described a 6-week-old term infant with a family history of simple febrile seizures, who presented with fever, cough, and 2 brief episodes of sustained upward gaze deviation and bilateral leg stiffening. Nasopharyngeal and anal swabs confirmed SARS-CoV-2 and rhinovirus C. Cerebral spinal fluid analysis was unremarkable. The infant was discharged after 1 day without further complications. A case report by Chacón-Aguilar et al described a 26-day-old infant who presented after several minutes of upward gaze deviation and generalized hypertonia, followed by another several minute episode of generalized hypertonia and facial cyanosis. The infant had a 12-hour history of fever, rhinorrhea, and vomiting at presentation. Extended (36-hour) electroencephalographic (EEG) monitoring found no evidence of seizure activity. PCR testing of a nasopharyngeal swab was positive for SARS-CoV-2, and all other infectious workup was negative. After a 6-day hospitalization, the infant was discharged without further complications. Bhatta et al reported a previously healthy 11-year-old boy who presented initially with a generalized tonic-clonic seizure witnessed by his mother, followed by another seizure in the emergency department necessitating 2 mg intravenous lorazepam. Of note, he was afebrile and did not feel unwell. PCR test for SARS-CoV-2 was positive. Furthermore, head computed tomograph and chest radiograph were both normal. He was treated with levetiracetam 500 mg twice daily and discharged the next day. No other symptoms or recurrence of seizures were reported at a 1-week follow-up. This case highlights an unusual presentation of new-onset seizure in the absence of any other COVID-19 symptoms.

Recently, Riphagen et al described a cluster of 8 children with hyperinflammatory shock with features similar to atypical Kawasaki disease, Kawasaki disease shock syndrome, or toxic shock syndrome. Of those children, a previously healthy 14-year-old with confirmed SARS-CoV-2 suffered a fatal right middle cerebral artery and anterior cerebral artery infarct. Laboratory results showed evidence of elevated inflammatory markers, and cardiac arrhythmia and refractory shock necessitated extracorporeal life support. In a case series, Abdel-Mannan et al further showed that out of 27 pediatric COVID-19 patients with multisystem inflammatory syndrome, 14.8% developed new-onset neurologic symptoms, including encephalopathy, headaches, brainstem and cerebellar signs, muscle weakness, and decreased reflexes along with splenium signal abnormalities on magnetic resonance imaging. Lin et al also described a case of COVID-19–associated multisystem inflammatory syndrome in a previously healthy 13-year-old with encephalopathy and findings of cytotoxic lesions of the corpus callosum on MRI. Additionally, Schupper et al reported other severe neurologic complications associated with multisystem inflammatory syndrome in pediatric patients. A previously healthy COVID-19–positive 5-year-old developed cardiogenic shock and required extracorporeal membrane oxygen. After day 5 of extracorporeal membrane oxygen, he developed a right mydriasis and was found to have a right middle cerebral artery infarction, cerebral edema, and diffuse contralateral subarachnoid hemorrhage on computed tomographic scan. He was ultimately declared brain dead several days later. Furthermore Schupper et al also described a 2-month-old requiring extracorporeal membrane oxygen who developed multiple hemorrhagic infarctions and refractory seizures; however, he tested negative for COVID-19 antibodies although his clinical presentation was suspicious for overt COVID infection with elevated interleukin-6 levels.

Other neurologic manifestations of COVID-19 in the pediatric population have also been reported. Savic et al described a previously healthy 13-year-old who presented with loss of consciousness with no other typical symptoms of COVID-19. She was found to have a ruptured pseudoaneurysm of the left middle cerebral artery and tested positive for SARS-CoV-2 via nasopharyngeal PCR. Enner et al reported a previously healthy 14-year-old who developed central apnea. She presented with tonic-clonic seizures after 6 days of upper respiratory symptoms and fever and was positive for SARS-CoV-2 via nasopharyngeal PCR. She had multiple apneic episodes accompanied by focal seizures, and required ventilator support for 2 weeks because of poor respiratory drive. A case report by Bhavsar et al described a previously healthy 16-year-old who developed severe encephalopathy and was positive for SARS-CoV-2 via nasopharyngeal PCR. However, cerebrospinal fluid testing was negative for SARS-CoV-2. A thorough workup revealed no other bacterial, viral, or autoimmune pathologies. However, MRI imaging was not obtained. As evidenced by recent findings, additional research is needed to fully assess the neurologic implications of COVID-19 in children.

### Vertical Transmission of COVID-19

The potential for vertical transmission of SARS-CoV-2 from mother to fetus is uncertain. A retrospective review of 9 COVID-19–positive mothers found no evidence of transmission. However, other reports have suggested evidence of congenital infection, including presence of IgM and IgG antibodies and positive nasopharyngeal swab. Vivanti et al were the first to confirm transplacental transmission of SARS-CoV-2 from mother to neonate during the third trimester of pregnancy. On day 3 of life, the infant developed poor feeding, hypertonia, and opisthotonos. A cerebrospinal fluid infectious workup, including SARS-CoV-2, was negative, except for the presence of leukocytes and mildly elevated protein. Reverse transcription PCR of blood, nonbronchoscopic
bronchoalveolar lavage fluid, and nasopharyngeal and rectal swabs taken at 1 hour, 3 days, and 18 days of life all tested positive for SARS-CoV-2. At 11 days of life MRI showed hyperintensities of the deep white periventricular and subcortical matter. No treatment for COVID-19 was initiated, and the infant was discharged at day 18. Repeat examination and MRI at 2 months showed improvements.

ACE-2 receptors have been identified in placental and fetal tissue, and expression appears to increase with gestation. The data thus far suggests that vertical transmission can occur toward the end of pregnancy and present with neurologic complications in the neonate. However, the potential for SARS-CoV-2 infection and its sequelae during the first and second trimesters remain poorly understood.

Current COVID-19 Treatment Recommendations for Children

Currently, general management of COVID-19 for pediatric patients includes bed rest and supportive therapy, such as maintaining adequate hydration and electrolyte balance, and monitoring vitals and oxygen saturation. If high fever is present (> 38.5°C), physical cooling and antipyretic drug administration is recommended. Currently, use of antivirals (lopinavir/ritonavir, ribavirin) or chloroquine phosphate is not recommended for the pediatric population. In early disease, interferon alpha administered via nasal spray or nebulizer can be used to reduce viral load. Based on preliminary findings from the RECOVERY trial, a randomized study evaluating different COVID-19 treatments, the Centers for Disease Control and Prevention (CDC) now recommends using dexamethasone in adult patients who are mechanically ventilated or who require supplemental oxygen. Prednisone, methylprednisolone, or hydrocortisone may be considered when dexamethasone is unavailable. Because only a few pediatric patients were included in the RECOVERY trial, it is difficult to extrapolate these recommendations for children. The CDC states that dex-amethasone may be used in pediatric patients requiring mechanical ventilation, but it is generally not recommended for those who require only minimal oxygen support.

Very few studies of experimental therapies for COVID-19 include the pediatric patient population. Of note, a pediatric population–focused phase 2/3 trial of remdesivir was initiated in June 2020 (ClinicalTrials.gov ID: NCT04431453). Remdesivir is a viral RNA–dependent RNA polymerase inhibitor initially developed for treatment of the Ebola virus. The efficacy of remdesivir in children is yet unknown. Conversely, in a double-blind, randomized, placebo-controlled trial of adults hospitalized with COVID-19, remdesivir was shown to significantly decrease time to recovery. Convalescent plasma, which has recently been approved for emergency use by the US Food and Drug Administration (FDA), has also shown some efficacy in reducing mortality in critically ill patients.

Although the study by Joyner et al included more than 35,000 patients, the study design did not include a placebo control or randomization of patients. A phase 1 clinical trial of convalescent plasma in children is ongoing (ClinicalTrials.gov ID: NCT04377672). The sphingosine-1-phosphate receptor regulator, fingolimod, is an immune modulator, which is currently FDA approved for the treatment of multiple sclerosis in ages 10 and older. Although immunomodulatory medications are not typically recommended in the treatment of COVID-19, a phase 2 clinical trial exploring the use of fingolimod in adults severely ill with SARS-CoV-2 is currently under way (ClinicalTrials.gov ID: NCT04280588).

A review by Orsucci et al described treatment recommendations for neurologic manifestations of COVID-19 in adults. Given the dearth of evidence at this time, they recommend adhering to standard management of neurologic complications, including ischemic stroke, seizures, and inflammatory neuro-pathies. Care should be taken to investigate potential drug interactions, in particular between antiepileptic drugs and treatments for COVID-19. Data are even more limited in pediatric patients, and thus caution should be taken when adhering to standard management for neurologic complications of COVID-19 in children.

Management of Neurologic Diseases in the COVID-19 Pandemic

Children with underlying neurologic conditions may be particularly vulnerable to the effects of COVID-19. In addition to following national and local guidelines, specific recommendations for management of Duchenne and Becker muscular dystrophies, spinal muscular atrophy, and infantile spasms are summarized below.

Expert consensus recommends Duchenne and Becker muscular dystrophy patients continue their current medication regimen, including corticosteroids with appropriate stress dosing in the setting of illness, exon-skipping agent infusions, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for cardiomyopathy treatment or prevention. Providers and patients should discuss risks and benefits of alternative care modalities, such as home health or virtual visits. In the setting of chronic respiratory failure, ventilatory support should always accompany supplemental oxygen, and pulmonary and/or anesthesiology collaboration is recommended. Because of serious potential side effects, use of hydroxychloroquine is not recommended.

Recent expert consensus promotes timely and consistent treatment for spinal muscular atrophy whenever possible to yield better outcomes. Adherence to nusinersen dosing timeline is important; missed doses should be given as soon as possible, and the original schedule resumed. For those receiving the one-time onasemnogene abeparvovec-xioi infusion, 2 or more months of corticosteroids are still recommended and should not be discontinued without approval from a specialist. Physicians and patients are encouraged to discuss risks and benefits of physical, occupational, and speech therapies during the pandemic.

The Child Neurology Society recommendation for infantile spasms treatment includes adrenocorticotropic hormone
(ACTH), high-dose prednisolone (6–8 mg/kg/d), and vigabatrin, unless all 3 are contraindicated. As discussed in the review paper by Christy,⁴ the significant immunosuppressive effect of ACTH may make infants particularly vulnerable to COVID-19, and the risks and benefits of using an alternative therapy, such as vigabatrin, should be weighed. For etiologies other than tuberous sclerosis complex, outpatient initiation of prednisolone is preferred. For tuberous sclerosis complex, vigabatrin is preferred if immediately available. When anticipating a treatment delay, prednisolone should be considered until vigabatrin can be obtained. Prednisolone is inexpensive, readily available, orally administered, and can be started outpatient. It does not require training of parents or caregivers, use of subspecialty pharmacies, or preapproval by insurance.

Conclusion

Neurologic manifestations of COVID-19 are being increasingly recognized in the adult population, however, there are only a few studies describing neurologic manifestations in children. Perhaps because of low expression of ACE2 receptors in the nasal epithelium of children, the pediatric population appears to be less susceptible to neurologic manifestations. Although this is somewhat reassuring, there is much that needs to be understood about the pathogenic behavior of SARS-CoV-2 in children. It is clear, however, that children with pre-existing neurologic diseases are more vulnerable to the severe complications of COVID-19, and thus special care and considerations should be taken to prevent poor outcomes.

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YK and SAW are co–first authors. YK, SAW, SJA, RJ, GM and AK contributed to conception or design, critically revised the manuscript for important intellectual content, gave final approval and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. YK, SAW, SJA and AK contributed to acquisition, analysis, or interpretation of data. YK and SAW drafted the manuscript.

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