Supplemental Online Content

LaRovere KL, Riggs BJ, Poussaint TY, et al; Overcoming COVID-19 Investigators. Neurologic involvement in children and adolescents hospitalized in the United States for COVID-19 or multisystem inflammatory syndrome. *JAMA Neurol*. Published online March 5, 2021. doi:10.1001/jamaneurol.2021.0504

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods:

The *Overcoming COVID-19* Public Health Surveillance Registry is funded by the United States (U.S.) Centers for Disease Control and Prevention (CDC) in collaboration with the Pediatric Intensive Care Influenza and Emerging Pathogens (PICFLU-EP) Network which is a subgroup of the Pediatric Acute Lung Injury and Sepsis Investigator's (PALISI) Network. Targeted retrospective and prospective surveillance in children and adolescents for acute COVID-19 and MIS-C has been ongoing since March 15, 2020 at pediatric surveillance sites across the U.S. The study organization and sites have been previously described.[1] Data collected included patient demographics, underlying medical conditions, presenting neurologic signs and symptoms, clinical course, laboratory values, diagnostic findings, treatments, complications, and outcomes.

For all patients with neurologic involvement, the central study team composed of experts in pediatric neurology (KLL), pediatric neuroradiology (TYP), and pediatric neurocritical care (BJR) and pediatric critical care medicine (AGR) reviewed the database for demographic information, clinical characteristics, neurologic signs and symptoms, laboratory and cerebrospinal fluid (CSF) results, and findings on clinical reports from brain magnetic resonance imaging (MRI), brain computed tomography (CT), and electromyography and nerve conduction velocity (EMG/NCV) studies. All cases that could involve severe neurologic involvement were flagged for further review.

Two experts (KLL, BJR) adjudicated local diagnoses for all cases with fatal and "life-threatening" COVID-19 neurologic conditions. For all deaths and cases with life-threatening neurologic

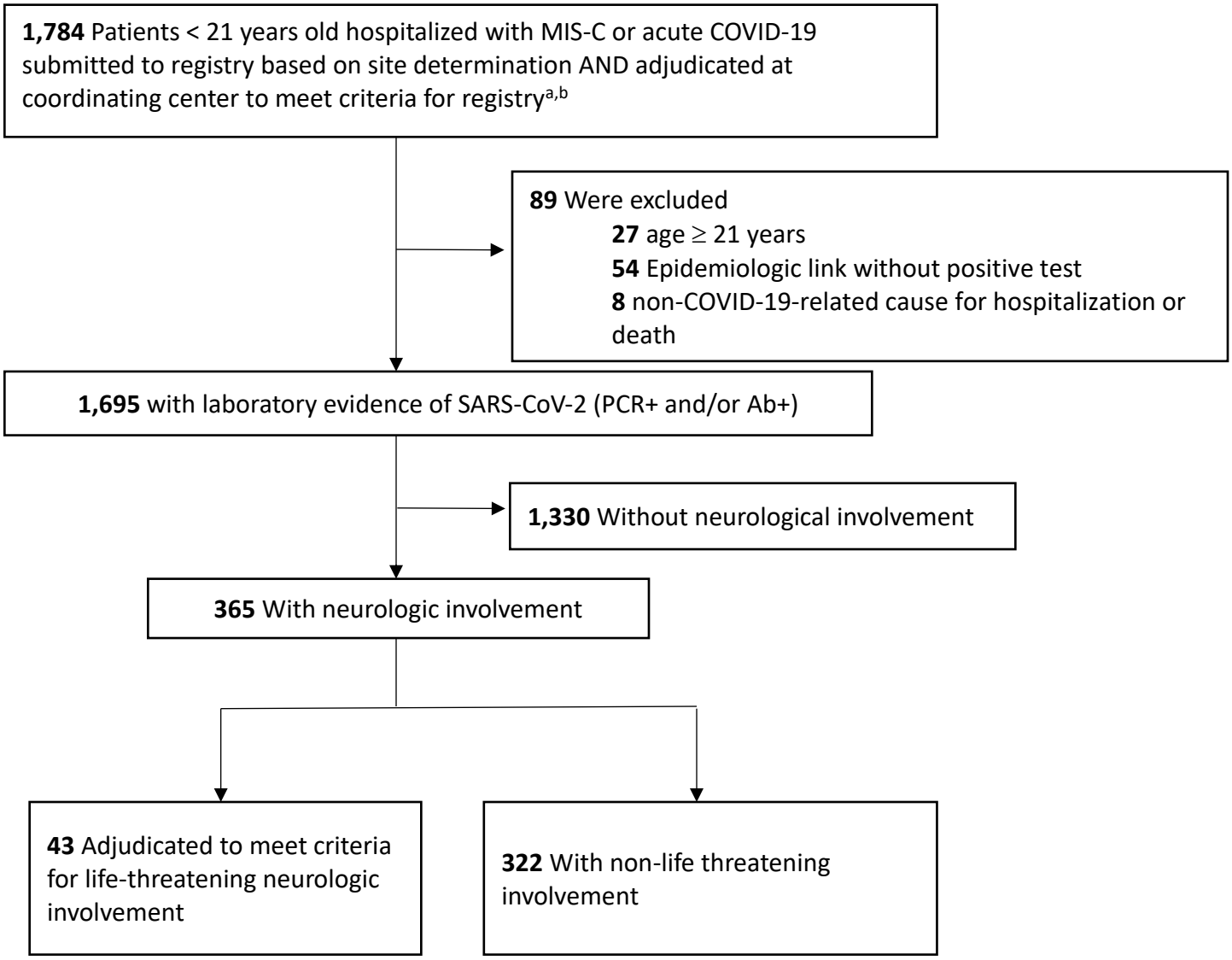
involvement, the experts reviewed additional local source data (e.g. anonymized admission notes, consultant notes, discharge summaries, laboratory and microbiology reports, clinical reports from brain MRI, brain CT and EMG/NCV studies, and actual brain MRI and CT images), and personally communicated with site clinicians about each case to confirm neurologic diagnoses and outcomes, discuss the nature of the relationship between neurologic involvement and COVID-19, and obtain further clinical information when needed. Cases with non-life threatening neurologic involvement and those without neurologic involvement were selected for formal review by the experts only if there were new neurologic deficits noted at hospital discharge. The experts reviewed local source documents (e.g. evaluations by rehabilitative services) and personally communicated with site clinicians to determine the type of deficits and whether they were most likely directly related to COVID-19 neurologic involvement or sequelae of critical illness (e.g. pneumonia and acute respiratory failure, multi-organ failure) and intensive care therapies (e.g. extracorporeal membrane oxygenation [ECMO], prolonged anesthetic/muscle relaxant use and immobilization).

Patients were included in the Acute Disseminated Encephalomyelitis (ADEM) category if site clinicians indicated a diagnosis of ADEM or imaging reports or actual images had an imaging pattern analogous to ADEM based on expert review. Stroke was defined as a sudden focal neurologic deficit lasting $\geq$ 24 hours of presumed vascular origin confirmed on imaging to be caused by infarction (ischemic stroke type) or atraumatic hemorrhage (hemorrhagic stroke type) and correlated with the clinical focal deficit.

All deaths and cases with life-threatening neurologic involvement were classified by 2 authors (KLL, BJR) as related to COVID-19 neurologic involvement either “directly” or “*secondary*” to a complication in another organ system (e.g., stroke during ECMOu therapy for heart or lung failure) or exacerbation of an underlying primary neurologic disease based on an understanding of the clinical spectrum of COVID-19 in critically ill children and what is expected during neurocritical illness outside of COVID-19.

Local site principal investigators determined whether patients met CDC criteria for MIS-C. When co-infections with other viruses (e.g. adenovirus, rhinovirus/enterovirus) and *Mycoplasma pneumoniae* were identified, causality was adjudicated by pediatric infectious disease experts (AJR, CVH, JES). Non-CNS organ-system involvement was categorized on the basis of symptoms, clinical findings, and laboratory measures as previously described.[1]

eFigure. Eligibility flowchart of hospitalized patients with COVID-19-related neurologic involvement, March 15–December 15, 2020



Abbreviations: RT-PCR, real-time reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; multisystem inflammatory syndrome in children (MIS-C); COVID-19, coronavirus disease 2019
[a]Registry data was based on voluntary case reporting by participating sentinel surveillance sites.
[b]Criteria for registry: meet case definition for MIS-C (eTable S1) or evidence of infection with SARS-CoV-2 based on a positive RT-PCR test during current illness with clinical suspicion for acute COVID-19.

eTable 1. Case definition used in this study for multisystem inflammatory syndrome in children (MIS-C) developed by the U.S. Centers for Disease Control and Prevention.[2]

• Fever > 38.0°C [a]
AND
• Laboratory evidence of inflammation [b]
AND
• Evidence of clinically severe hospitalized illness among children aged <21 years with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological)
AND
• One of the following: 1. SARS-CoV-2 positive RT-PCR test 2. SARS-CoV-2 positive antibody test 3. SARS-CoV-2 negative RT-PCR and antibody tests but with identified COVID exposure [c] within the four weeks prior to the onset of symptoms

[a] Fever >38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours

[b] Including, but not limited to, one or more of the following: neutrophilia; lymphopenia; hypoalbuminemia; and elevated levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6)

[c] Known exposure to a person with laboratory-confirmed COVID-19 or a clinical diagnosis of COVID-19 within 4 weeks prior to onset of MIS-C.

eTable 2. Life-threatening COVID-19-related neurologic disorders and outcomes in 43 children and adolescents (< 21 years) hospitalized for COVID-19

Disease (no. cases)	Age Category^	SARS-CoV-2 RT-PCR	SARS-CoV-2 Antibody	MIS-C	Previously Healthy	Underlying Neurologic Disorder	Outcome
Severe Encephalopathy (15 cases)	infant	POS	Not tested	No	Yes	No	Discharged home
	toddler	POS	NEG	No	Yes	No	New deficits, required outpatient physical therapy♦
	preschool	POS	POS	Yes	Yes	No	Discharged home
	preschool	POS	POS	Yes	Yes	No	Discharged home
	school age	POS	POS	Yes	Yes	No	Discharged home
	school age	NEG	POS	Yes	Yes	No	Discharged home♦
	school age	POS	POS	Yes	Yes	No	Discharged home♦
	school age	NEG	POS	Yes	Yes	No	New deficits, required outpatient physical therapy♦
	school age	POS	POS	Yes	Yes	No	Discharged home
	teen	POS	Not tested	No	No	Yes	Discharged home
	teen	NEG	POS	Yes	Yes	No	Died
	teen	POS	Not tested	No	No	No	Died
	teen	POS	Not tested	No	Yes	No	Discharged home
	teen	POS	Not tested	No	No	No	Died
	teen	POS	NEG	No	No	No	Died♦^^
Ischemic or Hemorrhagic Stroke (12 cases)	preschool	POS	Not tested	No	No	No	New deficits, required acute rehabilitation**
	school age	NEG	POS	Yes	Yes	No	New deficits, required acute rehabilitation**
	school age	NEG	POS	Yes	Yes	No	New deficits, required acute rehabilitation
	school age	POS	Not tested	No	No	No	Discharged home
	school age	POS	Not tested	No	Yes	No	New deficits, required transfer to different acute care facility
	school age	POS	POS	No	Yes	No	Died+
	teen	POS	Not tested	No	No	Yes	Died¶

	teen	POS	POS	No	Yes	No	New deficits, required acute rehabilitation
	teen	POS	Not tested	No	No	Yes	Died¶
	teen	POS	NEG	No	Yes	No	New deficits, required transfer to different acute care facility**
	teen	NEG	POS	No	Yes	No	New deficits, required acute rehabilitation
	young adult	POS	Not tested	Yes	Yes	No	Died‡
Acute CNS Infection or ADEM (8 cases)	infant	NEG	POS	Yes	Yes	No	Discharged home
	toddler	NEG	POS	Yes	Yes	No	New deficits, required acute rehabilitation#
	preschool	POS	Not tested	No	Yes	No	New deficits, discharged home
	preschool	POS	POS	Yes	Yes	No	New deficits, discharged home
	school age	POS	POS	Yes	Yes	No	Discharged home
	teen	POS	POS	Yes	Yes	No	Discharged home
	teen	NEG	POS	Yes	Yes	No	New deficits, required acute rehabilitation
	teen	POS	Not tested	No	Yes	No	New deficits, discharged home
Acute Fulminant Cerebral Edema (4 cases)	infant	POS	Not tested	No	Yes	No	Died
	preschool	POS	POS	Yes	Yes	No	Discharged home
	school age	POS	Not tested	Yes	Yes	No	Died*
	school age	POS	Not tested	No	Yes	No	Died
Guillain Barre Syndrome (4 cases)	school age	NEG	POS	No	Yes	No	New deficits, required outpatient physical therapy
	school age	POS	POS	No	Yes	No	New deficits, required acute rehabilitation
	teen	NEG	POS	Yes	Yes	No	New deficits, required acute rehabilitation
	teen	POS	POS	No	No	No	Discharged home

Abbreviations: Ab = antibody; ADEM = acute disseminated encephalomyelitis; CNS=central nervous system; CNS infection = encephalitis or acute meningitis; GBS = Guillain-Barre Syndrome; MIS-C = Multisystem Inflammatory Syndrome in Children; RT-PCR = reverse transcriptase polymerase chain reaction; POS = positive, NEG = negative, Not tested = test not sent in hospital.
^Age categories: infant < 1 year; toddler 1-2 years; preschool 3-5 years; school age 6-12 years; teen 13-17 years; young adult 18-21 years
#Movement disorder with severe dystonia
♦Brain MRI with abnormal signal intensity and restricted diffusion in corpus callosum and periventricular white matter
*Brain pathology from autopsy suggestive of meningoencephalitis
[+]Brain pathology suggestive of cerebral vasculitis
^^Electrophysiologic studies consistent with axonal GBS variant
**Stroke occurred while on extracorporeal membrane oxygenation (ECMO)
¶Stroke occurred while on ECMO, died from cerebral herniation
‡Died from pulmonary embolism

eTable 3. Detailed clinical descriptions for 5 patients who experienced stroke while supported by extracorporeal membrane oxygenation (ECMO)

Case 1: An adolescent girl with history of severe neurologic disability, epilepsy and cerebral glioma treated with surgical resection, chemotherapy and radiation presented with severe encephalopathy, hyponatremia, and hypoxemic respiratory failure in the setting of COVID-19 infection. She was cannulated to venoarterial (VA) ECMO in the emergency department. On hospital day four, she had fixed and dilated pupils and head imaging showed a large loculated subdural hemorrhage with significant midline shift and brain herniation.

Case 2: A previously healthy elementary school aged boy admitted for MIS-C associated with SARS-CoV-2 developed multiple organ system failure including liver dysfunction, acute kidney injury requiring continuous venovenous hemodialysis, and cardiopulmonary failure requiring VA ECMO for 2 days. Prior to decannulation he had a cardiac surgical procedure (balloon atrial septostomy). After decannulation, imaging showed a hemorrhagic right basal ganglia infarct associated with right basal ganglia and parietal lobe/postcentral gyrus reduced diffusivity. There was occlusion of the right common carotid artery in the lower neck which reconstituted with decreased caliber of the right internal carotid artery which had heterogeneous flow related enhancement likely related to thrombus. He was discharged to acute rehabilitation with new neurologic deficits, including impaired swallowing, reduced ability to protect airway, impaired speech (reduced spontaneity, single word responses), cognitive impairment (decreased alertness, impaired attention, delayed response time), diffuse decrease in muscle tone and unsteady gait.

Case 3: A previously healthy obese adolescent boy with acute COVID-19 presented with severe encephalopathy and profound cerebral edema confirmed by head CT in the setting of new onset hyperosmolar hyperglycemic syndrome. Several days after admission he abruptly developed acute respiratory distress syndrome (ARDS) and cardiogenic shock requiring VA-ECMO. After 2 months on ECMO, he suffered a large spontaneous intracranial parenchymal hemorrhage. He remained in the hospital at last assessment.

Case 4: An adolescent with acute COVID-19 with history of prematurity and mild cerebral palsy presented with acute hypoxemic respiratory failure requiring intubation and mechanical ventilation. He was clinically improving when he was abruptly cannulated onto VV-ECMO due to rapid development of ARDS, hyperinflammation, and cardiogenic shock. After ECMO cannulation, he was diagnosed with and treated for MIS-C, followed by clinical improvement. He abruptly became non-responsive and developed fixed and dilated pupils. Head CT revealed a large intracranial hemorrhage with cerebral herniation, after which medical support was withdrawn.

Case 5: A preschool boy with sickle cell disease found with acute COVID-19 presented with rapidly evolving acute chest syndrome requiring VV-ECMO. He remained hemodynamically stable while on ECMO and was decannulated after a few days. Post-ECMO brain MRI revealed several areas of bilateral diffusion restriction in the white matter in the watershed regions. At the time of discharge, he required intensive rehabilitation for generalized myopathy and poor coordination; however, three months later his neurological deficits had resolved.

eTable 4. Detailed clinical descriptions for 4 previously healthy patients (< 21 years) with acute ischemic stroke

Case 1: A previously healthy adolescent boy presented with acute onset of aphasia, right facial palsy, and right-sided hemiplegia one month after testing positive for SARS-CoV-2 PCR. Imaging showed an acute left middle cerebral artery stroke due to occlusion of the left middle cerebral artery (Figure 2B). During this hospitalization, he did not meet criteria for MIS-C. He was treated with low-molecular-weight heparin and at the time of discharge required rehabilitation for persistent aphasia and right-sided hemiparesis.

Case 2: A teenaged boy presented 5 days after COVID-19 symptoms with acute respiratory failure requiring intubation and mechanical ventilation, altered mental status, visual hallucinations, and acute left hemiplegia. He was diagnosed with MIS-C and required a heparin infusion due to systemic hypercoagulability. Extensive cerebral venous sinus thromboses involving the right internal jugular vein, right sigmoid sinus and superior sagittal sinus were seen on imaging with no alternate infectious etiology discovered by culture or broad range sequencing. He was noted to have persistent left hemiparesis on discharge and at 2 months follow up.

Case 3: An otherwise healthy school aged girl presented with acute hemiparesis and MIS-C one week after COVID-19 symptoms and ischemic stroke was found on imaging. Clinical course was notable for multiple subsequent ischemic strokes due to biopsy proven, large vessel CNS vasculitis refractory to intensive immunotherapies leading to rapid neurologic decline with a clinical neurologic examination prior to death that showed lack of brainstem and cortical

function. Extensive work-up for rheumatologic, genetic, other neurologic and infectious causes, including cerebrospinal fluid analysis (no pleocytosis, no oligoclonal bands, COVID PCR negative) was unremarkable.

Case 4: A school aged child presented in shock with fever, weakness, abdominal pain, nausea, diarrhea, fatigue and altered awareness/confusion. She was diagnosed with MIS-C and within 24 hours developed pulmonary edema due to left heart failure and was comatose. Brain MRI with vessel wall imaging demonstrated enhancement of the cavernous portions of the ICAs and proximal basilar artery suggestive of active inflammation from possible endotheliitis.[3, 4]Several weeks later she was discharged to inpatient rehabilitation due to persistent mild left sided weakness and gait disturbance.

eTable 5. Lumbar puncture and neurodiagnostic imaging results for children and adolescents (<21 years) hospitalized for COVID-19 by severity of neurological involvement

	All Patients with Neurological Involvement (n=365)	Life-Threatening (n=43)	Not Life-Threatening (n=322)	P Value
Lumbar puncture performed, no. (%)				
All ages LP performed	92 (25)	20 (47)	72 (22)	0.001
Age < 3 Months	57 (16)	0 (0)	57 (18)	0.005
Age < 3 Months- LP performed	45 (12)	0 (0)	45 (12)	0.02
Age ≥ 3 Months	308 (84)	43 (100)	265 (73)	0.005
Age ≥ 3 Months- LP performed	47 (13)	20 (47)	27 (7)	<0.001
Lumbar puncture, median (IQR)				
CSF WBC, 10^3/mcL	2 (1, 6), n=63	4 (2, 8.3), n= 18	2 (1, 5), n=45	0.12
CSF protein, mg/dL	45 (28, 74.5), n=75	29 (20, 75.5), n=19	48 (31.9, 74.3), n=56	0.31
CSF glucose, mg/dL	56 (49, 70), n=77	77 (69, 86.5), n=19	54 (47.3, 59.8), n=58	<0.001
CSF RBC, 10^3/mcL	5 (1, 814), n=71	2 (1, 87), n=17	8 (1, 1541), n=54	0.23
Neurodiagnostic Imaging, no. (%)				
Head CT performed	63 (17)	23 (53)	40 (12)	<0.001
Head MRI performed	54 (15)	26 (60)	28 (9)	<0.001

Abbreviations: IQR=interquartile range; LP= lumbar puncture; RBC=red blood cell count; WBC=white blood cell count; CT=computed tomography; MRI=magnetic resonance imaging

eTable 6. Most abnormal laboratory results for children and adolescents (<21 years) hospitalized for COVID-19 by severity of neurological involvement

Inflammatory Biomarker	All Patients with Neurological Involvement (n=365)		Life-Threatening (n = 43)		Not Life-Threatening (n=322)	
	n (%)	median (IQR)	n (%)	median (IQR)	n (%)	median (IQR)
Neutrophil Count (cells/µL)	314 (86)	7500 (3700, 13500)	37 (86)	12100 (7900, 18400)	277 (86)	7000 (3500, 12600)
Lymphocyte Count (cells/µL)	322 (88)	1100 (600, 2300)	38 (88)	700 (400, 1400)	284 (88)	1200 (600, 2500)
Neutrophil-to-Lymphocyte Ratio	309 (85)	5.2 (1.9, 12.5)	34 (79)	12.2 (5.5, 25.9)	275 (85)	4.4 (1.5, 13.1)
C-Reactive Protein (mg/dL)	232 (64)	12.0 (2.6, 22.3)	36 (84)	12.5 (4.6 24.9)	196 (61)	11.7 (2.4, 21.9)
D-dimer (ng/mL FEU)	183 (50)	3070 (1094, 6506)	32 (74)	3875 (2317, 12215)	151 (47)	2720 (1005, 5957)
Hemoglobin (g/dL)	332 (91)	10.7 (8.8, 12.4)	41 (95)	8.7 (7.2, 10.7)	291 (90)	10.9 (9.2, 12.7)
Platelets (cells/mm^3)	332 (91)	191,000 (125,000, 274,000)	41 (95)	125,000 (62,000, 189,000)	291 (90)	202,000 (132,000, 284,000)

Abbreviations: FEU fibrinogen equivalent units.

eTable 7. Detailed clinical descriptions of 3 patients with acute fulminant cerebral edema progressing to brain death

Case 1: A previously healthy male infant presented with fever, seizures, and gastrointestinal symptoms and was diagnosed with COVID-19. Within 24 hours, he developed status epilepticus and suffered a cardiac arrest leading to global cerebral edema on head CT. The patient had a clinical examination consistent with brain death although formal testing was not completed prior to care redirection. At autopsy, the brain showed global cerebral edema without hypoxemic injury, focal reactive gliosis in the orbitofrontal regions, and the left olfactory bulb and tract were necrotic. The lungs showed a focus of edema and macrophage inflammation in the interstitial tissue and airspaces with scattered megakaryocytes.

Case 2: A previously healthy elementary school aged girl was diagnosed with COVID-19 in the setting of fever and sore throat. Within hours of diagnosis, she developed status epilepticus and imaging revealed cerebral edema with tonsillar herniation. Less than 12 hours after admission, the patient had a cardiac arrest requiring cardiopulmonary resuscitation for 20 minutes, and died two days later due to brain death/death by neurologic criteria. At autopsy, the brain showed global cerebral edema with mass effect, red nucleons in the cerebrum/cerebellum, and chronic inflammatory cells in the leptomeninges. Heart and lungs showed evidence of myocyte necrosis of the left ventricle, infarcts of the left ventricular papillary muscles, and pulmonary aspiration and edema.

Case 3: A previously healthy elementary school aged boy presented one month after testing positive for COVID-19 with fever, rash, abdominal pain and a hypercoagulable state, meeting

criteria for MIS-C. Shortly after admission, he developed status epilepticus, and the head CT showed global edema and uncal herniation. An intracranial pressure monitor was placed with an opening pressure of 97 mmHg. Several hours after admission, the clinical examination was consistent with brain death, but care was redirected prior to formal brain death testing and there was no autopsy.

Supplemental References

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