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Topical Review

Coronavirus Infections in the Nervous System of Children: A Scoping Review Making the Case for Long-Term Neurodevelopmental Surveillance

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ABSTRACT

Background: The objective of this study was to describe the case literature of human coronavirus infections in the nervous system of children, including from SARS-CoV-2, and to provide guidance to pediatric providers for managing the potential long-term effects on neurodevelopment of human coronavirus infections in the nervous system.

Methods: Using a structured strategy, the PubMed and Ovid:Embase databases were queried for articles about the clinical presentation and pathophysiology of coronavirus infections in the nervous system of children and young adults, aged 0 to 24 years.

Results: Of 2302 articles reviewed, 31 described SARS-CoV-2 infections in the nervous system of children and 21 described other human coronaviruses: HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, MERS-CoV, SARS-CoV-1. Excepting MERS-CoV, we found cases of neurological disease in children from each human coronavirus. Children with non-SARS-CoV-2 infections have suffered acute flaccid paralysis, acute disseminated encephalomyelitis, encephalitis, and seizures. In addition, cases of ischemic, hemorrhagic, and microvascular strokes have occurred in children with SARS-CoV-2. Patients with multisystem inflammatory syndrome in children have suffered encephalitis, stroke, pseudotumor cerebri syndrome, and cytotoxic lesions of deep brain structures. Despite these reports, few articles evaluated the impact of human coronavirus infections on long-term neurodevelopmental domains including cognitive, language, academic, motor, and psychosocial outcomes.

Conclusions: Neurological manifestations of human coronavirus infections can cause severe disease in children. The case literature suggests a critical gap in knowledge of the long-term effects on child neurodevelopment of these infections. As the current SARS-CoV-2 pandemic continues, this gap must be filled to facilitate optimal outcomes in recovering children.

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Introduction

Although they primarily target the respiratory and enteric systems, six of the seven human coronaviruses (HCoV), including the novel SARS-CoV-2 virus, have been associated with severe neurological diseases in children.[1-4] The seventh, the Middle East respiratory syndrome coronavirus (MERS-CoV), has been identified in neurological diseases in adults.[5] Whether affected by direct HCoV infections or secondary neurological insults due to systemic illnesses, children are uniquely vulnerable to long-term cognitive or behavioral sequelae as a consequence of injury during critical stages of neurodevelopment.[6,7] These sequelae can range from mild neuromotor deficits to profound cognitive impairments following severe disease affecting the central nervous system (CNS). Resulting neurodevelopmental impairments, especially those more subtle, may not be apparent initially following infection and appear later with increasing demands or when a child reaches an age where a particular skill is expected to develop. However, even seemingly mild deficits can have a detrimental impact on a child's quality of life, academic achievement, mental health, and social interactions.[7] Given the relative rarity of neurological illnesses associated with HCoVs in children, there is a paucity of information on potential neurodevelopmental sequelae. This knowledge gap hinders the ability of providers to facilitate evaluation and management strategies for optimal outcomes in recovering children. As cases of neurological disease associated with SARS-CoV-2 infections in children continue to mount, such clinical guidance is urgently needed.

In this scoping review we evaluate the case literature describing primary and secondary neurological insults associated with HCoV infections in children for insights into the potential neurodevelopmental sequelae of similar SARS-CoV-2 infections in children. Drawing on past reports, we suggest clinical neurodevelopmental guidance for pediatric providers treating children with SARS-CoV-2 infections with neurological manifestations.

Coronavirus neuroinvasive potential in humans

Coronaviruses are enveloped, single-stranded RNA viruses that typically enter cells via interaction between their spike protein and tissue-specific cell surface receptors.[8] Within human neurons, the spike proteins of both SARS-CoV-1 and SARS-CoV-2 recognize the angiotensin-converting enzyme 2 protein, which is also widely expressed in the airways and gastrointestinal tract.[9]

HCoVs disseminate through the nervous system in two ways. Hematogenous spread occurs when circulating monocytes take up HCoV virions and subsequently express chemokines, increasing permeability of the blood-brain barrier. The virions then traverse the blood-brain barrier resulting in CNS disease.[1] Alternatively, following intranasal infection, HCoV virions cross the cribriform plate and infect the olfactory bulbs. Thereafter, neuron-to-neuron spread occurs via exocytosis/endocytosis of membrane-enclosed virions across synapses.[1]

In addition to direct infection, HCoVs sometimes trigger secondary disease processes that result in neurological illness. For example, in the peripheral nervous system, multiple case reports have described Guillain-Barré syndrome (GBS), the post-infectious demyelinating process associated with macrophage hyperactivity, following coronavirus infections in children. And, in the CNS, the recently described Kawasaki disease (KD)-like "multisystem inflammatory syndrome in children" (MIS-C) following SARS-CoV-2 infection appears to be associated with an acute, neuroinflammatory response, which predisposes children to cerebral edema, hemorrhage, stroke, and aseptic meningitis.[10]

SARS-CoV-2 and neurological disease in children

Neurological manifestations of SARS-CoV-2 such as encephalopathy, seizures, or peripheral nerve palsies have been reported in only a small fraction of children infected with SARS-CoV-2, perhaps as few as 1% of cases.[11] Notably, a recent case series of adults observed neurological complications including headache, altered mental status, and acute cerebrovascular events in 36% of patients.[12] The most severe neurological manifestations of SARS-CoV-2 infections in children have been associated with children suffering from MIS-C.[13] For example, a case review of 187 children with MIS-C found that 34% had suffered neurological involvement, with the vast predominance being central, rather than peripheral, manifestations.[10]

Neurodevelopmental implications of severe neurological disease

The rare occurrence of HCoV-related severe neurological illness in children underscores the need to better understand the potential neurodevelopmental sequalae associated with these infections. Until more evidence is gathered about the pathogenesis of SARS-CoV-2 in the nervous system of children, case reports from other HCoVs and viruses causing neurological manifestations can help us anticipate and manage the neurodevelopmental effects of pediatric SARS-CoV-2 infections.

Methods

Our scoping review was conducted according to the guidelines from the Joanna Brigs Institute Reviewers Manual Criteria and the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews checklist.[14,15]

Inclusion criteria

Included articles explored the clinical presentation and pathophysiology of HCoVs in the nervous system in children and young adults, aged 0 to 24 years. Only human clinical studies were included. Questions about inclusion were resolved by consensus among the authors.

Search strategy

Two electronic databases, PubMed and Ovid:Embase, were searched. First, we identified pediatric HCoV studies (Supplementary Table 1). The same terms were used for each database. The second search used index terms specific to the HCoV infections of the nervous system identified in the first search. Articles returned in multiple searches were analyzed and counted once. Finally, the reference lists of all included articles were reviewed for additional articles. Three searches were performed; April 21, 2020; April 28, 2020; and during revision of the manuscript on November 1, 2020.

Evidence sources

Eligibility criteria for inclusion were peer-reviewed articles, including articles in press, published between 1949 to November 1, 2020, as the first characterization of HCoV CNS infections was reported in an animal model in 1949.[1] All languages and geographic areas were included.

Critical appraisal of individual sources

Articles were evaluated for clinical data of patient presentation, chronic conditions, laboratory test results and imaging evaluation, and outcomes, including neurodevelopmental. Articles were included if they discussed a nervous system manifestation of HCoV infections in children. Articles were categorized as non-SARS-CoV-2 HCoVs and SARS-CoV-2 infections. Included articles were organized by article type, including case reports, case series, cohort studies, and review papers. Articles were excluded if there was no mention of a clinical presentation of a nervous system manifestation associated with an HCoV infection in a child. Articles were excluded if patients were adults, defined as older than 24 years. Conference abstracts and articles wherein full manuscript text was not available were excluded. Nonhuman studies were utilized only for understanding the pathophysiology. Studies that had possible neurological symptoms but where a neurological cause was ruled out were excluded. The reasons for excluding all articles were tabulated (Supplementary Tables 2-4).

Results

Search results

In total 2,302 articles were evaluated. Search 1 yielded 1,004 articles, 184 (18.3%) from Ovid:Embase and 820 (81.7%) from PubMed. Search 2 yielded 91 additional articles, 54 (59.3%) from Ovid:Embase and 37 (40.7%) from PubMed. Search 3 yielded 12 articles, seven of which were excluded because they were non-pediatric but were useful for understanding the pathophysiology of HCoV nervous system infections (Fig**)**. We identified 31 articles describing SARS-CoV-2 infections in the nervous system of children and 21 nervous system infections from other HCoVs. Within the SARS-CoV-2 studies, eight were cases of MIS-C with neurological involvement in children. There were 2,250 excluded articles.

Among the non-SARS-CoV-2 articles, five were case reports and 16 were case series (Table 1). Among the case reports, there were four infections from HCoV-OC43 and one child with both HCoV-OC43 and HCoV-229E. Case series were identified for HCoV-229E, HCoV-OC43, HCoV-HKU1, HCoV-NL63, and SARS-CoV-1 infections. No case series were identified for MERS-CoV. Clinical presentations of children due to these non-SARS-CoV-2 infections included acute flaccid paralysis (AFP), acute disseminated encephalomyelitis (ADEM), cranial nerve palsies, encephalitis, encephalopathy, febrile seizures, and weakness.

Among the 31 SARS-CoV-2 articles, there were 27 cases reports and four case series. In children without MIS-C, neurological presentations including peripheral and central etiologies of AFP (GBS and transverse myelitis), ADEM, encephalitis, and seizures, as well as cases of ischemic, hemorrhagic, and microvascular strokes (Table 2). Eight case reports detailed nervous system illness in patients with MIS-C including encephalitis, stroke, pseudotumor cerebri syndrome, and cytotoxic lesions of deep brain structures including the thalami and corpus callosum (Table 3).

Importantly, other than diagnoses based on pathologic specimens, these cases present only an association between coronavirus infection and neurological symptoms. However, in the literature where a definitive diagnosis was not made, each of the study authors reported that extensive evaluation for other etiologies was negative. Further, in instances of postinfectious neurological manifestations, the time course of symptom onset was within an accepted range for the reported disease processes. In addition, each of the HCoV-associated neurological manifestations discussed here in children has also been reported in adults with HCoVs, suggesting a common association between the virus and neurological

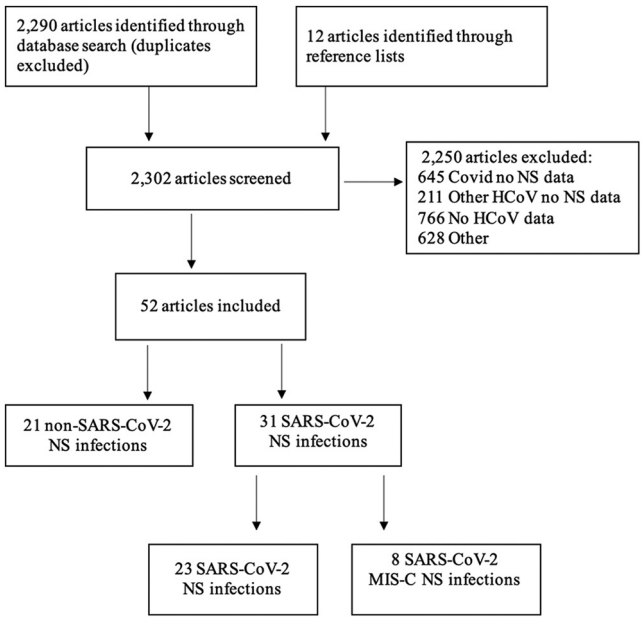

FIGURE. Study flow diagram. HCoV, human coronavirus; MIS-C, multisystem inflammatory syndrome in children; NS, neurological symptoms.

symptoms.[38] Given the severity of these clinical courses for patients, the World Health Organization (WHO) recently authored a provisional case definition for the association of SARS-CoV-2 with neurological diseases. Importantly, the preceding infection is more challenging in children given the increased propensity for asymptomatic infection in this population. Although the WHO case definition is based on adult presentations, these definitions were considered during evaluation and discussion of pediatric cases included in this review.[38]

A summary of pediatric case presentations, evaluation, and clinical outcomes follows here.

Acute flaccid paralysis

Multiple case reports described children with clinical features and laboratory studies consistent with the broad category of AFP including the more specific diagnosis of GBS, the postinfectious immune-mediated polyradiculoneuropathy. Notably, these cases were each consistent with the WHO provisional case definitions where HCoVs were “probably associated” with the child’s neurological condition, including symptom onset within six weeks of suspected acute infection, RNA or antibody evidence of infection, and absence of other probable etiology on evaluation.

Turgay et al. reported the case of a previously healthy three-year-old female in Turkey who presented with one day of dyspnea and inability to walk shortly after onset of fever, cough, and rhinorrhea.[17] Her neurological examination showed bulbar paralysis characterized by inability to chew, speak, or swallow; reduced motor strength (0/5); and absent deep tendon reflexes. She rapidly progressed to respiratory failure requiring intubation. Her initial evaluation was negative, including blood, urine, and CSF studies, as well as electromyography and magnetic resonance imaging (MRI) of the brain and spinal cord. The only positive finding was coinfection of HCoV-229E and HCoV-OC43 on a nasopharyngeal swab detected by reverse transcription-polymerase chain reaction (RT-PCR). The authors suspected GBS, one of several etiologies of AFP. After empirical treatment with intravenous immunoglobulin (IVIG), she made gains over three days but thereafter had persistent

TABLE 1
Non-SARS-CoV-2 Cases

Author	Journal	Year	Age	PMH	Neurological Examination	Neurological Diagnosis	Coronavirus Species	Selected Laboratory Test Results/Studies	Clinical Outcome
Yeh et al.[16]	Pediatrics	2004	15 years	Healthy	4/5 distal weakness in the right hand and foot, sensation above T10 normal, below patchy loss of vibration and temperature sensation, preserved proprioception and pinprick, mild dysmetria of the left hand, poor heel-to-toe walking, antalgic gait, negative Romberg	ADEM	HCoV-OC43	RT-PCR of nasopharyngeal specimens and CSF were positive for HCoV-OC43. All other testing for infectious agents was negative	Symptoms resolved over several weeks without therapeutic intervention. Follow-up MRI at 3 months showed changes in left cerebellum and right cerebral hemisphere. Despite these, the patient did not report additional symptoms
Turgay et al.[17]	Journal of Pediatric Neurosciences	2015	3 years	Healthy	Intact swallow, impaired chewing and speech, 0/5 muscle strength, absent deep tendon reflexes, plantar response was flexor	Acute flaccid paralysis	HCoV-OC43, HCoV-229E	CSF pressure, glucose, and protein were normal. Blood, urine, and CSF cultures were negative. EMG revealed no pathological findings. MRI brain and spine normal. Repeat LP and EMG at 3 weeks were normal. RT-PCR of nasal swab was positive for HCoV 229E and OC43	Treatment with intravenous immunoglobulin. At the end of the second week she could mobilize and walk with a guide
Morfopoulou et al.[18]	New England Journal of Medicine	2016	11 months	SCID	Encephalopathic	Encephalitis	HCoV-OC43	RNA sequencing of a brain biopsy positive for HCoV-OC43, confirmed on RT-PCR and brain immunohistochemistry. Negative conventional PCR of brain biopsy	Progressive encephalitis, death
Sharma et al.[19]	SAGE Open Medical Case Reports	2019	5 years	Healthy	Left Bell palsy. 4/5 muscle strength in upper extremities, 3/5 in lower, generalized hypotonia. Decreased proprioception, absent reflexes, unable to walk or raise the arms above the shoulder. Finger-to-nose, heel-to-shin tests dysmetria, appendicular ataxia, inability to handle secretions, voice with nasal intonation, dysphagia with drooling, weak cough	GBS	HCoV-OC43	Multiplex PCR of nasopharyngeal swab positive for HCoV-OC43. CSF with albuminocytologic dissociation with no cells and elevated CSF total protein, normal myelin basic protein no oligoclonal bands. Cultures of CSF, blood, and urine negative. MRI brain and spine enhancement of the left bulbar nerve complex and anterior and posterior cervical nerve roots with gadolinium	Noninvasive ventilation for acute respiratory failure. After intravenous immunoglobulin, uneventful clinical course with partial recovery within 2 weeks
Nilsson et al.[20]	Infectious Diseases	2020	9 months	Pre-B acute lymphoblastic leukemia without CNS involvement	Altered behavior and myoclonic seizures involving the abdominal wall	Encephalitis	HCoV-OC43	CSF negative for pathogens including HCoV-OC43, brain biopsy was HCoV-OC43-positive by metagenomic next-generation sequencing. EEG slow general activity without epileptic foci. MRI brain increased T2 signal in white matter near lateral ventricles and bilaterally in thalami and pons	Progressive encephalitis, death

Abbreviations:
ADEM = Acute disseminated encephalomyelitis
CSF = Cerebrospinal fluid
EEG = Electroencephalogram
EMG = Electromyography
HCoV = Human coronavirus
LP = Lumbar puncture
MRI = Magnetic resonance imaging
PMH = Past medical history
RT-PCR = Reverse transcription-polymerase chain reaction
SCID = Severe combined immunodeficiency

TABLE 2
SARS-CoV-2 Cases

Author	Journal	Year	Age	PMH	Neurological Examination	Neurological Diagnosis	Coronavirus Species	Selected Laboratory Test Results/Studies	Clinical Outcome
de Miranda Henriques-Souza et al.[21]	Neuroradiology	2020	12 years	Healthy	5 days of fever, headache, rash followed by acute, progressive, bilateral, symmetrical upper and lower extremity weakness. On hospital day #2 developed respiratory failure requiring intubation and lost several brainstem and deep tendon reflexes; flaccid quadriparesis with strength grade 0/5 in all extremities	ADEM	SARS CoV-2	CSF: normal; infectious studies negative MRI brain: extensive bilateral symmetric restricted diffusion involving the subcortical and deep white matter and corpus callosum; MRI cervical spine: longitudinally extensive myelopathy involving both white and gray matter	68 days after presentation spastic quadriparesis; strength 3/5 in left upper and bilateral lower extremities, 2/5 in right upper extremity. Regained cervical control, sitting with support and reaching for objects nearby. Global hyperreflexia. Incomplete sphincter control.
Theophanous et al.[22]	Brain and Development	2020	6 years	Prematurity (30 weeks' gestation), chromosome 17 and 19 deletions with associated otolaryngology, cardiology, immunology, pulmonary and gastroenterology conditions	1 day of right-sided facial droop presenting as an asymmetric smile, drooling, and inability to fully close the right eye. No fever or other infectious symptoms	Bell palsy	SARS CoV-2	Brain MRI: Unable to obtain Serum viral studies	3 weeks after presentation: Recovered without reported deficits
McAbee et al.[23]	Pediatric Neurology	2020	11 years	Healthy	2 days generalized weakness without respiratory symptoms or fever; presented with status epilepticus requiring four anticonvulsant medications and temperature 102.7°F	Encephalitis & seizure	SARS CoV-2 (note: also + rhinovirus and enterovirus)	CSF: 921 RBC, 16 WBC, normal glucose and protein; CSF PCR rhinovirus and enterovirus negative. Head CT: negative. EEG: frontal intermittent delta activity	6 days after presentation: recovered without reported deficits
Babar et al.[24]	Pediatric Infectious Disease Journal	2020	20 years	Obesity, anxiety	4 days of congestion, fever, ageusia, insomnia, and altered mental status (confusion, hypervigilance, obsessive thinking) although oriented and answered questions appropriately; persistent fevers, further decline in mental status over following 2 days to catatonic state with tremulousness	Encephalopathy	SARS CoV-2	CSF: normal including negative autoimmune encephalitis antibodies Brain MRI: normal × 2 EEG: generalized slowing; Serum: thyroid studies borderline normal with elevated thyroperoxidase antibody; rheumatologic studies normal	38 days after presentation: regained independence in activities of daily living. Nervous but normal speech and language, following commands
Freij et al.[25]	BMC Pediatrics	2020	5 years	Healthy	6 days of fever and severe headache, symptoms persisted and on day 10 developed confusion and had a 2-minute seizure. Waxing/waning cognition and headache until day 15 when she became lethargic and had	Encephalitis	SARS CoV-2	CSF: 7 RBC, 160 WBC 160/μL (44% neutrophils, 51% lymphocytes, 5% monocytes), glucose 30 mg/dL, protein 112 mg/dL. CSF infectious studies negative. Brain MRI: extensive meningoencephalitis of cerebellum and corpus callosum,	Deceased 32 days after illness onset

(*continued on next page*)

TABLE 2 (*continued*)

Author	Journal	Year	Age	PMH	Neurological Examination	Neurological Diagnosis	Coronavirus Species	Selected Laboratory Test Results/Studies	Clinical Outcome
					asymmetric pupils followed by ongoing neurological and overall clinical deterioration			leptomeningeal enhancement over the surface of the brainstem and into the auditory canals Brain MRA: normal; Cerebellar brain biopsy: positive for SARSCoV-2 RNA and *Mycobacterium tuberculosis* complex DNA	
Khalifa et al.[26]	Journal of the Pediatric Infectious Diseases Society	2020	11 years	Healthy	30 days after URI and fever, developed acute-onset symmetrical weakness of bilateral lower extremities and loss of deep tendon reflexes. Tingling, impaired sensation to pain and light touch of distal and impaired proprioception of lower extremities	GBS	SARS CoV-2	CSF: 5 WBC, glucose 65 mg/dL, protein 316.7 mg/dL. Spine MRI: enhancement of the cauda equina nerve roots. Nerve conduction velocity studies: delayed latencies and low amplitude with dispersion of compound muscle action potentials, No F-wave response with impaired sensory conduction	15 days after presentation: improved strength and sensory symptoms. Nerve conduction studies 1 week after discharge showed improved distal latencies, conduction velocities, and amplitudes with recorded but delayed F-waves
Swarz et al.[27]	Pediatric Neurology	2020	9 years	Healthy	Acute-onset focal status epilepticus and encephalopathy; no meningismus; 8 h after admission, developed fever with intractable vomiting	Status epilepticus and encephalopathy	SARS CoV-2	EEG: continuous delta slowing throughout the right hemisphere without epileptiform features. Head CT: normal. Brain MRI: normal	Recovered without reported deficits
Essajee et al.[28]	BMJ Case Reports	2020	2.5 years	Healthy	Lethargic (GCS 11), right pupillary dilatation with right ptosis, left-sided weakness (arm > leg), globally brisk deep tendon reflexes and bilateral extensor plantar responses	Cerebral sinus venous thrombosis in the setting of COVID-19 coagulopathy and tuberculosis meningitis	SARS CoV-2, *Mycobacterium tuberculosis*	CSF: acellular. Head CT: hydrocephalus, basal meningeal enhancement, and infarction involving the anterior limb of the right internal capsule, lentiform nucleus, and thalamus. Cerebral sinus venous thrombosis seen on sagittal postcontrast images as multiple filling defects in the venous system, mainly superior sagittal and transverse sinuses Blood culture: *Mycobacterium tuberculosis* GeneXpert MTB/RIF positive and rifampicin sensitive	Following 1 month of intensive neurorehabilitation, GCS 15, feeding orally with residual left hemiparesis
Kaur et al.[29]	Pediatric Neurology	2020	3 years	Healthy	Acute-onset progressive extremity weakness resulting in flaccid quadriparesis, areflexia, and decreased sensation. Normal mental status. Absent cough and gag reflexes	Transverse myelitis	SARS CoV-2	CSF: 42 WBC (96% neutrophils), protein 58 mg/dL; infectious studies negative. Brain MRI: normal Spine MRI: swelling of the cervical spinal cord with T2-hyperintense edema involving most of the transverse aspect of the spinal cord,	Ongoing flaccid quadriparesis. Spine MRI (follow-up): injury evolution with early myelomalacia of lower cervical cord, interval reduction in lesion length and decreased edema in the medulla and upper cervical cord

TABLE 2 (*continued*)

Author	Journal	Year	Age	PMH	Neurological Examination	Neurological Diagnosis	Coronavirus Species	Selected Laboratory Test Results/Studies	Clinical Outcome
								extending from the lower medulla to the midthoracic level Serum: rheumatologic evaluation and aquaporin-4 and myelin oligodendrocyte glycoprotein autoantibody testing negative	

Abbreviations:
ADEM = Acute disseminated encephalomyelitis
CSF = Cerebrospinal fluid
CT = Computed tomography
EEG = Electroencephalogram
GBS = Guillain-Barré syndrome
GCS = Glasgow Coma Scale
MRA = Magnetic resonance angiography
MRI = Magnetic resonance imaging
MTB/RIF = GeneXpert Mycobacterium tuberculosis/Rifampin assay
PMH = Past medical history
RBC = Red blood cells
RT-PCR = Reverse transcription-polymerase chain reaction
URI = Upper respiratory infection
WBC = White blood cells

motor weakness. Surprisingly, repeat CSF and electromyography studies three weeks after presentation were again normal, leading the authors to conclude that her presentation was more consistent with the less-specific diagnosis of AFP secondary to coronavirus infection given the known neurotrophic, neuroinvasive, and neuroinflammatory potential of the coronaviruses.

In another case, a five-year-old male presented with unilateral facial nerve palsy, progressive lower extremity weakness, and areflexia two weeks after having fever and nasal congestion.[19] The patient developed bulbar palsy characterized by dysphagia with drooling, a weak cough, and respiratory distress but did not require intubation. Diagnostic evaluation was consistent with GBS including CSF with albuminocytologic dissociation. MRI of the brain and spine demonstrated enhancement of the left bulbar nerve complex and anterior and posterior cervical nerve roots. Microbiology evaluation was negative except HCoV-OC43 by RT-PCR of the patient's blood. Following IVIG his respiratory status and bulbar palsy improved over a week.

Similarly, GBS has been reported in a child with SARS-CoV2.[26] An 11-year-old male in Saudi Arabia presented with onset of symmetrical leg weakness and loss of deep tendon reflexes three weeks after a fever and upper respiratory tract infection. In addition, the patient had lower extremity tingling and impaired sensation to pain, light touch, and proprioception. Supporting a diagnosis of GBS, CSF studies showed albuminocytologic dissociation, MRI of the spine demonstrated enhancement of the cauda equina nerve roots, and nerve conduction studies were consistent with a demyelinating process. Initially the authors evaluated the child for infectious pathogens more commonly associated with GBS-like presentations, all of which were found to be negative; this prompted a nasopharyngeal swab for SARS-CoV-2, which was positive approximately 22 days after symptom onset. He was treated with IVIG for GBS and then later received a week-long course of hydroxychloroquine. Over a two-week period, the patient regained the ability to ambulate, which was further reflected in improvement in nerve conduction studies repeated one week after discharge.

In all three cases, the patients made general recoveries, but weeks after presentation they had not yet regained full motor strength. Long-term neurodevelopmental outcomes were not reported.

A central cause of AFP, transverse myelitis (TM), was reported in a child with otherwise asymptomatic SARS-CoV-2 infection.[29] Three weeks following upper respiratory tract symptoms in multiple household family members, all of whom ultimately proved to have SARS-CoV-2 infection, a three-year-old girl presented with progressive weakness and decreased sensation in her extremities. She rapidly declined to flaccid quadriparesis and respiratory failure requiring intubation. MRI of the spine revealed spinal cord edema with a longitudinally extensive lesion involving most of the transverse spinal cord from the lower medulla to the midthoracic level. CSF studies revealed pleocytosis and mildly elevated protein. Extensive evaluation for possible infectious, rheumatologic, and autoimmune etiologies was negative other than positive SARS-CoV-2 RT-PCR from nasopharyngeal swab. Given the persistence of flaccid paresis, treatment of her TM escalated to plasmapheresis. Unfortunately, her examination eight days after presentation remained unchanged, and long-term outcome was not reported.

Acute disseminated encephalomyelitis

Central demyelination due to ADEM has also been reported in children with coronaviruses.

Yeh et al. cared for a 15-year-old male, previously healthy, who had one day of irritability, right hand clumsiness, and difficulty walking.[16] Abnormalities on neurological examination included distal weakness in his upper and lower extremities, left hand dysmetria, antalgic gait, and diminished vibration and temperature sensation below T10. MRI of the brain and spinal cord revealed hyperintensity in the white matter of the right centrum semiovale and left cerebellum and non-enhancing spinal lesions at the cervical and thoracic levels, all consistent with a diagnosis of ADEM. HCoV-OC43 was detected in nasopharyngeal secretions, and evaluation for more common pathogens was negative. Symptoms

TABLE 3
SARS-CoV-2 MIS-C Cases

Author	Journal	Year	Age	PMH	Neurological History and Examination	Neurological Diagnosis	SARS CoV-2 Positive Testing	Selected Laboratory Test Results/Studies	Clinical Outcome
Regev et al.[30]	Pediatric Infectious Disease Journal	2020	16 years	Healthy	3 weeks following COVID-19 exposure: onset fever, sore throat, fatigue and abdominal pain followed by headache and nuchal rigidity. On third day of hospitalization, developed warm shock requiring intubation and clonus	Cerebrovascular disease, diffuse microvasculature involvement	Nasopharyngeal swabs for SARS-CoV-2 were negative × 2 initially. Following clinical decompensation, one SARS-CoV-2 nasopharyngeal swab positive and associated serologic confirmation of past SARS-CoV-2 infection with positive IgG and IgA (tested on serum sampled before IVIG)	CSF: mild pleocytosis, normal glucose, infectious studies negative. Head CT: negative. Brain MRI/MRA: diffuse small low-signal foci of hemosiderosis in subcortical white matter of both hemispheres and corpus callosum suggestive of an inflammatory process of brain microvasculature Serum and other testing: blood and sputum culture, respiratory viral panels were negative Elevated troponin-I, pro-brain natriuretic peptide, CRP, and D-dimer; Very low levels of C3 and C4 Echocardiography: mildly reduced systolic left ventricular function, ejection fraction 50%, and mild mitral regurgitation. Coronary arteries normal	2 weeks after discharge: recovered except general muscle weakness
Verkuil et al.[31]	The Lancet	2020	14 years	Healthy	5 days of fever, headache, rash, diarrhea, dyspnea that progressed to septic shock requiring mechanical ventilation × 6 days. Post-extubation, new right eye abducens palsy. Dilated fundus examination revealed bilateral papilledema with left-disk hemorrhages. Neurological examination otherwise normal	Secondary pseudotumor cerebri syndrome	Nasopharyngeal and deep endotracheal sampling for SARS-CoV-2 by RT-PCR were negative following decompensation. After discharge, SARS-CoV-2 IgG antibody was positive	CSF: normal studies. Brain MRI/MRV: signs of increased intracranial pressure. Serum: leukopenia; elevated CRP and fibrinogen. Chest CT: diffuse ground glass airspace opacities with subpleural sparing Echocardiography: diffuse dilation of the right coronary artery	2 months after discharge: resolution of papilledema, disk hemorrhages, and abducens palsy
Schupper et al.[32]	Child's Nervous System	2020	Two cases: 2 months, 5 years	2 months: tracheomalacia with tracheostomy; 5 years: healthy	2 months: presented in respiratory failure progressing to require ECMO × 8 days. 5 years: several days of fever, cough, and abdominal pain progressing to cardiogenic shock and cardiopulmonary failure requiring ECMO. After 5 days on ECMO, developed bilateral fixed and	Stroke	2 months: negative for COVID-19 antibodies 5 years: positive for COVID-19 antibodies	2 months: head CT: bilateral middle and posterior cerebral artery infarctions with hemorrhagic transformation. Brain MRI: evolving hemorrhagic infarctions of bilateral occipitoparietal lobes, left temporal and frontal lobes, and stable bilateral subdural collections. EEG: nonconvulsive	2 months: undergoing weaning of ventilator at the time of publication 5 years: deceased

TABLE 3 (*continued*)

Author	Journal	Year	Age	PMH	Neurological History and Examination	Neurological Diagnosis	SARS CoV-2 Positive Testing	Selected Laboratory Test Results/Studies	Clinical Outcome
					dilated pupils and ultimately lost all brainstem reflexes.			status epilepticus Serum: high interleukin-6. 5 years: head CT: right middle cerebral artery infarction, cerebral edema, and diffuse contralateral subarachnoid hemorrhage	
Gaur et al.[33]	American Journal of Neuroradiology	2020	Two cases: 9 years, 12 years	Both healthy	9 years: fever, altered mental status, and lethargy with dysarthria and ataxia. 12 years: 5-day history of fever, lethargy, severe headache, vomiting, lower abdominal pain, and diarrhea with normal neurological examination; progressed to cardiogenic shock and worsening mental status requiring intubation	Cytotoxic lesions of the corpus callosum	9 years: nasopharyngeal swabs negative initially; subsequent bronchoalveolar lavage revealed positive SARSCoV-2 via RT-PCR testing 12 years: nasopharyngeal swab RT-PCR was negative × 2 initially. Subsequent SARS-CoV-2 IgG antibody was positive	9 years: brain MRI: extensive abnormal T2-weighted hyperintense signal and restricted diffusion in the entire corpus callosum and frontoparietal cerebral white matter. Serum: elevated CRP and ferritin 12 years. Brain MRI: a small, oval-shaped, T2-weighted hyperintense lesion in the splenium of the corpus callosum that exhibited restricted diffusion. Serum: elevated D-dimer, fibrinogen, CRP, ferritin, LDH, procalcitonin, and troponin	Not discussed
Abel et al.[34]	Neurology	2020	33 months	Healthy	2 days of fever, emesis, and rash with tachycardia, which progressed to respiratory distress, somnolence, diffuse hypotonia, and significant weakness	Encephalitis	Nasopharyngeal RT-PCR was initially negative and then indeterminate. SARS-CoV-2 antibody testing was positive	CSF: normal. Head CT: normal. Brain MRI: restricted diffusion in bilateral lateral thalamic nuclei. Brain MR angiography and spectroscopy normal. EEG: moderate diffuse slowing Echocardiography: decreased left ventricular systolic function. Serum: elevated inflammatory and cardiac markers, ammonia	12 days after presentation: following commands, communicating verbally and walking with support. Discharged home on day 15 with only mild residual weakness (strength 4/5)
Kihira et al.[35]	Pediatric Radiology	2020	5 years	Healthy	3 days fever, cough, abdominal pain. Clinically deteriorated, developed cardiogenic shock and placed on venoarterial ECMO. Acute onset, fixed dilated pupils, absent corneal and gag reflexes, and no movement to painful stimuli	Stroke	Plasma SARS CoV-2 antibody testing	Head CT: large right anterior and middle cerebral artery infarction with subarachnoid hemorrhage in the left hemisphere	Deceased
Hutchison et al.[36]	Psychosomatics	2020	14 years	Healthy	Acute-onset fever, abdominal pain and truncal rash,	Confusion and agitation	Nasopharyngeal RT-PCR was initially negative. SARS-CoV-	CSF: not collected. Brain MRI: unremarkable	11 days after presentation returned to

(*continued on next page*)

TABLE 3 (*continued*)

Author	Journal	Year	Age	PMH	Neurological History and Examination	Neurological Diagnosis	SARS CoV-2 Positive Testing	Selected Laboratory Test Results/Studies	Clinical Outcome
					confusion, disorientation, delusions, and aggression		2 antibody testing was positive	Serum: interleukin-6 elevated at 5651 pg/mL (normal < 17.4 pg/mL), Echocardiography: left ventricular ejection fraction of 58% and mild coronary artery dilation (*z* score < 2.5)	cognitive baseline, spontaneous movement, and speech; affect was reactive and appropriate; attention, concentration, and short-term memory were all improved
Tiwari et al.[37]	The Lancet	2020	9 years	Healthy	14 days high-grade fever, throbbing frontal headache, vomiting, and progressive weakness on the right side of the body. On presentation GCS of 11, upper motor neuron-type right-sided seventh cranial nerve palsy, complete hemiplegia, brisk deep tendon reflexes, and extensor plantar response on the right, normal pupils, no signs of meningeal irritation	Stroke	Nasopharyngeal RT-PCR was positive on admission	CSF: 50 WBC (lymphocytes 80%, polymorphs 20%), glucose 45, protein 60 mg/dL, negative microbiology. CT angiography: multifocal smooth stenosis of both intracranial internal carotid arteries, right middle cerebral artery, and both A2 segments of the anterior cerebral arteries. Diffuse narrowing of the M2 and M3 segment branches of both middle cerebral arteries	3 weeks in the pediatric intensive care unit reached a GCS of 13 and power 3/5 on the affected side. Transferred to general ward for further psychomotor rehabilitation

Abbreviations:
ADEM = Acute disseminated encephalomyelitis
CRP = C-reactive protein
CSF = Cerebrospinal fluid
CT = Computed tomography
ECMO = Extracorporeal membrane oxygenation
EEG = Electroencephalogram
GBS = Guillain-Barré syndrome
GCS = Glasgow Coma Scale
IVIG = Intravenous immunoglobulin
MRI = Magnetic resonance imaging
MRV = Magnetic resonance venography
PMH = Past medical history
RBC = Red blood cells
RT-PCR = Reverse transcription-polymerase chain reaction
URI = Upper respiratory infection
WBC = White blood cells

resolved over several weeks without therapeutic intervention. Follow-up MRI at three months showed a new demyelinating lesion in the left cerebellum and increased size of the right cerebral lesion. Despite these imaging changes, he did not report additional symptoms.

Similarly, a previously healthy 12-year-old female presented with five days of fever, headache, and rash followed by acute, progressive, bilateral, symmetrical upper and lower extremity weakness.[21] On the second hospital day, she developed respiratory failure requiring intubation with loss of several brainstem reflexes, inability to follow commands, and onset of profound flaccid quadriparesis and absence of deep tendon reflexes. As with the prior case, all infectious studies were negative, including CSF studies, except for a positive nasopharyngeal RT-PCR for SARS-CoV-2. Consistent with ADEM, MRI of the brain showed extensive bilateral restricted diffusion involving the subcortical and deep white matter and corpus callosum. Similarly, MRI of the cervical spine showed longitudinally extensive myelopathy involving both white and gray matter. Unlike the patient reported by Yeh et al. who recovered, more than two months after initial presentation, this patient had only begun to regain strength and motor control. She had persistent spastic quadriparesis with her maximal extremity strength being that she was able to move against gravity but not against resistance. The patient could sit with support and reach for objects nearby but had global hyperreflexia and incomplete sphincter control.

These cases illustrate the potential for persistent subclinical and severe clinical deficits following ADEM in children associated with coronavirus infections.

Seizures

Seizures, especially simple febrile seizures, were the most common neurological presentation associated with all coronavirus

infections among the cases evaluated. Simple febrile seizures are characterized by brief (less than 15 minutes) generalized seizures that occur in the absence of intracranial infection, metabolic disorders, or history of afebrile seizures. Simple febrile seizures are not associated with increased risk of epilepsy or neurodevelopmental disorders.[39] In particular, multiple case series reported the predominance of HCoV-associated simple febrile seizures in children younger than one year. Laurent et al. found that HCoV-OC43 infections occurred more frequently than influenza viruses in this age group.[40-42] Children with HCoV-related febrile seizures appear to recover well.[42,43] No studies included discussion of long-term neurodevelopmental outcomes following febrile seizures due to HCoV infections.

In addition to febrile seizures, Esper et al. and Garcia-Howard et al. describe onset of afebrile seizures concurrent with otherwise mild courses of HCoV-HKU1 and one of SARS-CoV-2 respiratory infections in a four-month-old and three-month-old, respectively.[44,45] Although a possible underlying etiology for the seizure in the case presented by Esper et al. was not further investigated, Garica-Howard et al. conducted whole exome sequencing for their patient and identified a mutation in the PRRT2 gene, which has been associated with benign familial infantile convulsions.

Furthermore, four case reports describe status epilepticus as the presenting symptom of children infected with SARS-CoV-2.[23,27,46,47] McAbee et al. describe an 11-year-old previously healthy male who presented with status epilepticus requiring four antiepileptic medications and a temperature of 102.7°F after two days of generalized weakness without respiratory symptoms or fever at home. The patient's nasopharyngeal swab was positive for SARS-CoV-2, and all other infectious studies were negative, including in the CSF. Electroencephalography showed frontal intermittent delta activity. Six days after presentation, the patient was reported to have made a complete recovery.

Swarz et al., Farley et al., and Saeed et al. also describe cases of status epilepticus as a presenting sign of SARS-CoV-2. Notably, Farley et al. describe an eight-year-old with an underlying tic disorder who remained afebrile throughout the entire course of his illness. All children reported to present with status epilepticus in the setting of SARS-CoV-2 recovered, although no description of long-term neurodevelopmental outcomes was included in the case reports.

Encephalitis

Encephalitis was the second most common neurological presentation of children with SARS-CoV-2 and other HCoVs. In both the non-SARS-CoV-2 encephalitis case reports, the patients were younger than one year, immunocompromised, and infected by HCoV-OC43. In 2016, Morfopoulou et al. reported an 11-month-old boy with fatal encephalitis and severe combined immunodeficiency deficiency.[18] The patient had undergone an unconditioned cord blood transplant with successful T cell engraftment. Unfortunately, one and a half months post-transplant he developed encephalitis and died. The patient had negative microbiology results on RT-PCR. However, RNA sequencing of the brain biopsy detected HCoV-OC43. Similarly, Nilsson et al. reported the case of a nine-month-old male with pre-B acute lymphoblastic leukemia who tested positive for HCoV-OC43 on a respiratory swab five months after diagnosis.[20] At the time, all evaluation was otherwise negative, including CSF for HCoV-OC43. An additional four months later, the patient was admitted with altered behavior and abdominal myoclonic seizures. Electroencephalography showed general slowing and MRI of the brain demonstrated increased T2 signal bilaterally in the white matter tracts adjacent to the lateral ventricles and in the thalami and pons. As the patient deteriorated, deep sequencing analysis of a brain biopsy sample was done and found to be positive for HCoV-OC43. An experimental trial of lopinavir, the human immunodeficiency virus protease inhibitor, was attempted, but the patient died shortly thereafter.

In addition to these case reports, Li et al. and Dominguez et al. found HCoV antibodies in the CSF of 22 of 183 (12%) and five of 63 (8%) of their respective cohorts of children with acute encephalitis-like presentations (seizure, headache, vomiting). The relative frequency of HCoV antibodies in these patients suggests that HCoV CNS infections may be underreported in children.[48,49]

We identified six cases of encephalitis in children with SARS-CoV-2; however, the patient described by Freij et al. was notable for similarity with those of Morfopoulou et al and Nilsson et al. for the concurrence of a severe coronavirus infection in the setting on systemic illness related to underlying immunocompromise.[25] In this case, a previously healthy five-year-old girl presented following six days of fever and severe headache. Notably, she had a normal head computed tomography (CT) on day 9 of illness, which was obtained due to persistence of her initial headaches. She was discharged on day 10, only to be readmitted later that day following onset of confusion and a two-minute seizure. Her course waxed and waned until day 15 when she became lethargic and had asymmetric pupils followed by ongoing neurological and overall clinical deterioration. She was intubated on day 17. CSF studies were negative for infectious etiology including SARS-CoV-2. MRI of the brain showed extensive progression of meningoencephalitis of the cerebellum and corpus callosum, with leptomeningeal enhancement especially over the surface of the brainstem and into the auditory canals. As her clinical case worsened, she underwent a midline suboccipital craniectomy and C1 laminectomy on day 30. The cerebellum was necrotic and edematous and herniated out of the surgical defect. Sadly, she died on day 32 of illness. Despite previously negative infectious studies, cerebellar brain biopsy was positive for SARS-CoV-2 RNA as well as for *Mycobacterium tuberculosis* complex DNA. Tracheal aspirates grew *M. tuberculosis* weeks after the patient's death. Freji and colleagues hypothesized that their patient was asymptomatically infected with *M. tuberculosis* but that eventually the host immune system could not concurrently respond to the SARS-CoV-2 virus and continue to suppress *M. tuberculosis* proliferation within macrophages.

These three cases are notable among multiple reports of encephalitis for their illustration of the role coronavirus infections may play in dysregulating the immune system or exacerbating underlying immunocompromise. Despite the prospect of life-threatening encephalitis, none of the cases identified included description of the neurodevelopmental outcomes.

Stroke

Cerebrovascular events were only reported in association with SARS-CoV-2 infections. Similar to the case presented by Freji et al., Essajee and colleagues in Cape Town, South Africa, reported concurrence of active *M. tuberculosis* infection and SARS-CoV-2 in a previously healthy 2.5-year-old girl.[28] Upon presentation, the patient had acute onset of lethargy (Glasgow Coma Scale: 11), right pupillary dilatation with right ptosis, left sided weakness (arm > leg), globally brisk deep tendon reflexes, and bilateral extensor plantar responses. In addition, she had progressively enlarging cervical lymphadenopathy and decreased appetite. Nasopharyngeal swab for SARS-CoV-2 was positive, and an emergency head CT showed pan-hydrocephalus, basal meningeal enhancement, and infarction involving the anterior limb of the right internal capsule, lentiform nucleus, and thalamus. Cerebral sinus venous thrombosis was seen on postcontrast images as

multiple filling defects in the venous system, mainly superior sagittal and transverse sinuses. Gastric aspirate was sent for GeneXpert MTB/RIF testing and found to be positive and rifampicin sensitive. Blood cultures also grew *M. tuberculosis*. Notably, she was coagulopathic on presentation with an international normalized ratio of 1.63, elevated prothrombin time, normal activated partial thromboplastin time, and elevated fibrinogen and D-dimer. Like Freji and colleagues, Essajee et al. postulated that SARS-CoV-2 likely caused a cytokine storm, which exhausted the patient's capacity to immunologically respond to both the virus and *M. tuberculosis* infections. In addition, the hyperinflammatory response is suspected to have resulted in endothelial damage, which exacerbated her coagulopathy and stroke risk.

This patient survived and following one month of intensive neurorehabilitation had regained the ability to feed orally, but she still had residual left hemiparesis. No mention is made in the report of her potential for long-term neurodevelopmental deficits.

Two additional case reports describe focal cerebral arteriopathy characterized by narrowing and banding of the left middle cerebral artery with acute infarctions of the left insula and basal ganglia in children with positive SARS-CoV-2 testing.[50,51] In both cases, additional etiologic evaluation was unremarkable. Based on current evidence from the adult population, the authors hypothesize that these strokes were secondary to SARS-CoV-2 cytokine storm resulting in inflammation-induced focal vasculitis. Notably, neither presentation met the diagnostic criteria of MIS-C.

Neurological manifestations associated with MIS-C

The WHO characterized MIS-C according to a six-part definition, which includes pediatric age, persistence of fever, laboratory evidence of inflammation, signs or symptoms of organ dysfunction, lack of an alternative diagnosis, and a close temporal onset with SARS-CoV-2 infection or exposure.[52] In our review, there were eight articles that reported neurological signs and symptoms in the setting of MIS-C including encephalitis, acute hemiparesis following cerebrovascular events, altered mental status associated with microinfarcts in deep brain structures, acute-onset neuropsychiatric symptoms including confusion and agitation, and cranial nerve palsies associated with elevated intracerebral pressure.

Among patients suffering from cerebrovascular disease, children with MIS-C appeared to have more evidence of microvascular infarcts in deep brain structures compared with cerebrovascular manifestations in patients without MIS-C. Regev et al. reported a 16-year-old male, previously healthy, who experienced fever, sore throat, fatigue, and abdominal pain three weeks following SARS-CoV-2 exposure.[30] He had headache and nuchal rigidity at presentation, and on the third day of hospitalization he developed warm shock requiring intubation. Initially nasopharyngeal swabs for SARS-CoV-2 were negative, but following clinical decompensation he had a positive nasopharyngeal swab and associated serologic confirmation of past SARS-CoV-2 infection with positive IgG and IgA antibodies. Initial head CT was negative, but brain MRI/magnetic resonance angiography showed diffuse small low-signal foci of hemosiderosis in subcortical white matter of both hemispheres and the corpus callosum suggestive of an inflammatory process of the cerebral microvasculature. The patient generally recovered from MIS-C without obvious cognitive deficits, although he was noted to have persistent weakness.

Similarly, Gaur et al. reported two cases in males, nine and 12 years old, who had onset of fever and altered mental status. In both cases MRI of the brain revealed restricted diffusion lesions throughout the corpus callosum.[33] Both patients were diagnosed with MIS-C and had a rapid response to immunotherapy. In the nine-year-old patient, repeat MRI showed near-complete resolution of the corpus callosum lesions, indicating that the suspected microinfarcts were likely secondary to an inflammatory, possibly cytokine-mediated, mechanism.

In addition to cerebrovascular lesions, atypical neurological presentations of other neurological disorders were observed in children with MIS-C.

Secondary pseudotumor cerebri was reported in a 14-year-old who presented after five days of fever, headache, rash, diarrhea, and dyspnea that progressed to septic shock requiring mechanical ventilation.[31] Following extubation, he had an apparent new right-eye abducens nerve palsy. Dilated fundoscopic examination revealed bilateral papilledema and left-disk hemorrhages with the remainder of his neurological examination otherwise normal. Brain MRI/magnetic resonance venography revealed signs of increased intracranial pressure consistent with secondary pseudotumor cerebri syndrome. Two months after discharge the patient has resolution of papilledema, disk hemorrhages, and abducens nerve palsy.

Neurobehavioral manifestations are exemplified by the case report of a 14-year-old previously healthy male who had acute onset of fever, abdominal pain, truncal rash, and altered mental status including disorientation, delusions, and aggression.[36] Initial evaluation included echocardiography, which found a diminished left ventricular ejection fraction of 58% and mild coronary artery dilation (z score < 2.5). He was begun at admission on a course of methylprednisolone, and he met the diagnostic criteria for atypical KD and received a course of IVIG. Early in the course, his neuropsychiatric status continued to deteriorate, eventually requiring sedation with dexmedetomidine. Notably, an MRI of the brain on day 3 was unremarkable and no CSF studies were done. Nasopharyngeal swab for SARS-CoV-2 was negative, but testing for SARS-CoV-2 IgG was positive one week following initial presentation. When his sedation was successfully discontinued, his neurological examination showed him to be sleepy, inattentive, and unable to follow multistep commands with an otherwise intact neurological examination. Gradually he regained his cognitive baseline including normal speech, attention, concentration, and short-term memory based on bedside examination and neurologist assessment. Formal measures of cognitive and behavioral function were not completed, and postdischarge neurocognitive assessment was not reported. The authors note confounding variables and likely multifactorial etiology contributing to severe agitation in a child in the pediatric intensive care unit (PICU). However, the consistency of this presentation to reported neuropsychiatric manifestations in KD lends weight to the role of cytokine storm-induced inflammation as one important contributor.

Discussion

In this scoping review we evaluated the case literature of HCoV infections in the nervous system in children to gain insight into the anticipated neurodevelopmental effects of pediatric SARS-CoV-2 infections. Six of the seven HCoVs, excepting MERS-CoV, have been associated with either primary or secondary neurological insults in children. In the most severe form, cases of HCoV infections were associated with AFP, ADEM, encephalitis, status epilepticus, and stroke. Particularly notable were CNS lesions associated with MIS-C secondary to SARS-CoV-2 infections, which included major vessel and microvascular cerebral infarcts, secondary pseudotumor cerebri, and acute-onset severe neuropsychiatric distress in previously healthy children. Fatalities have been reported in multiple children with neurological insults following MIS-C. In less-severe presentations, HCoV infections were associated with febrile seizures, particularly among infants, and focal nerve palsies.

Taken together these reports illustrate the rare but established ability for HCoVs to cause severe neurological disease resulting in ongoing functional impairments. Further, among the articles excluded for absence of neurological manifestations, there is an extensive body of literature demonstrating the potential of HCoVs to cause severe systemic illness requiring critical care, a risk factor itself for neurodevelopmental deficits. However, among all articles reviewed, we identified only brief exploration of the neurodevelopmental implications of HCoV infections. Given the risk to long-term child neurodevelopment of HCoV infections, greater guidance for neurodevelopmental monitoring is needed.

Neurodevelopmental monitoring for long-term developmental and behavioral sequelae

Neurodevelopmental monitoring may be intuitive for many of these diagnoses in many child neurology clinical practices. However, there is variability in the duration of monitoring, the extent of evaluation, and the availability of testing options. Rapid global recovery of skills may mask more subtle long-term yet impairing deficits, some of which may appear years later when a child is expected to develop a specific skill. Many of these deficits are either not readily apparent before discharge from neurological clinical care or are not specifically queried in clinic and thereafter may persist without additional evaluation. Furthermore, the role of the neurologist in managing developmental and behavioral sequelae is not standardized, with some providers preferring to refer learning-, behavior-, and motor function-related deficits to colleagues in developmental and behavioral pediatrics, psychiatry, and physical medicine and rehabilitation, respectively.

Therefore, at out institution, we have developed the practice that children with direct neurological involvement or critical illness and factors associated with increased risk for developmental and behavioral sequelae are followed by neurodevelopment and, when needed, neuropsychology specialists. However, given that such specialty care is not always easily accessed, primary care providers must be familiar with the common, age-related signs of potential neurodevelopmental impairment following acquired brain injury. Guidance by age is provided in Table 4.

Although some parents or the child may express concerns about neurodevelopmental changes following illness, physicians often need to inquire specifically about each area of neurological function to comprehensively address sequelae. Asking in depth about skills outlined in Table 4 provides a cognitive construct that can guide providers in eliciting further standardized evaluation. For example, when asked if their child remembers to do their chores or turn in their homework, a parent may acknowledge that their child is "not remembering anything," which could represent a working memory deficit, inattention, mood interference, or a more global injury affecting memory. Although the specific tests used may vary across clinical practices, neuropsychologists are able to administer standardized testing to help better understand the underlying cognitive deficit to guide targeted management. The overarching goals of neurodevelopmental monitoring are to anticipate and mitigate functionally disruptive symptoms, to optimally transition into home, school, and community, and to maximize outcome through timely therapeutic and medical interventions.

Neurodevelopmental insights of SARS-CoV-2 infections from other pathogens

From our review, it is apparent that a knowledge gap exists about the long-term neurodevelopmental sequelae of HCoV infections in children and particularly SARS-CoV-2. Until more robust clinical evidence is available, the sequalae associated with other pathogens causing similar clinical presentations are useful case studies for anticipating the neurodevelopmental effects of pediatric SARS-CoV-2 infections.

Acute flaccid paralysis

GBS primarily affects the peripheral nerves, whereas both acute flaccid myelitis (AFM) and TM are immune-mediated conditions affecting the CNS, especially the spinal cord. Under the category of AFP, GBS, AFM, and TM present with substantial weakness and potentially respiratory depression.[53,54] Despite the consistency of weakness at onset, reported outcomes reveal a great deal of variability in long-term motor strength and function for all three pathologies.

Data from several pediatric GBS cohorts suggest full motor recovery in 66% to 94% patients. However, one-fourth of the children report adverse effects on schoolwork and quality of life.[54] Follow-up studies of adults who had GBS during childhood have shown that many patients experience residual pain, unsteadiness, and fatigue in their daily lives.[55] A recent review of pediatric TM discusses the variability in reported outcomes.[56] Overall, nearly half of the children make a complete recovery, although individuals with ongoing weakness can experience substantial functional

TABLE 4
Signs of Potential Neurodevelopmental Impairment Following Acquired Brain Injury

Developmental Domain	0-3 Years Old	3-6 Years Old	6-18 Years Old
Cognitive	Lack of object exploration; does not develop pretend play; slower development of self-help skills (e.g., spoon use)	Slower or lack of self-help skills; slower than peers to learn (e.g., rules of game, colors, shapes); inattention	Needs longer time to process and/or repetition when learning or completing tasks; forgetfulness (e.g, "not remembering anything"); inattention; executive dysfunction (e.g., poor organization and planning)
Language	Delay in expressive and receptive language milestones (e.g., pointing to identify; novel 2-word sentences; concept of "one")	Does not ask or understand "Why" questions; difficulty with prepositions, word-finding, and/or following conversation	Incorrect word use or word-finding problems; difficulty with social communication and interactions; struggles with multistep instructions
Academic	Difficulty learning colors, sorting, matching, counting etc.; does not join in rhyming games	Difficulty learning letters, letter sounds, numbers, counting with one-to-one correlation	Struggling in school, most commonly with reading comprehension, written expression, and math
Motor	Delay in gross motor (e.g., walking, jumping) and/or fine motor milestones (e.g., unzipping, drawing lines, or a circle); poor oromotor skills (feeding difficulty)	Trouble learning gross motor skills (e.g., hopping on one foot, skipping, riding bike); difficulty drawing shapes; draws an immature person for age; struggles with cutting with scissors or shoe tying	More clumsy than peers; poor handwriting, struggles with fine motor skills
Mood/behavior	Excessive or persistent irritability; excessive outbursts; changes in sleep initiation or duration	Emotional dysregulation; hyperactivity and impulsivity; changes in sleep initiation or duration	Emotional dysregulation; hyperactivity and impulsivity; depression or anxiety; changes in sleep initiation or duration

impairment. In addition, there is a high frequency of ongoing sensory disturbance and bladder dysfunction. Data on the long-term outcomes of the recent United States AFM outbreak from 2012 to 2016, which was associated primarily with Enterovirus D68, indicate that the majority of children make notable functional gains, such as the ability to walk short distances, over several months. Yet, 75% to 95% may still have residual weakness and significant functional impairments with a minority remaining technology dependent and severely disabled.[53,57] Children presenting with AFP of any etiology, including GBS, TM, and AFM, associated with SARS-CoV-2 should receive long-term neurodevelopmental surveillance.

Seizures

Children generally do well and do not typically develop major neurodevelopmental sequelae following febrile seizures. However, one large population-based prospective study reported a 20% to 35% increase in the diagnosis of attention-deficit/hyperactivity disorder in children with febrile seizures that followed into adulthood compared with the general population.[58] In addition, both febrile status epilepticus and recurrent febrile seizures have been associated with long-term neurodevelopmental difficulties including weaker motor development and expressive and receptive language delays.[59,60] The association between more severe febrile seizures and developmental delays does not imply causality as children with neurodevelopmental disorders are already at increased risk for epilepsy. The history and severity of febrile seizures should guide referral for neurodevelopmental follow-up.

In addition to febrile seizures, our review included multiple cases of children in whom an afebrile seizure concurrent with HCoV infection unmasked a potential genetic predisposition to seizure disorders. In the case presented by Garcia-Howard and colleagues, the authors used whole exome sequencing to identify a mutation in the PRRT2 gene that has been associated with benign familial infantile convulsions.[45] Although this finding does not carry the neurodevelopmental risk of more severe genetic-associated causes of epilepsy, it is a notable given that four cases in our review report that status epilepticus was the presenting symptom of SARS-CoV-2 infection without exploration of the underlying genetic etiology of seizures in the patients. For children experiencing status epilepticus, the risk of developing epilepsy is high, with estimates ranging from 20% to 40%.[61] And, with this comes the associated risks to neurodevelopmental outcomes in children including motor and intellectual disability, educational difficulties, and decline in quality of life as described widely including in the recent review by Sculier and colleagues and an eight-year prospective follow-up study of more than 200 children who presented with convulsive status epilepticus by Pujar and colleagues.[61,62] Therefore, children presenting with febrile seizures should be evaluated routinely by their primary care providers for general signs and symptoms of neurodevelopmental consequences following SARS-CoV-2 infections. Those who experience severe symptoms, including status epilepticus, should receive appropriate neurodevelopmental and neuropsychologic follow-up.

Acute disseminated encephalomyelitis

ADEM is a predominantly monophasic immune-mediated inflammatory demyelinating disorder of the CNS that typically occurs after a viral infection. A recent meta-analysis indicated that global neurocognitive sequelae (i.e., intellectual disability) are not observed following ADEM.[63] However, a sizable subset of children, 20% to 43%, demonstrate specific but persistent impairments in sustained attention and processing speed. The adolescent patients described by Yeh et al. and de Miranda Henriques-Souza et al. infected with HCoV-OC43 and SARS-CoV-2, respectively, would ideally receive ongoing neurodevelopmental and neuropsychologic monitoring.

Encephalitis

Survivors of pediatric encephalitis demonstrate long-term neurological sequelae ranging from neurocognitive impairments and related learning challenges to behavioral and personality changes.[64-66] A 2016 meta-analysis found that a nearly half of the children who recover from viral encephalitis demonstrate ongoing neurodevelopmental impairments.[7] Long-term sequelae included developmental delay (35%), behavior problems (18%), intellectual impairments (17.6%), and motor deficits (18%).[7] Importantly, neurocognitive sequelae may be less obvious in infants and young children as their functional skills are more globally, versus specifically, assessed at this age. For instance, discharge outcome measures studied by Britton et al. indicated that the majority of infants with parechovirus encephalitis had a "good outcome."[67] However, specific developmental testing 12 months after hospital discharge showed that 50% had developmental concerns and nearly one-fourth had severe developmental delay.[67] Similar findings were reported by Michaeli et al. who observed high rates of attention-deficit/hyperactivity disorder and learning disabilities in children who survived encephalitis.[66] In our review multiple cases of encephalitis were identified including in the setting of MIS-C following SARS-CoV-2 as reported by Abel et al.[34] Any cases of SARS-CoV-2 encephalitis will require neurodevelopmental surveillance.

Stroke

Cerebrovascular events were associated with SARS-CoV-2 infections among the case literature we reviewed. Among these, all were in children beyond the perinatal period (less than one month old). In the cases presented, children suffered a breadth of stroke etiologies. Mirazee et al. and Gulko et al. reported cases of focal cerebral arteriopathy involving the left cerebral artery causing damage to the basal ganglia.[50,51] Kihira et al. reported a large right anterior and middle cerebral artery infarction with subarachnoid hemorrhage in the left hemisphere in the setting of MIS-C.[35] Even more extensively, Tiwari et al. reported extensive bilateral lesions in a nine-year-old girl with MIS-C and SARS-CoV-2 including smooth stenosis of both internal carotid arteries, both A2 segments of the anterior cerebral arteries, and diffuse narrowing of the M2 and M3 of both middle cerebral arteries.[37] The unifying risk factor cited by multiple cases of stroke in children with SARS-CoV-2 infections appears to be a severe acute, neuroinflammatory response.[32] To date, however, clinical evidence for neuroprotective measures in children infected with SARS-CoV-2 is scarce, and further understanding remains urgently needed.

Outcomes following stroke in children are more nuanced than a localization-based understanding of neuroanatomy as pediatric stroke recovery occurs in the contexts of innate brain developmental processes which vary by age, neuroplasticity, and the sequence of brain injury recovery. In addition, long-term functional deficits following pediatric stroke vary by mechanism of insult and extent of injury. Large vessel strokes typically result in corresponding impairments of function controlled by that region, whereas microhemorrhages may result in more subtle cognitive or behavioral deficits that are difficult to predict. However, with all etiologies of pediatric stroke there is a great of variability in the extent of these deficits in the existing literature.[68] Therefore, in the absence of current clinical knowledge of pediatric recovery

following SARS-CoV-2 stroke, consideration of the extent of injury and a child's early clinical course can guide aggressiveness of rehabilitation. However, even if major deficits are not present, children with cerebrovascular disease associated with HCoV infections should undergo neurodevelopmental follow-up for evaluation of deficits resulting from minor disruptions in neural connectivity.

Multisystem inflammatory syndrome in children and pediatric neurodevelopment

Multisystem inflammatory syndrome in children, or MIS-C, is now an established manifestation of SARS-CoV-2 infection seen in the pediatric population.[69] As a hyperinflammatory syndrome, MIS-C has been compared with KD, the pediatric vasculitis that most notably can result in coronary artery aneurysms and also can lead to other neurological and neurodevelopmental sequelae. Of note, previous associations between KD and HCoV-229E have been established.[70] The most commonly reported neurological presentations of KD include aseptic meningitis (up to 50% patients), hemiplegia, facial palsy, and encephalopathy.[71] Patients with KD have been shown to experience long-term behavioral impairments including internalizing behaviors, attention, and social interactions.[72]

The main differences between KD and MIS-C include the age of onset, with older children and adolescents presenting with MIS-C, and increased cardiovascular involvement in MIS-C.[73] Of 186 children with MIS-C across 26 states, a majority of children had involvement of four or more organs and required admission to intensive care.[73] Unfortunately, neurological outcomes are not reported in this population. Given the neurocognitive and behavioral sequelae in KD, high frequency of severe illness in children with MIS-C, and lack of knowledge on potential short- and long-term neurodevelopmental deficits, neurodevelopmental monitoring is highly recommended to support optimal outcomes.

Coronavirus and critical illness

In addition to MIS-C, our literature search demonstrated that HCoVs can cause critical illness, whether associated with neurological manifestations of disease or not, and especially in young children and those with immunodeficiencies. This potential is well illustrated by a recent report of 48 children with SARS-CoV-2 admitted to the PICU.[74] In this study, 68% children were categorized as "severe-critical," 38% required mechanical ventilation, 25% needed vasoactive support, and the average length of PICU admission was greater than 2.5 days. Children with critical illness, even without neurological injury, are at high risk for acquired functional deficits following PICU discharge. Up to 81.5% experience a decline in one or more functional domains six months following PICU admission and functional disability increases over time postdischarge.[75,76] Therefore, children admitted to the PICU due to SARS-CoV-2 should receive neurodevelopmental follow-up regardless of infectious presentation.

Psychosocial outcomes

Studies of children enduring viral encephalitis, ADEM, and KD have demonstrated a severe psychosocial effect on patients and their families including an increase in internalizing symptoms such as anxiety and depression even when neurocognitive outcomes are generally positive.[63,64,77] In addition to neurodevelopmental sequelae, PICU admissions are associated with an alarming risk of post-traumatic stress disorder and anxiety for both children and their parents.[75,78] The tremendous stress and trauma of severe illness courses can have chronic consequences for quality of life. Neurodevelopmental surveillance can play a critical role in reducing these effects.

Limitations

Our review is not exhaustive in capturing all articles on HCoV nervous system infections in children. Notably, the full text of 84 articles (3.7%) was not available through our databases. Many of the cases also present only an association between HCoVs and neurological manifestations. It is important to acknowledge that association in chronicity between infections and symptoms is not diagnostic of causality, particularly in instances where study authors transparently report that the presence of an HCoV was effectively the only notable positive finding after a thorough diagnostic evaluation, and therefore the "favored" diagnosis. Further, the exclusion of adult studies may limit our understanding of the pathophysiology and additional clinical manifestations of HCoV in the nervous system, although the presented pediatric neurological manifestations have also been reported in adults.[37] In addition, we did not identify evidence of long-term neurodevelopmental sequelae in adults who had severe HCoV infections as children. Finally, our study is limited, inherently, by the novel nature of the SARS-CoV-2 pandemic.

Conclusion

In this scoping review we evaluated the rare but serious neurological manifestations that HCoVs, including the novel SARS-CoV-2 virus, can cause in children and the threat that such serious illnesses may pose to long-term neurodevelopmental outcomes. Although awareness of and testing for coronaviruses is heightened in the current pandemic, prior reports suggest that pediatric HCoV infections may have been underdetected, especially as a cause of febrile seizures and encephalitis. SARS-CoV-2 and other coronaviruses should be ruled out in children with acute onset of neurological disease who have likely risk factors, including age less than one year and immunocompromise. Current literature provides insufficient evidence on long-term function in children with neurological manifestations or critical illness from HCoVs. However, evidence from other etiologies suggests a high likelihood of impairing neurodevelopmental sequelae that should be deliberately queried in clinical follow-up. Altogether, to achieve optimal functional outcomes and quality of life, children who experience severe neurological illness due to coronaviruses, including all those who require intensive care, should receive longitudinal neurodevelopmental monitoring to detect overt and subtle deficits and guide therapy.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pediatrneurol.2021.01.007.

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