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.
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). 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). Reported neurologic and psychiatric symptoms in adult patients with COVID-19 include anosmia/ageusia, headaches, dizziness/ataxia, psychosis, dementia, depression, anxiety, and mania. Reported severe neurologic involvement in adult patients with COVID-19 includes acute encephalopathy or encephalitis, acute necrotizing encephalopathy, epilepsy/seizures, Guillain-Barré syndrome (GBS), posterior reversible encephalopathy syndrome, and acute ischemic or hemorrhagic stroke.

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. 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. 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. Using the Overcoming COVID-19 US public health surveillance registry of children and adolescents hospitalized with COVID-19–related complications, 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). Patients were excluded if they had asymptomatic SARS-CoV-2 infection or a non–COVID-19–related cause 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 (I) suspected acute neurologic disease (eg, CNS infection/demyelination or stroke) or that developed during hospitalization (eMethods in Supplement 1) or (II) acute neurologic signs or symptoms on presentation.

Severities 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, and Brighton criteria), 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 leukoencephalopathy and/or cytotoxic splenial lesions). 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.
Neurologic Involvement in Children and Adolescents With COVID-19 or Multisystem Inflammatory Syndrome

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%], respectively). 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 μg/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 14 (82%) required rehabilitative services on discharge (eTable 2 in Supplement 1).

(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 means and interquartile range. Categorical variables were expressed as counts and percentages. Between-group differences were analyzed using a χ² 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).

[Figure 1](https://jamanetwork.com/journals/jamaneurol/files/2021/05/Figure1-min.png)

[Figure 2](https://jamanetwork.com/journals/jamaneurol/files/2021/05/Figure2-min.png)

[Figure 3](https://jamanetwork.com/journals/jamaneurol/files/2021/05/Figure3-min.png)
Table 1. Characteristics and Outcomes of 1695 Patients (Age <21 Years) Hospitalized for COVID-19–Related Illness by Reported Neurologic Involvement

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>No. (%)</th>
<th>Neurological involvement</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients (N = 1695)</td>
<td>Yes (n = 365)</td>
<td>No (n = 1330)</td>
</tr>
<tr>
<td>Male</td>
<td>909 (54)</td>
<td>204 (56)</td>
<td>705 (53)</td>
</tr>
<tr>
<td>Female</td>
<td>786 (46)</td>
<td>161 (44)</td>
<td>625 (47)</td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>9.1 (2.4-15.3)</td>
<td>9.2 (2.5-15.6)</td>
<td>9.0 (2.4-15.1)</td>
</tr>
<tr>
<td>Race/ethnicity*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>311 (18)</td>
<td>83 (23)</td>
<td>228 (17)</td>
</tr>
<tr>
<td>Black</td>
<td>442 (26)</td>
<td>108 (30)</td>
<td>334 (25)</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>638 (38)</td>
<td>125 (34)</td>
<td>513 (39)</td>
</tr>
<tr>
<td>Other race, non-Hispanic</td>
<td>111 (7)</td>
<td>21 (6)</td>
<td>90 (7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>216 (13)</td>
<td>31 (8)</td>
<td>185 (14)</td>
</tr>
<tr>
<td>SARS-CoV-2 testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT-PCR performed</td>
<td>1589 (94)</td>
<td>359 (98)</td>
<td>1230 (92)</td>
</tr>
<tr>
<td>Positive RT-PCR result</td>
<td>1248 (74)</td>
<td>298 (82)</td>
<td>950 (71)</td>
</tr>
<tr>
<td>Antibody test performed</td>
<td>672 (40)</td>
<td>140 (38)</td>
<td>532 (40)</td>
</tr>
<tr>
<td>Positive antibody test result</td>
<td>589 (35)</td>
<td>121 (33)</td>
<td>468 (35)</td>
</tr>
<tr>
<td>Underlying conditionb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previously healthy*</td>
<td>918 (54)</td>
<td>195 (53)</td>
<td>723 (54)</td>
</tr>
<tr>
<td>≥1 Comorbidity, excluding obesity</td>
<td>714 (42)</td>
<td>156 (43)</td>
<td>558 (42)</td>
</tr>
<tr>
<td>Neurological, any condition</td>
<td>194 (11)</td>
<td>81 (22)</td>
<td>113 (8)</td>
</tr>
<tr>
<td>Seizure disorder</td>
<td>100 (6)</td>
<td>57 (16)</td>
<td>43 (3)</td>
</tr>
<tr>
<td>Neuromuscular disorderse</td>
<td>59 (3)</td>
<td>25 (7)</td>
<td>34 (3)</td>
</tr>
<tr>
<td>Autism or developmental delay</td>
<td>42 (2)</td>
<td>18 (5)</td>
<td>24 (2)</td>
</tr>
<tr>
<td>Static encephalopathy</td>
<td>40 (2)</td>
<td>18 (5)</td>
<td>22 (2)</td>
</tr>
<tr>
<td>Congenital neurologic disorders*</td>
<td>35 (2)</td>
<td>16 (4)</td>
<td>19 (1)</td>
</tr>
<tr>
<td>Prior stroke/HIE</td>
<td>15 (1)</td>
<td>6 (2)</td>
<td>9 (1)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>321 (19)</td>
<td>75 (21)</td>
<td>246 (18)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>110 (6)</td>
<td>25 (7)</td>
<td>85 (6)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>173 (10)</td>
<td>44 (12)</td>
<td>129 (10)</td>
</tr>
<tr>
<td>Oncologic or immune compromised</td>
<td>122 (7)</td>
<td>17 (5)</td>
<td>105 (8)</td>
</tr>
<tr>
<td>Hematological</td>
<td>88 (5)</td>
<td>17 (5)</td>
<td>71 (5)</td>
</tr>
<tr>
<td>Kidney</td>
<td>72 (4)</td>
<td>13 (4)</td>
<td>59 (4)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>129 (8)</td>
<td>25 (7)</td>
<td>104 (8)</td>
</tr>
<tr>
<td>Genetic or metabolic (not obesity)</td>
<td>69 (4)</td>
<td>23 (6)</td>
<td>46 (3)</td>
</tr>
<tr>
<td>Clinically diagnosed obesityf</td>
<td>184 (11)</td>
<td>39 (14)</td>
<td>145 (14)</td>
</tr>
<tr>
<td>Non–CNS organ system involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Met MIS-C criteria</td>
<td>616 (36)</td>
<td>126 (35)</td>
<td>490 (37)</td>
</tr>
<tr>
<td>Other organ systems involved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>182 (11)</td>
<td>36 (10)</td>
<td>146 (11)</td>
</tr>
<tr>
<td>1</td>
<td>341 (20)</td>
<td>74 (20)</td>
<td>267 (20)</td>
</tr>
<tr>
<td>2</td>
<td>319 (19)</td>
<td>64 (18)</td>
<td>255 (19)</td>
</tr>
<tr>
<td>3</td>
<td>286 (17)</td>
<td>56 (15)</td>
<td>230 (17)</td>
</tr>
<tr>
<td>4</td>
<td>567 (34)</td>
<td>135 (37)</td>
<td>432 (33)</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>836 (49)</td>
<td>227 (62)</td>
<td>609 (46)</td>
</tr>
<tr>
<td>ECMO</td>
<td>32 (2)</td>
<td>16 (4)</td>
<td>18 (1)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>225 (13)</td>
<td>103 (28)</td>
<td>122 (9)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>All patients (N = 1695)</th>
<th>Neurological involvement</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (%)</td>
<td>Yes (n = 365)</td>
<td>No (n = 1330)</td>
</tr>
<tr>
<td>Length of stay, median (IQR), d</td>
<td>4 (2-7)</td>
<td>4 (2-9)</td>
<td>4 (2-6)</td>
</tr>
<tr>
<td>ICU</td>
<td>5 (2-9)</td>
<td>5 (2-11)</td>
<td>5 (2-8)</td>
</tr>
<tr>
<td>Hospital</td>
<td>Died</td>
<td>Survived, new neurological deficit</td>
<td>Discharged to rehabilitation</td>
</tr>
<tr>
<td></td>
<td>22 (1)</td>
<td>20 (5)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td></td>
<td>25 (1)</td>
<td>13 (4)</td>
<td>12 (1)</td>
</tr>
</tbody>
</table>

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 Neutrophilic 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 involvement and n = 1077 for patients without neurological involvement).

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 ×10⁹/L, multiply by 1.

*Neutrophilia was defined as a maximum absolute neutrophil count higher than 7700/μL.

b Lymphocytopenia was defined as an absolute lymphocyte count of less than 1500/μL in patients 8 months or older and of less than 4500/μL in patients younger than 8 months.
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 de-cannulation 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 re-

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Life-threatening COVID-19-related neurologic conditions, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
</tr>
<tr>
<td>No.</td>
<td>43</td>
</tr>
<tr>
<td>Age, median (IQR), y*</td>
<td>12 (7-15)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>27 (63)</td>
</tr>
<tr>
<td>RT-PCR or antibody results</td>
<td></td>
</tr>
<tr>
<td>Positive RT-PCR result only</td>
<td>19 (44)</td>
</tr>
<tr>
<td>Positive antibody result only</td>
<td>11 (26)</td>
</tr>
<tr>
<td>Positive RT-PCR and antibody results</td>
<td>13 (30)</td>
</tr>
<tr>
<td>MIS-C diagnosis</td>
<td>20 (47)</td>
</tr>
<tr>
<td>No major underlying conditions</td>
<td>34 (79)</td>
</tr>
<tr>
<td>Underlying neurologic disorder</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Death</td>
<td>11 (26)</td>
</tr>
<tr>
<td>Discharged alive, new CNS deficit</td>
<td>17 (40)</td>
</tr>
</tbody>
</table>

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.

* 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).
ported patients had neurologic involvement. Approximately
half of patients with and without neurologic involvement were
previously healthy, a similar percentage had MIS-C, but more
patients with neurologic involvement had underlying neuro-
logic disorders (22% vs 8%). Neurologic involvement in most
patients was transient and resolved by hospital discharge; how-
ever, 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 pa-
tients and reports of anosmia and/or ageusia, headache, and
fatigue/weakness in older patients. Approximately 1 in 4 pa-
tients with neurologic involvement across age groups pre-
sewed 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 thrombo-
sis, and focal cerebral arteriopathy), and diffuse CNS involve-
ment (CNS infection, ADEM, severe encephalopathy with white
matter and corpus callosum lesions, and acute fulminant cere-
bral edema) make it likely that multiple mechanisms under-
lie 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 (ACE2) and/or olfactory tract (55,56)),
neuroinflammatory (exaggerated cytokine/immune mediated
response leading to blood brain barrier breakdown (57,58),

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

A. Meningoencephalitis (ADEM-like)

B. Acute arterial ischemic stroke

C. Acute hemorrhagic stroke

D. Acute fulminant cerebral edema

E. Guillain-Barré syndrome

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 decompression 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.
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 antiganglioside 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 COVID-19 may have exacerbated an underlying pathophysiologic 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.⁶⁴,⁶⁵,⁷⁰

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 adults⁵⁰,⁷¹ 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
Neurologic Involvement in Children and Adolescents With COVID-19 or Multisystem Inflammatory Syndrome

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.40,41 Case reports and small case series also support a link between meningoencephalitis and COVID-19 in adults81,82 and children.43,77-79

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-1990 and is a recognized phenotype with high mortality in adults81,82 and children43,83 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 reporting 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 under routine clinical conditions may have missed non-COVID-19-related causes of life-threatening neurologic 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 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.

ARTICLE INFORMATION

Accepted for Publication: February 12, 2021.
Published Online: March 5, 2021.

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Neurologic Involvement in Children and Adolescents With COVID-19 or Multisystem Inflammatory Syndrome

Original Investigation Research


Conflict of Interest Disclosures: Dr Riggs reported grants from the US Centers for Disease Control and Prevention (CDC) Funding through Boston Children’s Hospital during the conduct of the study. Dr Newhams reported grants from the CDC during the conduct of the study. Dr Maamari reported other support from the CDC during the conduct of the study. Dr McLaughlin reported grants from Boston Children’s Hospital and the CDC during the conduct of the study. Dr Maddux reported grants from the National Institutes of Health (NIH)/Eunice Kennedy Shriver National Institute of Child Health and Human Development during the conduct of the study. Dr Rowan reported grants from the CDC during the conduct of the study and from the NIH outside the submitted work. Dr McLaughlin reported grants from the CDC during the conduct of the study. Dr Fitzgerald reported grants from the CDC during the conduct of the study and from the NIH outside the submitted work. Dr Gertz reported grants from Boston Children’s Hospital as a pass-through for the CDC during the conduct of the study. Dr Shein reported grants from the CDC during the conduct of the study. Dr Coronado Munoz reported grants from the CDC during the conduct of the study. Dr Levy reported grants from the CDC during the conduct of the study and from the National Institute of Allergy and Infectious Diseases outside the submitted work. Dr Staat reported other support from Boston Children’s Hospital during the conduct of the study. Dr Halasa reported grants from the CDC during the conduct of the study; grants from Sanofi and Quidel; and personal fees from Genentech outside the submitted work. Dr Hall reported grants from the CDC during the conduct of the study and personal fees from La Jolla Pharmaceuticals outside the submitted work. Dr Schuster reported other from the CDC during the conduct of the study; other support from Merck; and grants from the CDC outside the submitted work. Dr Doymaz reported grants from the CDC during the conduct of the study. Dr Tarquini reported grants from the CDC during the conduct of the study. Dr Noziger reported other from the CDC during the conduct of the study. Dr Kleinman reported grants from Boston Children’s Hospital during the conduct of the study and grants from Health Services Research Administration and NICHD outside the submitted work. Dr Cijavanovic reported grants from the CDC during the conduct of the study and grants from Cincinnati Children’s Medical Center and Boston Children’s Hospital outside the submitted work. Dr Humle reported grants from the CDC during the conduct of the study. Dr Wellnitz reported other support from the CDC and NIH during the conduct of the study. Dr Michelson reported grants from the CDC during the conduct of the study and grants National Palliative Care Research Center and the National Institutes of Health outside the submitted work. Dr Randolph reported grants from the CDC during the conduct of the study and other support from UpToDate outside the submitted work. Dr Poussaint received grants from the National Institutes of Health and royalties from Springer Publishing outside of the submitted work. No other disclosures were reported.

Funding/Support: This study was funded by the US Centers for Disease Control and Prevention under a contract to Boston Children’s Hospital.

Role of the Funder/Sponsor: The US Centers for Disease Control and Prevention designed and conducted the study; collected, managed, analyzed, and interpreted the data; prepared, reviewed, and approved the manuscript; had a role in the decision to submit the manuscript for publication and journal choice; and had the right to veto publication.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

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

Additional Contributions: We appreciate and thank the many research coordinators at the Overcoming COVID-19 hospitals who assisted in data collection for this study. We thank the leadership of the Pediatric Acute Lung Injury and Septic Investigator’s (PALIS) Network for their ongoing support.

REFERENCES
Infect Dis

transverse myelitis associated with SARS-CoV-2: 24


Neurologic Involvement in Children and Adolescents With COVID-19 or Multisystem Inflammatory Syndrome


