

Neurologic Involvement in Children and Adolescents Hospitalized in the United States for COVID-19 or Multisystem Inflammatory Syndrome

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 Supplemental content

IMPORTANCE Coronavirus disease 2019 (COVID-19) affects the nervous system in adult patients. The spectrum of neurologic involvement in children and adolescents is unclear.

OBJECTIVE To understand the range and severity of neurologic involvement among children and adolescents associated with COVID-19.

SETTING, DESIGN, AND PARTICIPANTS Case series of patients (age <21 years) hospitalized between March 15, 2020, and December 15, 2020, with positive severe acute respiratory syndrome coronavirus 2 test result (reverse transcriptase-polymerase chain reaction and/or antibody) at 61 US hospitals in the Overcoming COVID-19 public health registry, including 616 (36%) meeting criteria for multisystem inflammatory syndrome in children. Patients with neurologic involvement had acute neurologic signs, symptoms, or diseases on presentation or during hospitalization. Life-threatening involvement was adjudicated by experts based on clinical and/or neuroradiologic features.

EXPOSURES Severe acute respiratory syndrome coronavirus 2.

MAIN OUTCOMES AND MEASURES Type and severity of neurologic involvement, laboratory and imaging data, and outcomes (death or survival with new neurologic deficits) at hospital discharge.

RESULTS Of 1695 patients (909 [54%] male; median [interquartile range] age, 9.1 [2.4-15.3] years), 365 (22%) from 52 sites had documented neurologic involvement. Patients with neurologic involvement were more likely to have underlying neurologic disorders (81 of 365 [22%]) compared with those without (113 of 1330 [8%]), but a similar number were previously healthy (195 [53%] vs 723 [54%]) and met criteria for multisystem inflammatory syndrome in children (126 [35%] vs 490 [37%]). Among those with neurologic involvement, 322 (88%) had transient symptoms and survived, and 43 (12%) developed life-threatening conditions clinically adjudicated to be associated with COVID-19, including severe encephalopathy (n = 15; 5 with splenial lesions), stroke (n = 12), central nervous system infection/demyelination (n = 8), Guillain-Barré syndrome/variants (n = 4), and acute fulminant cerebral edema (n = 4). Compared with those without life-threatening conditions (n = 322), those with life-threatening neurologic conditions had higher neutrophil-to-lymphocyte ratios (median, 12.2 vs 4.4) and higher reported frequency of D-dimer greater than 3 µg/mL fibrinogen equivalent units (21 [49%] vs 72 [22%]). Of 43 patients who developed COVID-19-related life-threatening neurologic involvement, 17 survivors (40%) had new neurologic deficits at hospital discharge, and 11 patients (26%) died.

CONCLUSIONS AND RELEVANCE In this study, many children and adolescents hospitalized for COVID-19 or multisystem inflammatory syndrome in children had neurologic involvement, mostly transient symptoms. A range of life-threatening and fatal neurologic conditions associated with COVID-19 infrequently occurred. Effects on long-term neurodevelopmental outcomes are unknown.

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Coronaviruses primarily cause respiratory disease; however, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus, and newly identified SARS-CoV-2 have been associated with a range of disorders of the peripheral and central nervous system (CNS).¹⁻⁹ Early reports from Wuhan, China, described a spectrum of neurologic conditions associated with SARS-CoV-2 infection in 36% of 214 adults hospitalized with coronavirus disease 2019 (COVID-19).¹⁰ Reported neurologic and psychiatric symptoms in adult patients with COVID-19 include anosmia/ageusia,^{11,12} headaches,¹³ dizziness/ataxia,¹⁰ psychosis, dementia, depression, anxiety, and mania.¹⁴ Reported severe neurologic involvement in adult patients with COVID-19 includes acute encephalopathy or encephalitis,¹⁵⁻¹⁸ acute necrotizing encephalopathy,^{19,20} epilepsy/seizures,^{21,22} acute transverse myelitis,²³⁻²⁵ Guillain-Barré syndrome (GBS),^{26,27} posterior reversible encephalopathy syndrome,²⁸ and acute ischemic or hemorrhagic stroke.^{14,29-34}

Although most children and adolescents are spared from severe COVID-19, there have been reports of life-threatening neurologic involvement in patients developing multisystem inflammatory syndrome in children (MIS-C), a relatively rare, hyperinflammatory, severe illness temporally associated with SARS-CoV-2 infection, presumably postinfectious.^{35,36} Across case series published between March and August 14, 2020, between 6% and 58% of children and adolescents hospitalized with MIS-C developed central and/or peripheral nervous system involvement.³⁶⁻⁴⁰ The frequency of neurologic involvement in children hospitalized with acute COVID-19 is unclear with 150 of 4190 patients reported across 9 international case series.⁴¹⁻⁴⁶ Using the Overcoming COVID-19 US public health surveillance registry of children and adolescents hospitalized with COVID-19-related complications,³⁶ we aimed to describe the type and severity of neurologic involvement and documented hospital outcomes.

Methods

Study Design and Participants

Active surveillance was performed at 61 hospitals in 31 states in the Overcoming COVID-19 network to identify children and adolescents (age <21 years) with SARS-CoV-2-related illness hospitalized from March 15, 2020, to December 15, 2020. The study was approved by the central institutional review board at Boston Children's Hospital and determined to meet the requirement of public health surveillance as defined in 45 CFR 46.102(I)(2) at Boston Children's Hospital and the US Centers for Disease Control and Prevention under a waiver of consent.

Patients were included if they were hospitalized for acute illness at a participating site, were younger than 21 years, had a positive SARS-CoV-2 test result (reverse transcriptase-polymerase chain reaction and/or antibody) and symptoms associated with acute COVID-19, or met US Centers for Disease Control and Prevention criteria for MIS-C (eTable 1 in Supplement 1).⁴⁷ Patients were excluded if they had asymptomatic SARS-CoV-2 infection or a non-COVID-19-related cause

Key Points

Question What is the extent of neurologic involvement in US hospitalized children and adolescents with coronavirus disease 2019 (COVID-19)?

Findings In this study of 1695 patients 21 years or younger hospitalized for acute COVID-19 or multisystem inflammatory syndrome, 365 (22%) had neurologic involvement. Forty-three patients (12%) developed COVID-19-related life-threatening neurologic disorders, 11 (26%) died, and 17 (40%) survived with new neurologic sequelae.

Meaning In this study, COVID-19-related neurologic involvement was common in hospitalized children and adolescents and mostly transient.

for hospitalization or death. Race and ethnicity were extracted from the patient's medical record and included to evaluate risk of neurologic involvement.

Classification of Neurologic Involvement

Patients were stratified by the presence of neurologic involvement, defined as (1) suspected acute neurologic disease (eg, CNS infection/demyelination or stroke) on presentation or that developed during hospitalization (eMethods in Supplement 1) or (2) acute neurologic signs or symptoms on presentation.

Severity of neurologic involvement was adjudicated by neurology and critical care experts on the central study team (K.L.L., B.J.R., T.Y.P., and A.G.R.; eMethods in Supplement 1). Cases were classified as life-threatening based on clinical and/or neuroradiologic features associated with more severe outcomes and included the following diagnoses: acute CNS infection (aseptic meningitis, encephalitis by International Encephalitis Consortium definition,⁴⁸ and Brighton criteria⁴⁹), central demyelinating disorder (acute disseminated encephalomyelitis [ADEM]), acute ischemic or hemorrhagic stroke, GBS and variants, or severe encephalopathy with or without COVID-19-related neuroimaging abnormalities (eg, virus-associated necrotizing disseminated acute leukoencephalopathy⁵⁰ and/or cytotoxic splenial lesions^{44,51,52}). Cases with neurologic involvement that did not meet any of these criteria and had cerebrospinal fluid and/or neuroimaging results that were normal or not performed were categorized as non-life-threatening neurologic involvement.

Neurologic Outcome Classification

Neurology and critical care experts (K.L.L., B.J.R., and A.G.R.) determined through case review and consensus whether life-threatening neurologic conditions were directly associated with COVID-19 or secondary to exacerbation of primary neurologic disease or complication of critical illness associated with COVID-19. Sites with abnormal neuroimaging studies sent deidentified brain magnetic resonance imaging (MRI) and computed tomography studies for central review. Images were reviewed by a pediatric neuroradiologist (T.Y.P.) and discussed with a pediatric neurologist (K.L.L.) reaching consensus opinion about whether the clinicoradiologic link was directly associated with COVID-19 or secondary to an alternate etiology

(eg, extracorporeal membrane oxygenation [ECMO] or preexisting neurologic condition).

Outcomes were determined at hospital discharge. Neurologic deficits were defined as gross impairment in motor, cognitive, or speech and language functions. Psychiatric sequelae (eg, anxiety, depression, and/or suicidal ideation) were not included. New neurologic deficits were determined by medical record review at each site and adjudicated by the experts for all patients with and without neurologic involvement (eMethods in [Supplement 1](#)).

Statistical Analyses

We report the frequency of clinical characteristics, underlying conditions, type of neurologic involvement on admission or during hospitalization, and hospital outcomes. Continuous variables were expressed as medians and interquartile range. Categorical variables were expressed as counts and percentages. Between-group differences were analyzed using a χ^2 test, Fisher exact test, or Kruskal-Wallis test where appropriate. Two-sided P values less than .05 were considered statistically significant. We did not impute missing data. We analyzed all data using R software, version 3.6.1 (R Project for Statistical Computing).

Results

Demographics and Clinical Characteristics

Among All Patients

From March 15, 2020, to December 15, 2020, a total of 1784 hospitalized children and adolescents with COVID-19-related illness were reported to the registry. Of these, 89 patients were excluded on the basis of being 21 years or older ($n = 27$), epidemiologic link to SARS-CoV-2 without a positive test result ($n = 54$), and non-COVID-19-related cause for hospitalization or death ($n = 8$) (eFigure in [Supplement 1](#)). We describe 1695 patients (909 male [54%]; median [interquartile range] age, 9.1 [2.4-15.3] years) from 61 sites in 31 states ([Table 1](#)). Most patients were either Hispanic or Latino (638 of 1695 [38%]) or non-Hispanic Black (442 of 1695 [26%]).

Neurologic vs Nonneurologic Involvement

There were 365 patients (22%) with neurologic involvement reported from 52 sites in 29 states. The characteristics of the patients with and without neurologic involvement are shown in [Table 1](#). The frequencies of previously healthy patients (195 [53%] vs 723 [54%]) and patients meeting MIS-C criteria (126 [35%] vs 490 [37%]) were similar. Patients with neurologic involvement were more likely to have underlying neurologic disorders (81 [22%]) compared with those without (113 [8%]), including seizure disorders, neuromuscular disorders, and autism or developmental delay. Presenting neurologic signs and symptoms differed by age with seizures or status epilepticus most common in children younger than 5 years and anosmia and/or ageusia most common in patients between ages 13 and 20 years ([Figure 1A](#)).

Most patients with and without neurologic involvement were discharged alive (351 [96%] and 1322 [99%], respec-

tively). Children with neurologic involvement had a higher rate of survival with new neurologic deficits (20 of 365 [5%]) compared with those without COVID-19-associated neurologic involvement (2 of 1330 [0.2%]) ([Table 1](#)). Neurologic deficits in those without neurologic involvement included cognitive and motor impairments as a result of sequelae of critical illness and intensive care therapies.

Life-threatening Neurologic Involvement

Among 365 patients with neurologic involvement, 43 (12%) had life-threatening neurologic involvement associated with COVID-19 ([Table 2](#)). Among these, 34 of 43 (79%) had no major underlying conditions, 20 (47%) met criteria for MIS-C, and 3 (7%) had a preexisting neurologic disorder. Life-threatening neurologic conditions included severe encephalopathy ($n = 15$; 5 with white-matter hyperintensities and splenial lesions), acute ischemic or hemorrhagic stroke ($n = 12$), acute CNS infection/ADEM ($n = 8$), acute fulminant cerebral edema ($n = 4$), and GBS ($n = 4$) ([Table 2](#); eTable 2 in [Supplement 1](#)). Eight patients with stroke had underlying risk factors (5 experienced stroke during ECMO [eTable 3 in [Supplement 1](#)]; 2 were attributed to possible COVID-19-related exacerbation of an underlying primary neurologic disorder [eg, arteriovenous malformation rupture and ischemic stroke in a patient with history of moyamoya syndrome]; and a previously healthy patient presented with a new diagnosis of acute myelogenous leukemia). Four patients were previously healthy and did not have stroke risk factors (eTable 4 in [Supplement 1](#)). Five children with severe encephalopathy had brain MRI findings of diffuse white-matter hyperintensities on T2-weighted images and restricted diffusion in the periventricular white matter, deep white matter, and/or corpus callosum (60% with MIS-C; 3 of 5 with unfavorable neurologic outcomes). Representative CNS images from patients with life-threatening neurologic involvement associated with COVID-19 are shown in [Figure 2](#) and [Figure 3](#).

Compared with those with non-life-threatening neurologic involvement, children with life-threatening neurologic disease were more likely to undergo lumbar puncture (20 of 43 [47%] vs 72 of 322 [22%]), head computed tomography (23 of 43 [53%] vs 40 of 322 [12%]) or brain MRI (26 of 43 [60%] vs 28 of 322 [9%]). The cerebrospinal fluid results showed unremarkable findings in both groups (eTable 5 in [Supplement 1](#)). As shown in [Figure 1B](#), patients with life-threatening neurologic conditions were more inflamed and coagulopathic than those with no or non-life-threatening neurologic involvement. Patients with life-threatening vs non-life-threatening neurologic involvement had higher neutrophil-to-lymphocyte ratios (median, 12.2 vs 4.4), and higher reported frequency of D-dimer >3 μ g/mL fibrinogen equivalent units (21 [49%] vs 72 [22%]; to convert D-dimer to nanomoles per liter, multiply by 5.476; [Figure 1](#); eTable 6 in [Supplement 1](#)).

In patients who developed life-threatening neurologic involvement, 11 (26%) died and 17 (40%) were discharged from hospital with new neurologic deficits ([Table 2](#)). Of survivors with new deficits, 16 (94%) were previously healthy, none had prior neurologic disorders, 7 (41%) met MIS-C criteria, and

Table 1. Characteristics and Outcomes of 1695 Patients (Age <21 Years) Hospitalized for COVID-19-Related Illness by Reported Neurologic Involvement

Clinical characteristics	No. (%)			P value	
	All patients (N = 1695)	Neurological involvement			
		Yes (n = 365)	No (n = 1330)		
Male	909 (54)	204 (56)	705 (53)	.36	
Female	786 (46)	161 (44)	625 (47)		
Age, median (IQR), y	9.1 (2.4-15.3)	9.2 (2.5-15.6)	9.0 (2.4-15.1)	.94	
Race/ethnicity ^a					
Non-Hispanic					
White	311 (18)	83 (23)	228 (17)		
Black	442 (26)	108 (30)	334 (25)		
Hispanic or Latino	638 (38)	125 (34)	513 (39)	.004	
Other race, non-Hispanic	111 (7)	21 (6)	90 (7)		
Unknown	216 (13)	31 (8)	185 (14)		
SARS-CoV-2 testing					
RT-PCR performed	1589 (94)	359 (98)	1230 (92)	<.001	
Positive RT-PCR result	1248 (74)	298 (82)	950 (71)	<.001	
Antibody test performed	672 (40)	140 (38)	532 (40)	.61	
Positive antibody test result	589 (35)	121 (33)	468 (35)	.51	
Underlying condition ^b					
Previously healthy ^c	918 (54)	195 (53)	723 (54)	.80	
≥1 Comorbidity, excluding obesity	714 (42)	156 (43)	558 (42)	.83	
Neurological, any condition	194 (11)	81 (22)	113 (8)	<.001	
Seizure disorder	100 (6)	57 (16)	43 (3)	<.001	
Neuromuscular disorders ^d	59 (3)	25 (7)	34 (3)	<.001	
Autism or developmental delay	42 (2)	18 (5)	24 (2)	.001	
Static encephalopathy	40 (2)	18 (5)	22 (2)	<.001	
Congenital neurologic disorders ^e	35 (2)	16 (4)	19 (1)	<.001	
Prior stroke/HIE	15 (1)	6 (2)	9 (1)	.11	
Respiratory	321 (19)	75 (21)	246 (18)	.42	
Cardiac	110 (6)	25 (7)	85 (6)	.85	
Gastrointestinal	173 (10)	44 (12)	129 (10)	.22	
Oncologic or immune compromised	122 (7)	17 (5)	105 (8)	.04	
Hematological	88 (5)	17 (5)	71 (5)	.70	
Kidney	72 (4)	13 (4)	59 (4)	.56	
Endocrine	129 (8)	25 (7)	104 (8)	.61	
Genetic or metabolic (not obesity)	69 (4)	23 (6)	46 (3)	.02	
Clinically diagnosed obesity ^f	184 (11)	39 (14)	145 (14)	>.99	
Non-CNS organ system involvement					
Met MIS-C criteria	616 (36)	126 (35)	490 (37)	.45	
Other organ systems involved					
None	182 (11)	36 (10)	146 (11)	.61	
1	341 (20)	74 (20)	267 (20)	.99	
2	319 (19)	64 (18)	255 (19)	.53	
3	286 (17)	56 (15)	230 (17)	.42	
4	567 (34)	135 (37)	432 (33)	.12	

(continued)

Table 1. Characteristics and Outcomes of 1695 Patients (Age <21 Years) Hospitalized for COVID-19-Related Illness by Reported Neurologic Involvement (continued)

Clinical characteristics	All patients (N = 1695)	Neurological involvement			P value
		Yes (n = 365)	No (n = 1330)		
Outcomes					
ICU	836 (49)	227 (62)	609 (46)	<.001	
ECMO	32 (2)	16 (4)	18 (1)	<.001	
Mechanical ventilation	225 (13)	103 (28)	122 (9)	<.001	
Length of stay, median (IQR), d					
ICU	4 (2-7)	4 (2-9)	4 (2-6)	.02	
Hospital	5 (2-9)	5 (2-11)	5 (2-8)	.004	
Died	22 (1)	14 (4)	8 (1)	<.001	
Survived, new neurological deficit	22 (1)	20 (5)	2 (0.2)	.02	
Discharged to rehabilitation	25 (1)	13 (4)	12 (1)	<.001	
Abbreviations: CNS, central nervous system; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; HIE, hypoxic ischemic encephalopathy; ICU, intensive care unit; IQR, interquartile range; MIS-C, multisystem inflammatory syndrome in children; RT-PCR, reverse transcriptase-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.					
^a Race and ethnic group were reported by the patient or by the patient's parent or guardian. Race/ethnicity categories are not mutually exclusive.					
^b Patients may have more than 1 underlying condition.					
^c Previously healthy was defined as an absence of reported underlying					
conditions and taking no prescription medications.					
^d Neuromuscular disorders include spastic quadriplegia, muscular dystrophy, neuromuscular weakness, and neuromuscular scoliosis.					
^e Congenital neurologic disorders include hydrocephalus, neurogenetic, and neurometabolic disorders.					
^f The determination of clinically diagnosed obesity was based on reporting by clinicians among patients who were aged at least 2 years (n = 278 for patients with neurological involvements and n = 1017 for patients without neurological involvement).					

14 (82%) required rehabilitative services on discharge (eTable 2 in *Supplement 1*).

Association of COVID-19 Neurologic Involvement With Fatality

Fourteen patients with COVID-19 neurologic involvement died in the hospital. Three deaths were associated with acute COVID-19 cardiorespiratory disease. Two patients with asthma had cardiac arrest on hospital presentation, and 1 previously healthy teenager with anosmia/ageusia died of multiorgan failure. These patients were excluded from further evaluation. The other 11 deaths were classified by expert consensus as either directly associated with COVID-19 neurologic involvement or with catastrophic neurologic events secondary to COVID-19-related critical illness (Table 2). These cases are briefly summarized below (eTable 2 in *Supplement 1*).

Three previously healthy children with acute fulminant cerebral edema died within 48 hours of hospital admission (eTable 7 in *Supplement 1*). One male infant with COVID-19 presented with fever, seizures, and gastrointestinal symptoms and within 24 hours of hospitalization developed status epilepticus and had a cardiac arrest, with subsequent imaging showing global cerebral edema. One elementary school-aged girl presented with fever and sore throat, then developed status epilepticus with subsequent imaging revealing cerebral edema with tonsillar herniation. One elementary school-aged boy met criteria for MIS-C 1 month after a positive SARS-CoV-2 respiratory test result. He developed status epilepticus shortly after hospital admission and imaging showed global cerebral edema and uncal herniation.

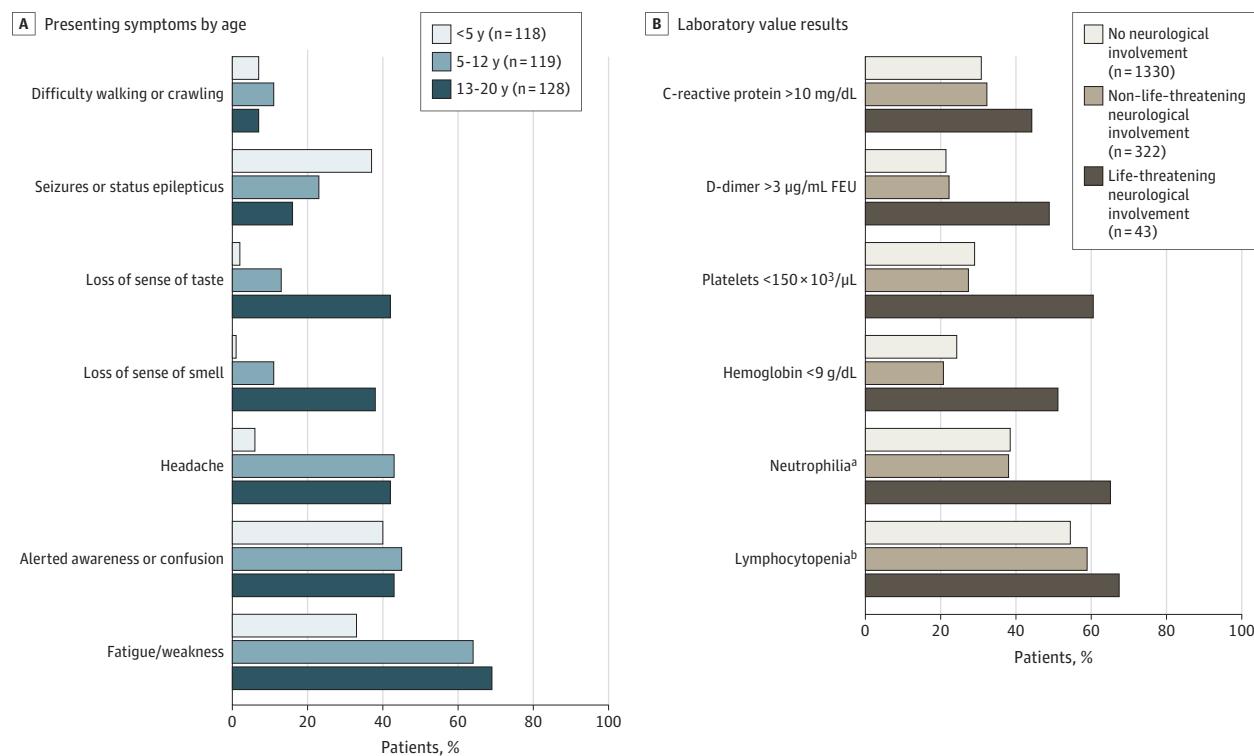
Four patients with stroke died. Three of these patients had strokes with malignant edema and examinations consistent with brain death on ECMO. The fourth died of multiple ischemic strokes owing to rapidly progressive large-vessel CNS vasculitis despite intensive immunotherapies.

Four patients who developed severe encephalopathy died. One immunocompromised adolescent with leukemia and acute COVID-19 pneumonia had diffuse T2 prolongation and reduced diffusivity in the bilateral periventricular white matter, with involvement of the splenium and genu of the corpus callosum, who also developed acute motor-sensory axonal neuropathy confirmed by electromyography/nerve conduction study. Two other patients who died required intubation for severe encephalopathy, complicated by cardiovascular collapse with cannulation for venoarterial ECMO and progression to brain death. One teenager with obesity who died had preexisting hypertension and diabetes and received venoarterial ECMO for cardiorespiratory failure. A brain MRI on decannulation obtained for prolonged encephalopathy showed multifocal areas of restricted diffusion and hemorrhage throughout the posterior white matter and brainstem.

Discussion

In a large, multicenter case series of US children and adolescents hospitalized with acute COVID-19 or MIS-C, 22% of reported patients had neurologic involvement. Approximately half of patients with and without neurologic involvement were previously healthy, a similar percentage had MIS-C, but more

Figure 1. Presenting Neurologic Symptoms and Most Abnormal Laboratory Values in Patients (Age <21 Years) Hospitalized for Coronavirus Disease 2019 (COVID-19)



A, Presenting neurologic symptoms by age in 365 patients (age <21 years) with COVID-19-related neurologic involvement. B, Most abnormal laboratory results in 1695 patients (age <21 years) with COVID-19 by severity of neurologic involvement. Denominators varied and are provided in eTable 6 in *Supplement 1*. FEU indicates fibrinogen equivalent units.

SI conversion factors: To convert C-reactive protein to mg/L, multiply by 10; D-dimer to nmol/L, multiply by 5.476; hemoglobin to d/L, multiply by 10;

platelet count to $\times 10^9/L$, multiply by 1.

^a Neutrophilia was defined as a maximum absolute neutrophil count higher than 7700/ μ L.

^b Lymphocytopenia was defined as an absolute lymphocyte count of less than 1500/ μ L in patients 8 months or older and of less than 4500/ μ L in patients younger than 8 months.

patients with neurologic involvement had underlying neurologic disorders (22% vs 8%). Neurologic involvement in most patients was transient and resolved by hospital discharge; however, 43 patients (12%) developed a range of life-threatening neurologic conditions associated with COVID-19, and 66% of these patients had unfavorable outcomes, including death or new neurologic disability at hospital discharge.

The range of neurologic symptoms associated with COVID-19 in children and adolescents was broad and varied by age including seizures/status epilepticus in the younger patients and reports of anosmia and/or ageusia, headache, and fatigue/weakness in older patients. Approximately 1 in 4 patients with neurologic involvement across age groups presented with altered awareness or confusion. The range of severe neurologic complications including peripheral nerve disorders (GBS and variants), focal CNS disease (ischemic stroke due to large vessel occlusion, cerebral venous sinus thrombosis, and focal cerebral arteriopathy), and diffuse CNS involvement (CNS infection, ADEM, severe encephalopathy with white matter and corpus callosum lesions, and acute fulminant cerebral edema) make it likely that multiple mechanisms underlie this wide spectrum of disease. These include putative

mechanisms such as neuroinvasive or neurotropic (direct viral entry and/or neuronal infection via angiotensin-converting enzyme 2^{53,54} and/or olfactory tract^{55,56}), neuroinflammatory (exaggerated cytokine/immune mediated response leading to blood brain barrier breakdown^{57,58}), postinfectious immune dysregulation,^{59,60} and/or as secondary injury from complications of systemic inflammation or other non-CNS organ failure.⁶¹

We observed 4 cases of GBS that presented with classic neurologic signs, symptoms, and electrophysiologic features within 1 month following SARS-CoV-2 exposure, similar to reports in adults and children in association with COVID-19,^{26,27} and 1 case of acute motor-sensory axonal neuropathy. Animal models and clinicopathological evidence support an autoimmune mechanism and potential molecular mimicry between antibodies against myelin and gangliosides in the nervous system and recent infectious agents, now including COVID-19 infection,^{62,63} and suggests a potential role for anti-ganglioside antibodies in immunomodulatory therapies.

We report 12 cases of acute ischemic or hemorrhagic stroke, with 8 having underlying stroke risk factors. Five of these cases occurred while receiving ECMO, but were included because

Table 2. Life-threatening COVID-19-Related Neurologic Conditions and Deaths in 43 Patients (Age <21 Years) Hospitalized for COVID-19

Variable	Life-threatening COVID-19-related neurologic conditions, No. (%)					
	Overall	Severe encephalopathy	Ischemic or hemorrhagic stroke	Acute CNS infection or ADEM	Acute fulminant cerebral edema	Guillain-Barré syndrome
No.	43	15	12	8	4	4
Age, median (IQR), y ^a	1 Infant	1 Preschooler	1 Infant	1 Infant	2 School aged	
	1 Toddler	5 School-aged	1 Toddler	1 Preschooler	2 Adolescents	
	12 (7-15)	2 Preschoolers	5 Adolescents	2 Preschoolers	2 School-aged	NA
	5 School-aged	1 Young adult	1 School-aged	NA	NA	
	6 Adolescents	NA	3 Adolescents	NA	NA	
Male	27 (63)	11 (73)	6 (50)	4 (50)	2 (50)	4 (100)
RT-PCR or antibody results						
Positive RT-PCR result only	19 (44)	7 (47)	7 (58)	2 (25)	3 (75)	0
Positive antibody result only	11 (26)	3 (20)	3 (25)	3 (38)	0	2 (50)
Positive RT-PCR and antibody results	13 (30)	5 (33)	2 (17)	3 (38)	1 (25)	2 (50)
MIS-C diagnosis	20 (47)	8 (53)	3 (25)	6 (75)	2 (50)	1 (25)
No major underlying conditions	34 (79)	11 (73)	8 (67)	8 (100)	4 (100)	3 (75)
Underlying neurologic disorder	3 (7)	1 (7)	2 (17)	0	0	0
Death	11 (26)	4 (27)	4 (33)	0	3 (75)	0
Discharged alive, new CNS deficit	17 (40)	2 (13)	7 (58)	5 (63)	0	3 (75)

Abbreviations: ADEM, acute disseminated encephalomyelitis; CNS, central nervous system; COVID-19, coronavirus disease 2019; IQR, interquartile range; MIS-C, multisystem inflammatory syndrome in children; NA, not applicable; RT-PCR, reverse transcriptase-polymerase chain reaction.

^a Age categories reported for privacy reasons for subcategories of complications: infant (age <1 year), toddler (age 1-2 years), preschool (age 3-5 years), school-aged (age 6-12 years), adolescent (age 13-17 years), and young adult (age 18-21 years).

COVID-19 may have exacerbated an underlying pathophysiological state (eg, hypercoagulability, hyperinflammation, increased risk of bleeding, and endothelial dysfunction) predisposing to stroke while receiving ECMO.^{64,65} The 4 cases without stroke risk factors were directly associated with COVID-19. In the pediatric literature consisting of case reports and 2 international case series, ischemic stroke type has been reported in 18 children with COVID-19 with stroke mechanisms similar to those observed in our study.^{44,66-69} Acute ischemic stroke in hospitalized adults with COVID-19 is not uncommon.^{8,33,70}

We also describe global cerebral involvement in 15 patients (8 with MIS-C) with severe encephalopathy, 8 patients with acute CNS infection (encephalitis, aseptic meningitis) or postinfectious, central demyelination (ADEM), and 4 patients with acute fulminant cerebral edema. We identified 5 previously healthy patients who presented with severe encephalopathy, focal neurologic deficits, and visual hallucinations (4 of 5 cases) and had diffuse abnormal T2 hyperintensities and reduced diffusivity involving the white matter and genu or splenium of the corpus callosum on MRI. These imaging features have been ascribed to COVID-19 in adults^{50,71} and in children with MIS-C.^{44,51,52} Cytotoxic lesions in the corpus callosum are thought to be associated with increased numbers of glutamate and cytokine receptors in the corpus callosum, particularly the splenium.^{44,72,73} Similar to the range of outcomes in 1 small adult case series,⁵⁰ 3 patients had unfavorable outcomes (1 died and 2 were discharged with new deficits including cognitive impairment and painful

neuropathy requiring gabapentin). Of those with acute CNS infections/ADEM, 7 patients in our study could be confirmed as having probable acute CNS infection using published case definitions.^{48,49} Case reports and small case series also support a link between meningoencephalitis and COVID-19 in adults⁷⁴⁻⁷⁶ and children.^{44,77-79}

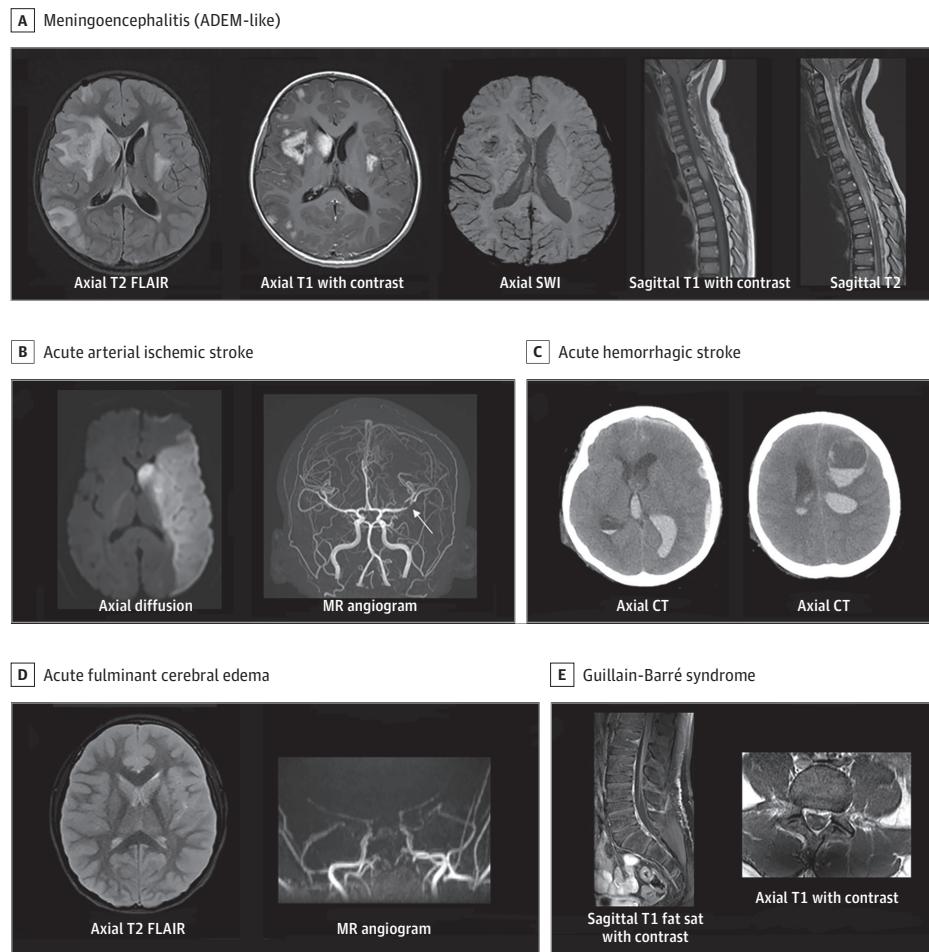
There were 4 cases of previously healthy children who developed acute fulminant cerebral edema directly associated with COVID-19 or MIS-C, and 3 died. Acute fulminant cerebral edema has been previously reported in a child with COVID-19⁸⁰ and is a recognized phenotype with high mortality in adults^{81,82} and children^{44,83} associated with other viral causes.

Our study has several strengths. There was expert adjudication of cases with fatal and life-threatening neurological involvement and new neurologic deficits by pediatric neurology, pediatric critical care, and pediatric neuroradiology experts. The central study team also had personal communication with site clinicians contributing cases with fatal and life-threatening neurologic involvement or new neurologic deficits to confirm diagnoses and clinical course. Neuroimaging was associated with clinical information to document supportive imaging findings and confirm diagnoses. We also captured patients across most US states from a large number of pediatric centers.

Limitations

The study has certain limitations. First, cases of COVID-19-related neurologic involvement were identified only at report-

Figure 2. Representative Central Nervous System Images From Patients With Life-threatening COVID-19-Related Neurologic Involvement



A, Young boy with headache, fatigue, and weakness. Enhancing cerebral lesions with basal ganglia punctate blood products, and abnormal spinal cord signal with focal nodular enhancement. B, Male adolescent with right-sided hemiparesis, confusion, and conjunctivitis. Left middle cerebral artery infarct with middle cerebral artery bifurcation intraluminal thrombus (arrow). C, Adolescent with cerebral palsy in acute hypoxic respiratory/kidney failure. During recovery sudden respiratory decompensation and shock requiring venovenous extracorporeal membrane oxygenation for 3 to 4 weeks. Computed tomography (CT) for mental status change and anisocoria shows intraventricular,

subdural, and frontal intraparenchymal hemorrhage. D, Acute fulminant cerebral edema. Young girl with altered awareness, seizure, nausea, vomiting, acute respiratory failure, and shock requiring vasopressors. Severe cerebral edema with reduced diffusivity and magnetic resonance (MR) angiography with little flow above the level of the supraclinoid internal carotid arteries consistent with brain death. E, Adolescent presents with lethargy, paresthesia, and extremity weakness. There are enhancing cauda equina nerve roots. COVID-19 indicates coronavirus disease 2019; fat sat, fat saturation; FLAIR, fluid-attenuated inversion recovery; SWI, susceptibility weighted imaging.

ing hospitals and may not accurately reflect the true range and severity of COVID-19 neurologic involvement. Second, in patients with underlying neurologic diseases, neurologic presentations may be owing to COVID-19 neurologic effects or exacerbation of underlying neurologic conditions. Third, not all patients underwent neuroimaging (possibly owing to infection control concerns or critical illness-related instability) and image acquisition was not standardized, which could result in misclassification or an underestimation of neurologic involvement. Fourth, although standardized case report forms were used, we may not have captured certain variables completely, such as the indications for procedures (eg, lumbar puncture and imaging). Fifth, some neurologic symptoms (eg, anosmia or ageusia) may be underreported in very young patients. Sixth, nonstandardized diagnostic workups performed un-

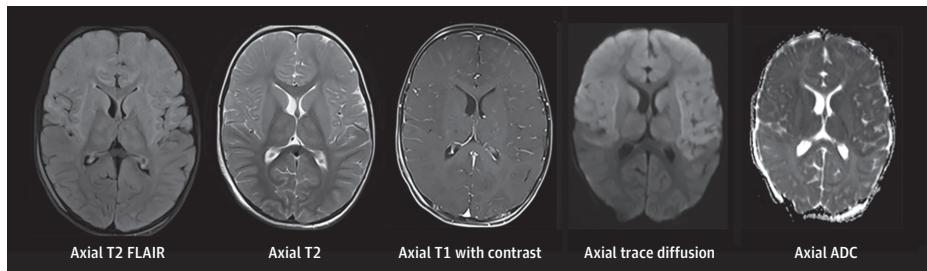
der routine clinical conditions may have missed non-COVID-19-related causes of life-threatening neurological conditions attributed to COVID-19. Seventh, standardized and validated assessments of neurologic outcomes at or after hospital discharge were not performed, likely underestimating the nature and extent of neurologic sequelae. Eighth, this is not a prospective cohort study but a case series, and caution is warranted in interpreting these data to identify risk factors for neurologic involvement.

Conclusions

In this study, neurologic involvement was common in children and adolescents with COVID-19-related hospitalization

Figure 3. Representative Central Nervous System Images From Patients With Life-Threatening COVID-19-Related Neurologic Involvement

A Encephalitis

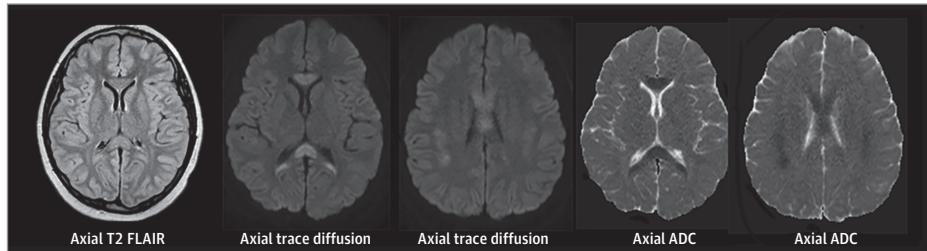


A, Previously healthy toddler with multisystem inflammatory syndrome in children (Ab+) with fever, rash, fatigue, vomiting, decreased oral intake, compensated cardiogenic shock, and generalized tonic-clonic status epilepticus. There is diffuse T2 hyperintensity, leptomeningeal enhancement, and reduced diffusivity within the bilateral frontal lobes, basal ganglia, and thalamus.

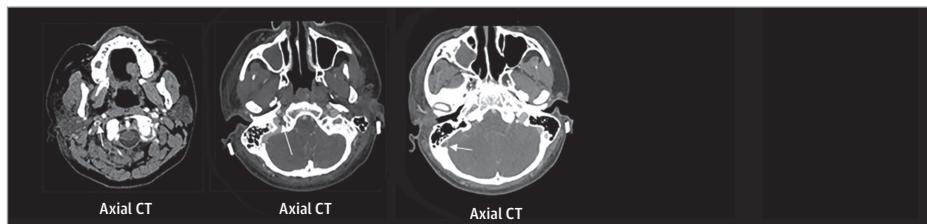
B, School-aged child with coronavirus disease 2019 (COVID-19) and multisystem inflammatory syndrome in children presented with fever, headache, neck pain, abdominal pain, encephalopathy, and visual hallucinations. T2 prolongation with reduced diffusivity in the genu and splenium of corpus callosum, periventricular, and parietal white matter. C, Previously healthy teenager with fever, vomiting, diarrhea, headache, and fatigue presented with altered mental status, visual hallucinations, left hemiparesis, septic shock, and respiratory distress requiring intubation. Axial computed tomography (CT) images demonstrate nonocclusive thrombus in the right internal jugular vein within the upper neck, jugular bulb, and right sigmoid sinus.

ADC indicates apparent diffusion coefficient map; FLAIR, fluid-attenuated inversion recovery.

B Severe encephalopathy



C Cerebral venous sinus thrombosis



and is mostly transient. A spectrum of life-threatening neurologic involvement infrequently occurred and was associated with more extreme inflammation and severe sequelae. Future immunologic studies of cell-mediated and cytokine immune responses in young individuals may provide insight

into the pathogenesis of neurologic disease in COVID-19 and MIS-C.⁸⁴ Patients with less severe neurologic involvement could have future sequelae. Long-term follow-up of pediatric patients with COVID-19-related neurologic involvement is needed to evaluate effects on cognition and development.

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Group Information: The Overcoming COVID-19 Investigators are listed in *Supplement 2*.

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