Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Pediatric Neurology 142 (2023) 89–94

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Research Paper

SARS-CoV-2 Infection and Increased Risk for Pediatric Stroke

MaryGlen J. Vielleux, MD [a, b], Shanna Swartwood, MD [a, b], Dan Nguyen, MD [c], Karen E. James, MD [d], Bree Barbeau, MPH [e], Joshua L. Bonkowsky, MD, PhD [a, b, *]

[a] Division of Pediatric Neurology, Department of Pediatrics, University of Utah School of Medicine
[b] Brain and Spine Center, Primary Children's Hospital, Intermountain Healthcare
[c] Department of Neurology, University of Utah School of Medicine
[d] Division of Pediatric Rheumatology, Department of Pediatrics, University of Utah School of Medicine
[e] Disease Response, Evaluation, Analysis, & Monitoring Program, Bureau of Epidemiology, Utah Department of Health

ARTICLE INFO

Article history:
Received 30 April 2022
Accepted 9 October 2022
Available online 20 November 2022

Keywords:
Coronavirus
COVID-19
Pediatric
Ischemic
Stroke
MIS-C

ABSTRACT

Background: There is an increased risk of stroke in adults with severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019 [COVID-19]) infection, but whether there is a similar association with stroke in children is unclear. Our objective was to determine whether there is a correlation between COVID-19 infection, multisystem inflammatory syndrome in children (MIS-C), and pediatric ischemic stroke.

Methods: This was a retrospective, population-based cohort analysis between March 1, 2020, and June 30, 2021, conducted at a children's hospital. Pediatric patients with a diagnosis of ischemic stroke were identified using ICD-10 diagnoses of ischemic stroke, cerebrovascular accident, or cerebral infarction.

Results: We identified 16 patients, seven male and nine female, with ischemic stroke. Ages were 8 months to 17 years (median 11.5 years). More Asian (6%) and black (13%) patients had strokes compared with population prevalence (2% each, respectively). No patients had active COVID-19 infection. COVID-19 antibodies were identified in five of 11 patients tested (45%), of whom three were diagnosed with MIS-C. 82% of the strokes occurred between February and May 2021. The peak incidence was in February 2021, which was two months after peak incidence of pediatric cases of COVID-19 and one month after the peak of MIS-C cases.

Conclusions: Our study suggests that prior COVID-19 infection, but not acute infection, is correlated with a risk for stroke in the pediatric population. The risk for stroke appears to be distinct from the risk for MIS-C.

Introduction

Coronavirus disease 2019 (COVID-19) infection has been associated with stroke in adults, including up to 5% of hospitalized patients with COVID-19,[1,2] and with large-vessel stroke in patients younger than 50 years.[3] Proposed mechanisms in adults include immune-mediated thrombosis and hypercoagulability, alternative renin-angiotensin pathway activation, cardioembolism and COVID-19 cardiopathy, and direct COVID-19-mediated damage of the neurovascular unit.[4,5] Furthermore, the neuroinvasive propensity of coronaviruses is well-documented, potentially through transsynaptic transfer.[6] Biochemical properties of COVID-19, including its ability to enter cells via angiotensin-converting enzyme-2 receptors, may further contribute to its neurotropism and multiorgan effects.[7]

Conflict of Interest Disclosures: The authors have no conflicts of interest relevant to this article to disclose.

Funding: No funding to report.

Contributors' Statement: Drs. Vielleux, Swartwood, Nguyen, and James and Ms. Barbeau collected data, carried out the analyses, and reviewed and revised the manuscript. Dr. Bonkowsky conceptualized and designed the study, coordinated and supervised data collection, and drafted the initial manuscript. All authors provided edits to the manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

* Communications should be addressed to: Dr. Bonkowsky; Division of Pediatric Neurology; Department of Pediatrics; University of Utah School of Medicine; 295 Chipeta Way; Salt Lake City, Utah 84108.

E-mail address: joshua.bonkowsky@hsc.utah.edu (J.L. Bonkowsky).

https://doi.org/10.1016/j.pediatrneurol.2022.10.003
0887-8994/

However, whether COVID-19 is associated with stroke in the pediatric population remains largely unclear. In two large reports on pediatric patients (<18 years) with COVID-19,[8,9] there were no reports of stroke, cerebral vasospasm, or other focal neurological features. An international cohort study reported pediatric stroke as an uncommon (<5%) association with COVID-19 and did not find an increase in the rate of pediatric ischemic stroke in the early pandemic compared with the months preceding its onset.[10] Further, the correlation between multisystem inflammatory syndrome in children (MIS-C) related to COVID-19 infection and pediatric stroke is also poorly understood. Neurological manifestations have been described in approximately one quarter of patients with MIS-C,[11] as has a Kawasaki-like cardiac vasculopathy.[12] Stroke and thromboembolism in MIS-C has been described as a rare complication,[13,14] but the extent and whether there is a causal relationship remains unclear. Our goal was to understand whether COVID-19 infection was associated with pediatric ischemic stroke, and to characterize the relationship to MIS-C and other risk factors.

Methods

Standard protocol approvals, registrations, and patient consents

The study was approved by the Institutional Review Board of the University of Utah and the Privacy Board of Intermountain Healthcare (IH).

Setting

This retrospective study was performed at Primary Children's Hospital (PCH) in Salt Lake City, Utah, which is the sole tertiary pediatric center for an estimated pediatric population of >1.7 million children in the Intermountain West region. PCH is also the primary hospital for the majority of pediatric hospitalizations along the Wasatch Front, an urban region centered on Salt Lake City with a total population (adult and pediatric) of >2 million. PCH is a freestanding, 289-bed tertiary care children's hospital operated by IH, a regional, not-for-profit integrated health care delivery system, with 22 hospitals and 160 clinics and urgent care facilities located in Utah and southeastern Idaho, serving about 60% of Utah's 3.5 million residents and 85% of Utah's children.[15]

Study design

The study was a retrospective population-based cohort analysis of all children younger than 18 years with an ICD-10 diagnosis of ischemic stroke, intracranial hemorrhage, cerebrovascular accident, or cerebral infarction, between March 1, 2020, and June 30, 2021, compared with patients with stroke hospitalized at PCH between March 1, 2015, and February 29, 2020.

Cohort development

Patients in both the pandemic and historical cohorts were identified electronically through the IH Enterprise Data Warehouse (EDW), which records administrative, financial, clinical, pharmacy, laboratory, and radiological data associated with patients seen at any IH facility. Strokes outside of the perinatal period and strokes of uncertain etiology were included. For example, strokes secondary to traumatic brain injury, cardiac arrest, extracorporeal membrane oxygenation therapy or surgical complications for conditions not related to COVID-19 were excluded from the study.

Data collection

Patient demographic information and other covariates were collected from the EDW, including age, gender, race/ethnicity, insurance, and socioeconomic status. Race/ethnicity status stored in the EDW is self-reported at the time of clinical presentation. Race and ethnicity data were recorded at patient registration at each hospital and clinic visit. Insurance type was categorized into two groups: “private” commercial insurance (~89% of the cohort) and “public” insurance if patients were enrolled in either Medicaid or Children's Health Insurance Program. If the patient had different insurance coverages, the insurance coverage type (public or private) that was most frequently listed for their visits was used. If the patient had double coverage, their primary insurance type was used.

Patients identified through the EDW who met inclusion criteria were then further reviewed for past medical history, admission information (length of admission, time in critical care unit), COVID-19 status (polymerase chain reaction [PCR] result, antibody result, vaccination status, and time from COVID-19 positivity to onset of stroke), presenting symptoms, National Institute of Health Stroke Scale (NIHSS) on presentation, stroke characteristics (type/location/vascular territory), acute treatment (tissue plasminogen activator [tPA] and/or thrombectomy), inpatient diagnostic evaluation, secondary stroke prevention, and stroke outcomes.

We obtained state COVID-19 data, including timing of positivity, race/ethnicity, and age, from the Utah Department of Health to approximate the incidence of pediatric COVID-19 infection in Utah.[16] The University of Utah Division of Pediatric Rheumatology manually tabulated all MIS-C admissions at PCH over the same time frame. Utah state race/ethnicity information was obtained through US Census Bureau data for 2020.[17]

Results

We identified 101 patients with an ICD-10 diagnosis of stroke who were hospitalized between March 1, 2020, and June 30, 2021. Of these, 85 were excluded from our pandemic cohort (strokes in the prenatal period or of uncertain etiology, or patients with stroke before March 1, 2020, who presented for follow-up in an outpatient clinic appointment during the study time frame). Of the 16 patients who were included, there were seven male (44%) and nine female (56%) patients whose ages ranged from 8 months to 17 years, with a median age of 11.5 years. Race/ethnicity data showed higher proportions of Asian (6%) and black (13%) patients, compared with Utah state race/ethnicity data for the same period (Asian [2%], black [1%]) (Tables 1 and 2).

All patients in the pandemic cohort had COVID-19 reverse transcription PCR testing performed at time of hospitalization; two were positive, although they were both also found to be COVID-19 IgG antibody positive. COVID-19 antibodies were tested in 11 patients and were positive in five (45%) patients. Co-occurring MIS-C diagnosis was present in three patients. One of the patients had received the first dose of the Pfizer COVID-19 vaccine one week before presentation with stroke. No other patients had been vaccinated against COVID-19. The majority (n = 13, 81%) of patients were previously healthy, without significant comorbidities (Tables 1 and 2).

In the pandemic cohort, large-vessel occlusive (LVO) stroke was the most common stroke type (n = 9, 56%). Other stroke types included central nervous system vasculitis/primary angiitis (n = 3, 19%), spontaneous dissection (n = 2, 13%), watershed infarct (n = 1, 6%), and focal cerebral arteriopathy (n = 1, 6%). Nine (56%) of the strokes involved the middle cerebral artery territory, three (19%) were occipital, three (19%) involved the basal ganglia, and one (6%)

TABLE 1.
Clinical and Demographic Characteristics of the Early Pandemic (March 1, 2020, to June 30, 2021) Pediatric Ischemic Stroke Cases (n = 16) versus the Historical (March 1, 2015, to February 29, 2020) Pediatric Ischemic Stroke Cases (n = 25) at PCH

Characteristic	Pandemic Stroke Cases Number (%)	Historical Stroke Cases Number (%)
Age, years		
<1	1 (6)	1 (4)
1-4	1 (6)	10 (40)
5-10	4 (25)	6 (24)
11-15	5 (31)	5 (20)
16-18	4 (25)	3 (12)
Sex		
Female	9 (56)	10 (40)
Male	7 (44)	15 (60)
Race/ethnicity		
Hispanic	3 (19)	4 (16)
Asian or Pacific Islander	1 (6)	1 (4)
Black or African American	2 (13)	1 (4)
White Non-Hispanic	10 (63)	19 (76)
COVID-19 PCR status		
Positive	2 (13)	
Negative	14 (88)	
COVID-19 IgG status	11 (69)	
Positive	5 (31)	
Negative	6 (38)	
Not tested	5 (31)	
History of known or presumed COVID-19 infection	2 (13)	
Diagnosis of MIS-C	3 (19)	
NIHSS		
0-5	1 (6)	0 (0)
6-10	2 (13)	1 (4)
11-15	1 (6)	0 (0)
16-20	2 (13)	0 (0)
>20	0 (0)	0 (0)
Not tested/result not found	10 (63)	24 (96)
Type of stroke		
Large-vessel occlusive	9 (56)	12 (48)
CNS vasculitis/primary angiitis	3 (19)	0 (0)
Spontaneous dissection	2 (13)	1 (4)
Watershed infarct	1 (6)	2 (8)
Lacunar, embolic	0 (0)	4 (16)
Focal cerebral arteriopathy	1 (6)	6 (24)
Location		
Anterior cortical region	0 (0)	2 (8)
Lateral (MCA territory)	9 (56)	10 (40)
Posterior cortical region	3 (19)	3 (12)
Basal ganglia/thalamus	3 (19)	5 (20)
Brainstem	0 (0)	3 (12)
Spinal cord	1 (6)	0 (0)
Multifocal	0 (0)	2 (8)
Presenting symptoms		
Hemiparesis	13 (81)	20 (80)
Gaze deviation	5 (31)	1 (4)
Aphasia	5 (31)	3 (12)
Dysarthria	4 (25)	5 (20)
Altered mental status	3 (19)	6 (24)
Fever	3 (19)	3 (12)
Seizure	2 (13)	1 (4)
Headache	2 (13)	4 (16)
Neglect	1 (6)	0 (0)
Ataxia	1 (6)	3 (12)
Numbness	1 (6)	4 (16)
Acute management		
tPA alone	1 (6)	0 (0)
Thrombectomy alone	1 (6)	0 (0)
tPA thrombectomy	2 (13)	2 (8)
None	12 (75)	23 (92)
Secondary prevention		
Aspirin alone	9 (56)	14 (56)
Aspirin clopidogrel	1 (6)	1 (4)
Warfarin	1 (6)	2 (8)
Apixaban	1 (6)	0 (0)
Enoxaparin	1 (6)	3 (12)
None	3 (19)	5 (20)

(*continued on next page*)

TABLE 1. (*continued*)

Abbreviations:
COVID-19 = Coronavirus disease 2019
CNS = Central nervous systeml
QR = Interquartile range
MCA = Middle cerebral artery
MIS-C = Multisystem inflammatory syndrome in children
NIHSS = National Institute of Health Stroke Scale
PCH = Primary Children's Hospital
PCR = Polymerase chain reactiont
PA = Tissue plasminogen activator

involved the spinal cord. The most common presenting symptom was hemiparesis (n = 13, 81%), followed by aphasia (n = 5, 31%) and gaze deviation (n = 5, 31%). Fever was present in the three patients (19%) who were concomitantly diagnosed with MIS-C. NIHSS scoring was completed on six patients (38%), which ranged from scores of 0 to 5 (n = 1, 6%), 6 to 10 (n = 2, 13%), 11 to 15 (n = 1, 6%), and 16 to 20 (n = 2, 13%), and none scored greater than 20 (Tables 1 and 2).

The majority of patients (12, 75%) presented outside of the timing to be eligible for intravenous tPA treatment in the pandemic cohort. Four patients (25%) underwent acute stroke management in the form of tPA, thrombectomy, or both tPA and thrombectomy. For secondary prevention, nine patients (56%) were treated with aspirin, and one patient each (6%) with aspirin and clopidogrel, warfarin, enoxaparin, or apixaban. Three patients (19%) were not started on a form of secondary prevention (Tables 1 and 2).

Thirteen (81%) of the strokes occurred between February and May 2021, with a peak of seven strokes in February. During the study time frame at the study hospital (PCH), MIS-C cases peaked in January 2021 with a total of 17 cases. The initial pediatric COVID-19 surge reached its highest numbers in Utah in November and December 2020. The MIS-C cases at PCH reached their maximum one to two months after the pediatric COVID-19 surge, whereas stroke cases peaked two to three months after the pediatric COVID-19 surge in Utah (Fig. 1).

When compared with strokes of uncertain etiology from the previous six years at PCH (2015: n = 1; 2016: n = 0; 2017: n = 5; 2018: n = 6; 2019: n = 9; 2020: n = 4), there were significantly more strokes in the pandemic timeframe (paired Sign test p-value of 0.031). The first six months of 2021 had more than triple (n = 13) the average yearly stroke rate (n = 4) (Fig. 2). Most of the historical strokes (10, 40%) were in the one- to four-year age range compared with most (13, 81%) over the age of five in the pandemic cohort. Like the pandemic cohort, the majority of historical strokes (12, 48%) were LVOs, but there were more lacunar strokes (four, 16%) and cases of focal cerebral arteriopathy (six, 24%) than in the pandemic cohort (one, 6%). Only one patient (4%) in the historical cohort had NIHSS scoring documented, and only two patients (8%) underwent acute intervention in the form of tPA and thrombectomy (Table 1).

Discussion

Our study found a correlation between an increase in pediatric ischemic strokes and a peak in pediatric COVID-19 cases that was distinct from timing of MIS-C cases. We found an increased number in pediatric strokes at PCH from March 2020 to June 2021, with a peak in incidence of cases in February 2021. Of these patients, over one-third had a history of prior COVID infection, were unvaccinated

TABLE 2.
Case Descriptions of Early Pandemic (March 1, 2020, to June 30, 2021) Pediatric Ischemic Stroke Cases at PCH

Patient Number	Demographics	COVID-19 Result/MIS-C Status	Stroke Type	Treatment/Length of Stay	Outcomes
1	<1-year-old previously healthy, white, presented with right hemiparesis	PCR negative	Watershed stroke in left MCA distribution secondary to compressive effects from subdural hematoma	None/2 days PICU, 7 total days admitted	No residual deficits
2	3-year-old previously healthy, black, presented with encephalopathy, right hemiparesis, left gaze preference	PCR negative, IgG positive/MIS-C diagnosis	Left M2 embolic stroke	Heparin drip/19 days PICU, 31 total days admitted	Mild persistent right hemiparesis
3	6-year-old previously healthy, white, presented with right hemiparesis and receptive aphasia	PCR and IgG negative	Left anterior choroidal and distal M3 territory stroke secondary to primary angiitis of the CNS	Prednisone, ASA/8 total days admitted	Mild persistent right hemiparesis
4	9-year-old with trisomy 21, white, presented with seizure, encephalopathy, left hemiparesis, right gaze preference	PCR negative	Left MCA embolic stroke	ASA/12 days PICU, 65 total days admitted	Residual aphasia and left hemiparesis
5	10-year-old previously healthy, black, presented with right hemiparesis	PCR and IgG negative	Left M1 embolic stroke	ASA + clopidogrel/2 days PICU, 8 total days admitted	Mild persistent left upper extremity weakness
6	10-year-old previously healthy, Asian M presented with headache and left hemiplegia	PCR negative	Right MCA embolic stroke secondary to CNS vasculitis	Prednisone, ASA/2 days PICU, 30 total days admitted	Mild persistent left hemiparesis
7	10-year-old previously healthy, white F presented with right hemiparesis, left gaze preference, and right neglect	PCR negative, IgG positive/MIS-C diagnosis	Left M1 embolic stroke	tPA and thrombectomy, ASA/2 days PICU, 8 total days admitted	No residual deficits
8	11-year-old, previously healthy, presented with right hemiparesis, headache, dysarthria	PCR negative, IgG positive	Left basal ganglia infarction secondary to bilateral ICA dissection	ASA/5 total days admitted	Mild right spasticity and hemiparesis
9	12-year-old, previously healthy, presented with fevers and abdominal pain	PCR positive, IgG positive/MIS-C diagnosis	Bilateral PCA territory ischemia from focal cerebral arteriopathy	Prednisone, ASA/4 days PICU, 8 total days admitted	Persistent bilateral superior hemianopia and episodic memory impairment
10	14-year-old with hypoplastic left heart syndrome, presented with aphasia and right hemiplegia 1 week after first dose of Pfizer COVID-10 vaccine	PCR negative, IgG negative	Left M1 embolic stroke	tPA and thrombectomy, ASA, warfarin/3 days PICU, 7 total days admitted	No residual deficits
11	14-year-old with remote history of thoracic spine compression fracture, presented with back pain and bilateral lower extremity weakness and numbness	PCR negative	Anterior spinal artery thrombotic stroke	None/31 total days admitted	Persistent bilateral lower extremity weakness and numbness
12	15-year-old, previously healthy, presented with ataxia, encephalopathy, nystagmus	PCR negative, IgG negative	Left vertebral artery thrombus versus dissection	Enoxaparin/2 days PICU, 5 total days admitted	No residual deficits
13	16-year-old, previously healthy, presented with right hemiparesis and dysarthria	PCR positive 2 months before admission	Left medial lenticulostriate artery stroke secondary to primary angiitis of CNS	Prednisone, ASA/2 total days admitted	Mild right lower extremity weakness and spasticity
14	16-year-old, previously healthy, presented with left hemiparesis and dysarthria	PCR positive, IgG positive	Right MCA embolic stroke	tPA, ASA/1 day PICU, 3 total days admitted	Mild left lower extremity weakness
15	16-year-old with bicuspid aortic valve, presented with right hemiparesis and aphasia	PCR negative, IgG negative	Left M2 embolic stroke	Thrombectomy/10 days PICU, 10 total days admitted	Decreased
16	17-year-old with epilepsy, presented with left hemiparesis, dysarthria, seizure	PCR negative, IgG negative	Right M1 embolic stroke	ASA, apixaban/10 days PICU, 31 total days admitted	Mild left hemiparesis

Abbreviations:
ASA = Aspirin
CNS = Central nervous system
COVID-19 = Coronavirus disease 2019
F = Female
ICA = Internal carotid artery
M = Male
MCA =Middle cerebral artery
MIS-C = Multisystem inflammatory syndrome in children
PCA = Posterior cerebral artery
PCH = Primary Children's Hospital
PCR = Polymerase chain reaction
PICU = Pediatric intensive care unitt
PA = Tissue plasminogen activator

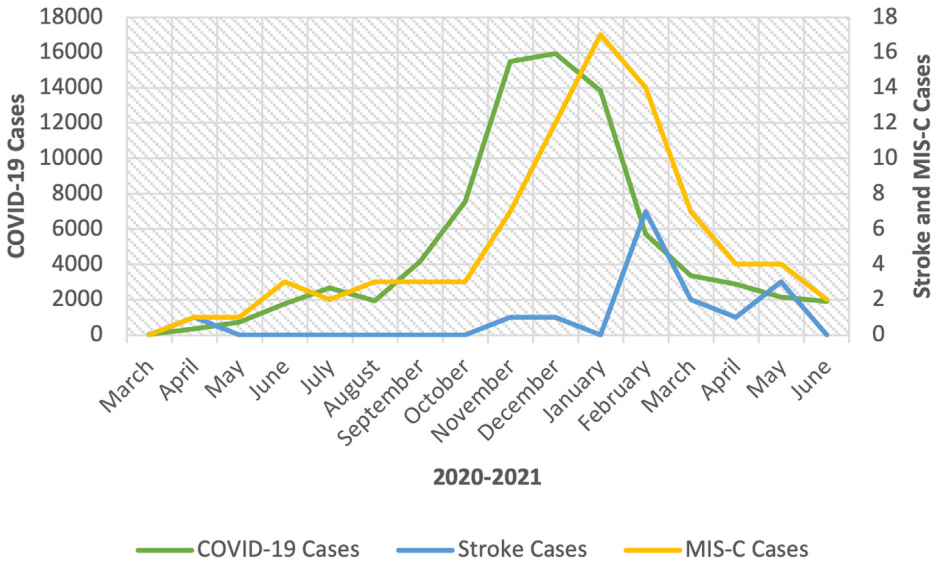

FIGURE 1. Timing of pediatric coronavirus disease 2019 (COVID-19) cases in Utah, and pediatric stroke and multisystem inflammatory syndrome in children (MIS-C) cases at Primary Children's Hospital between March 1, 2020, and June 30, 2021. The color version of this figure is available in the online edition.

and had COVID-19 antibodies at the time of stroke, and/or had active diagnosis of MIS-C. This peak had a temporal relationship with the pediatric COVID-19 case rate in Utah, which peaked in December 2020. Our data suggest that prior COVID-19 infection, but not acute infection, may be related to the development of stroke in the pediatric population. Viral infection has been described as a potential trigger of pediatric ischemic stroke.[18] Our study suggests that COVID-19 infection specifically could be a trigger, as rates of other pediatric viral infections were relatively low during our timeframe.[19] LVO strokes of the middle cerebral artery territories were the most common stroke type in both our pandemic and historical cohorts, which differs from other recent studies on pediatric stroke and COVID-19 infection, wherein focal cerebral arteriopathy was more implicated.[10] However, acute intervention in the form of tPA and/or thrombectomy was only performed in one-quarter of patients in the pandemic cohort, with the majority of patients presenting with delayed diagnoses of stroke in both the pandemic and historical cohorts. These data have important clinical and public health implications and could broaden our understanding of long-term health consequences of COVID-19 infection in pediatrics and potentially provide guidance for stroke prevention moving forward.

MIS-C and hyperinflammatory syndrome following COVID-19 infection, and its distinction from acute COVID-19 infection in children, is increasingly understood.[20] In a few patients of the pandemic cohort (n = 3), there was temporal overlap between MIS-C and diagnosis of stroke. The same number of patients (n = 3) had prior mild or asymptomatic COVID-19 infection, did not develop MIS-C, but did present with stroke. In terms of timing, there was a one- to two-month lag in MIS-C cases, but a two- to three-month time lag of stroke cases at PCH, following the peak pediatric COVID-19 rates in Utah in December 2020.

We did not see a relationship between acute COVID-19 infection (PCR positivity) and stroke in our pandemic cohort, as the patients

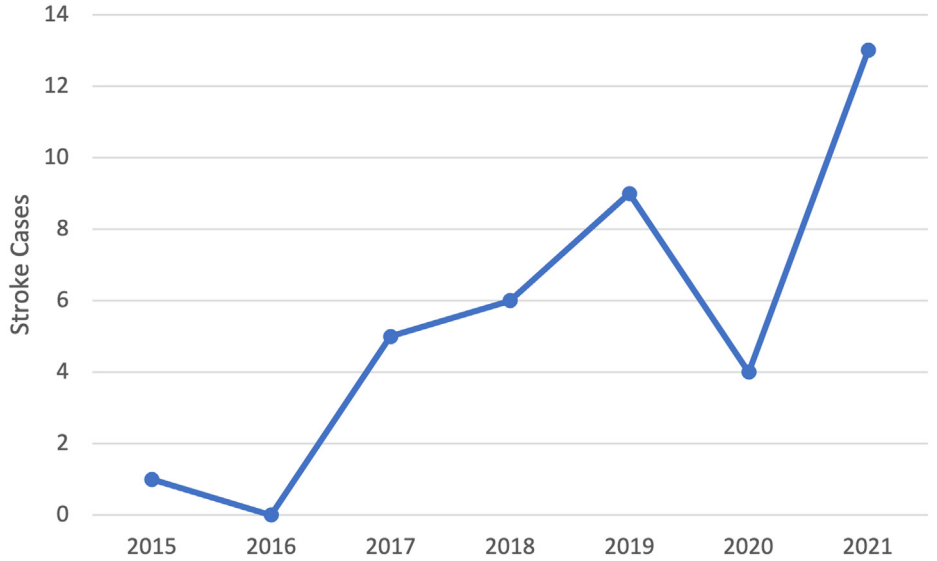

FIGURE 2. Ischemic pediatric stroke cases of uncertain etiology at Primary Children's Hospital between January 1, 2015, and June 30, 2021. The color version of this figure is available in the online edition.

who were PCR positive at time of admission were also found to be COVID-19 antibody positive, suggesting that stroke could be a delayed complication of COVID-19 infection, similar to, and perhaps related to, the hyperinflammatory state that has been described two to six weeks following acute infection.[21] Likewise, hypercoagulability has been broadly recognized in the setting of COVID-19,[22] to the extent that many pediatric inpatients meet NIH COVID-19 Treatment Guidelines criteria for therapeutic anticoagulation.[23] A proposed mechanism for this hyperinflammatory and prothrombotic state is from viral activation of the clotting cascade and simultaneous endothelial disruption.[24]

Despite our setting at a major pediatric referral center, with a large pediatric catchment (>1.7 million), and with essentially near-complete ascertainment as all pediatric stroke patients are referred or transferred to PCH in this region, pediatric stroke remains relatively rare, and thus sample size was a limitation of our study. Within our pandemic cohort, the specific timing of COVID-19 infection in relation to stroke onset was difficult to delineate because many of our patients were asymptomatic and subsequently found to be antibody positive at the time of admission. Furthermore, antibody testing for COVID-19 was not performed in a third of our stroke cohort, so it is unknown whether they had prior COVID-19 infection. As such, our assumption about timing to stroke is based on population data in our region. Follow-up to this study could be bolstered by continued review for pediatric strokes with new surges in COVID-19 infection rates associated with the Delta and Omicron variants. We did note higher rates of black or Asian children who had stroke in our cohort, relative to population prevalence of these racial/ethnicity groups.[17] However, we do not have data on relative rates of COVID-19 infection in different racial/ethnic groups of pediatric populations in Utah, so we cannot determine whether the higher stroke incidence reflects a higher risk of stroke, or reflects a higher incidence of COVID-19 infections.

There is mounting evidence that COVID-19 infection can lead to a delayed hyperinflammatory response, and our study suggests that stroke, particularly LVO stroke, with or without co-occurring diagnosis of MIS-C, could be a presentation of this prothrombotic state. Based on epidemiologic data, we hypothesize that there is likely a delay of at least one month from the timing of initial COVID-19 infection to the development of stroke.

We did find a correlation of increased risk of stroke after COVID-19 infection in children; this is in contrast to initial reports of no increased risk, but which only had data on the first three months of the pandemic.[10] Furthermore, our finding is matched by a more recent multicenter study reporting an increased stroke risk.[25] Our study also highlights the delay in pediatric stroke diagnosis, as the majority of patients in our study presented outside of the window for acute intervention; this underscores the need for greater education surrounding early stroke detection in children. Stroke in the pediatric population is often diagnosed late or misdiagnosed altogether, likely because it is relatively rare and often presents with vague symptoms. Understanding stroke risk factors and association with other disease states such as COVID-19 is imperative in guiding early diagnosis and potential prevention strategies of stroke in children.

Declaration of interests

M.J.V.: No competing interests.
S.S.: No competing interest.
D.N.: No competing interests.
K.E.J.: No competing interests.
B.B.: No competing interests.
J.L.B.: Consultant: Bluebird Bio, Calico, Enzyvant, Denali Therapeutics, Neurogene, Passage Bio; Board of Directors: wFluidx; writing: Up-to-Date; stock: Orchard Therapeutics; royalties: Manson Publishing, BioMerieux (spouse); research support: NIH, European Leukodystrophy Foundation, Vanishing White Matter Foundation.

References

1. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol. 2020;92:552–555.
2. Maury A, Lyoubi A, Peiffer-Smadja N, de Broucker T, Meppiel E. Neurological manifestations associated with SARS-CoV-2 and other coronaviruses: a narrative review for clinicians. Rev Neurol (Paris). 2021;177:51–64.
3. Oxley TJ, Mocco J, Majidi S, et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. N Engl J Med. 2020;382:e60.
4. Sagris D, Papanikolaou A, Kvernland A, et al. COVID-19 and ischemic stroke. Eur J Neurol. 2021;28:3826–3836.
5. Gu SX, Tyagi T, Jain K, et al. Thrombocytopathy and endotheliopathy: crucial contributors to Covid-19 thromboinflammation. Nat Rev Cardiol. 2020;18:194–209.
6. Li YC, Bai WZ, Hirano N, et al. Neurotropic virus tracing suggests a membranous-coating-mediated mechanism for transsynaptic communication. J Comp Neurol. 2013;521:203–212.
7. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci. 2020;11:995–998.
8. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. Pediatrics. 2020;145:e20200702.
9. Parri N, Magistà AM, Marchetti F, et al. Characteristic of COVID-19 infection in pediatric patients: early findings from two Italian Pediatric Research Networks. Eur J Pediatr. 2020;179:1315–1323.
10. Beslow LA, Linds AB, Fox CK, et al. Pediatric ischemic stroke: an infrequent complication of sars-cov-2. Ann Neurol. 2021;89:657–665.
11. LaRovere KL, Riggs BJ, Poussaint TY, et al. Neurologic involvement in children and adolescents hospitalized in the United States for Covid-19 or multisystem inflammatory syndrome. JAMA Neurol. 2021;78:536.
12. Akca UK, Kesici S, Ozsurekci Y, et al. Kawasaki-like disease in children with COVID-19. Rheumatol Int. 2020;40:2105–2115.
13. Menon NM, Srivaths LV. Thromboembolism in children with multisystem inflammatory syndrome: a literature review. Pediatr Res. 2022;92:946–950.
14. Chang J, Bulwa Z, Breit H, et al. Acute large vessel ischemic stroke in patients with COVID-19–related multisystem inflammatory syndrome. Pediatr Neurol. 2022;126:104–107.
15. About: Primary Childrens. Intermountain Healthcare. Available at: https://intermountainhealthcare.org/primary-childrens/about. Accessed October 21, 2021.
16. Utah Department of Health. Bureau of epidemiology. Disease response, evaluation, analysis, and monitoring program. Salt Lake City, UT: Utah Department of Health; 2021.
17. 2020 Census Demographic Data Map Viewer. Census.gov. Available at: https://mtgis-portal.geo.census.gov/arcgis/apps/MapSeries/index.html?appid=2566121a73de463995ed2b2fd7ff6eb7; 2021. Accessed October 21, 2021.
18. Fullerton HJ, Hills NK, Elkind MS, et al. Infection, vaccination, and childhood arterial ischemic stroke: Results of the VIPS study. Neurology. 2015;85:1459–1466.
19. Olsen SJ, Winn AK, Budd AP, et al. Changes in influenza and other respiratory virus activity during the COVID-19 pandemic — United States, 2020–2021. MMWR Morb Mortal Wkly Rep. 2021;70:1013–1019.
20. Feldstein LR, Tenforde MW, Friedman KG, et al. Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. JAMA. 2021;325:1074.
21. Rubens JH, Akindele NP, Tschudy MM, Sick-Samuels AC. Acute Covid-19 and multisystem inflammatory syndrome in children. BMJ. 2021;372:n385.
22. Connors JM, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19. J Thromb Haemost. 2020;18:1559–1561.
23. Information on covid-19 treatment, prevention and research. National Institutes of Health. Available at: https://www.covid19treatmentguidelines.nih.gov/. Accessed December 17, 2021.
24. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with COVID-19. N Engl J Med. 2020;382:e38.
25. Beslow LA, Agner SC, Santoro JD, et al. International pediatric stroke study group. International prevalence and mechanisms of SARS-CoV-2 in childhood arterial ischemic stroke during the COVID-19 pandemic. Stroke. 2022;53:2497–2503.