Beslow Lauren (Orcid ID: 0000-0003-0571-980X)

Hassanein Sahar (Orcid ID: 0000-0002-0191-8425)

Felling Ryan (Orcid ID: 0000-0002-0845-9356)

PAGE

Article Type: Research Article

Title: Pediatric Ischemic Stroke: An Infrequent Complication of SARS-CoV-2
(60 characters)

Authors: Lauren A. Beslow, MD, MSCE,[1] Alexandra B. Linds, MSc,[2] Christine K. Fox, MD, MAS,[3] Manoëlle Kossorotoff, MD, PhD,[4] Yenny C. Zuñiga Zambrano, MD,[5] Marta Hernández-Chávez, MD,[6] Sahar M. A. Hassanein, MD, PhD,[7] Susan Byrne, MD, PhD,[8] Ming Lim, MD,[9] Nkechi Maduaka, MbChB, BSc,[10] Dimitrios Zafeiriou, MD, PhD,[11] Michael M. Dowling MD, PhD, MSCS,[12] Ryan J. Felling, MD, PhD,[13] Mubeen F. Rafay, MBBS, MSc,[14] Laura L. Lehman, MD,[15] Michael J. Noetzel, MD,[16] Timothy J. Bernard, MD, MSCS,[17] Nomazulu Dlamini, MBBS, MSc, PhD,[18] on behalf of the International Pediatric Stroke Study Group[‡]

Author Affiliations: [1]Division of Neurology, Children's Hospital of Philadelphia; Departments of Neurology and Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [2]Division of Neurology, Child Health Evaluative Sciences Program, The Hospital for Sick Children, Toronto, ON, Canada; [3]Departments of Neurology and Pediatrics, University of California San Francisco, San Francisco, CA, USA; [4]French Center for Pediatric Stroke, Pediatric Neurology Department, APHP University Hospital Necker-Enfants maladies, Paris, France; [5]Unit of Pediatric Neurology, Fundación, Hospital de la Misericordia, Bogotá, Colombia; [6]Unit of Neurology, Division of Pediatrics, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile; [7]Department of Pediatrics, Faculty of Medicine, Ain Shams University, Cairo, Egypt; [8]Evelina London Children's Hospital, London, UK, FutureNeuro, Royal College of Surgeons, Ireland; [9]Evelina London Children's Hospital and Faculty of Life Sciences and Medicine, King's College London, London, UK; [10]Paediatric Department, King's College Hospital, London, UK; [11]Department of Pediatrics, Hippokratio General Hospital, Aristotle University, Thessaloniki, Greece; [12]Departments of Pediatrics and Neurology, University of Texas Southwestern Medical Center, Dallas, TX, USA; [13]Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD, USA; [14]Section of Neurology, Department of Pediatrics and Child Health, Children's Hospital Research Institute of Manitoba, University of Manitoba, Winnipeg, MB, Canada; [15]Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA; [16]Departments of Neurology and Pediatrics, Division of Pediatric and Developmental Neurology, Washington University School of Medicine, Neurorehabilitation Program, St. Louis Children's Hospital, St. Louis, MO, USA; [17]Section of Child Neurology, Children's Hospital Colorado, Departments of Pediatrics and Neurology, Hemophilia and Thrombosis Center, University of Colorado School of Medicine, Aurora, CO, USA; [18]Division of Neurology, Department of Pediatrics, The Hospital for Sick Children, Child Health Evaluative Sciences Program, University of Toronto, Toronto, ON, Canada

[‡]International Pediatric Stroke Study and British Paediatric Neurology Association Cerebrovascular Special Interest Group participating sites and co-investigators listed in Supplement 1

Corresponding author: Lauren A. Beslow, MD MSCE FAHA
Corresponding author's address: 3501 Civic Center Boulevard
1st Floor Colket Building
Philadelphia, PA 19104
Corresponding author's phone and fax: (p) 215-590-1719 (f) 215-590-1771
Corresponding author's e-mail address: beslow@email.chop.edu
Running head (limit 50 characters): Pediatric Stroke and SARS-Co-V-2 (29 characters)

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ana.25991

ABSTRACT (limit 250 words)

Objective: Severe complications of SARS-CoV-2 include arterial ischemic stroke (AIS) in adults and pediatric multisystem inflammatory syndrome. Whether stroke is a frequent complication of pediatric SARS-CoV-2 is unknown. This study aimed to determine the proportion of pediatric SARS-CoV-2 cases with ischemic stroke and the proportion of pediatric strokes with SARS-CoV-2 in the first three months of the pandemic in an international cohort.

Methods: We surveyed 61 international sites with pediatric stroke expertise. Survey questions included: numbers of hospitalized pediatric (≤18 years) SARS-CoV-2 patients; numbers of incident neonatal and childhood ischemic strokes; frequency of SARS-CoV-2 testing for pediatric stroke patients; and numbers of stroke cases positive for SARS-CoV-2 March 1-May 31, 2020.

Results: Of 42 centers with SAR-CoV-2 hospitalization numbers, 8/971 (0.82%) with SARS-CoV-2 had ischemic strokes. Proportions of stroke cases positive for SARS-CoV-2 from March-May 2020 were: 1/108 neonatal AIS (0.9%), 0/33 neonatal cerebral sinovenous thrombosis (CSVT; 0%), 6/166 childhood AIS (3.6%), and 1/54 childhood CSVT (1.9%) cases. However, only 30.5% of neonates and 60% of children with strokes were tested for SARS-CoV-2. Therefore, these proportions represent 2.9%, 0%, 6.1%, and 3.0% of stroke cases tested for SARS-CoV-2. Seven of eight with SARS-CoV-2 had additional established stroke risk factors.

Interpretation: As in adults, pediatric stroke is an infrequent complication of SARS-CoV-2, and SARS-CoV-2 was detected in only 4.7% of pediatric ischemic stroke patients tested. However, <50% of strokes were tested. SARS-CoV-2 testing should be considered in pediatric stroke patients as the pandemic continues to determine SARS-CoV-2's role in pediatric stroke.

INTRODUCTION

A novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), identified in Wuhan, China in late 2019 causes coronavirus disease 2019 (COVID-19). The World Health Organization declared a global pandemic on March 11, 2020. As data have accumulated about COVID-19, stroke emerged as an infrequent but clinically important neurological complication in adults,[1, 2] including in those younger than age 50 years.[3] In children with COVID-19, a novel multisystem inflammatory syndrome has been described in centers throughout the world.[4-7] Several causes of pediatric stroke like focal cerebral arteriopathy have inflammatory and/or infectious triggers.[8-11] While plausible that SARS-CoV-2 could incite childhood strokes, to date only two pediatric patients with the newly described multisystem inflammatory syndrome and two with arteriopathies in the setting of SARS-CoV-2 have been reported to have arterial ischemic stroke (AIS).[4, 12-14]

With rising concern for SARS-CoV-2-related stroke among adults and inflammation among children, parent and caregiver anxiety are high. Pediatric neurologists, infectious disease experts, and pediatricians have been asked by parents whether COVID-19 is a risk factor for pediatric stroke. By surveying pediatric stroke experts from across the globe, we aimed to address these concerns by determining: (1) the proportion of SARS-CoV-2 positive cases with ischemic stroke; (2) numbers of new ischemic strokes at participating centers in the first three months of the global pandemic compared to the preceding two months, and (3) the proportion of ischemic stroke cases testing positive for SARS-CoV-2 in the first three months of the pandemic.

SUBJECTS/MATERIALS AND METHODS

Study design, participants, and data collection The Publications Committee of the International Pediatric Stroke Study designed the data collection tool (found at https://internationalpediatricstroke.org/ipss-research/) in April and May 2020. On June 1, 2020, we surveyed active International Pediatric Stroke Study and British Paediatric Neurology Association Cerebrovascular Special Interest Group members to ascertain (1) institutional numbers of SARS-CoV-2 cases (symptomatic or asymptomatic), (2) institutional numbers of incident neonatal (age ≤28 days) AIS, neonatal cerebral sinovenous thrombosis (CSVT), childhood (age ≥29 days-≤18 years) AIS, and childhood CSVT at each center monthly from January through May 2020, (3) institutional practices for SARS-CoV-2 testing in neonates and children with AIS and CSVT, and (4) institutional numbers of each ischemic stroke subtype from March 1 to May 31, 2020 with positive nasopharyngeal polymerase chain reaction or positive serological assay for SARS-CoV-2. Centers that reported pediatric ischemic stroke patients positive for SARS-CoV-2 completed an additional case report form that included questions about stroke type and location, presence of established stroke risk factors, severity of COVID-19 illness, and whether the investigator thought SARS-CoV-2 was a definite or possible contributor to the stroke. Sites with multiple investigators completed one survey. The survey received an institutional review board (IRB) waiver. Participating institutions utilized internal SARS-CoV-2 and stroke tracking systems to obtain case numbers. Local IRBs approved the case report form for pediatric ischemic stroke patients who tested positive for SARS-CoV-2, and written informed consent was obtained from guardians according to institutional guidelines.

Statistical analysis Categorical variables are described using counts and frequencies. For the proportion of strokes among pediatric patients hospitalized with SARS-CoV-2, stroke cases positive for SARS-CoV-2 were only included in the numerator if the center provided its number of SARS-CoV-2 hospitalizations. The number of ischemic stroke cases from January and February (SARS-CoV-2 not widespread outside of China) were compared to numbers from March to May 2020. A nonparametric test of trend determined whether cases of each stroke subtype increased from January to May 2020. Stata 12.0 (StataCorp, College Station, TX) was used for analyses. A p-value of <0.05 was considered statistically significant.

RESULTS

Participating centers

Sixty-one centers of 87 approached (70.1%) from 26 countries representing all continents (except Antarctica) participated and completed the original survey once between June 1 and July 26, 2020. Supplement 1 lists participating sites and co-investigators, and indicates sites contributing institutional numbers of SARS-CoV-2 positive cases as well as incident stroke numbers. All survey respondents are medical doctors with pediatric stroke expertise (56 pediatric neurologists, 3 pediatric hematologists, 1 neonatologist, 1 pediatric neurosurgeon). Countries represented included Argentina, Australia, Brazil, Canada (five sites in four provinces), Chile, Colombia (four sites), Egypt, France, Germany, Greece, India, Ireland, Israel, Italy, Kenya, Netherlands, Philippines, Poland, Serbia, Spain, South Africa, Switzerland, United Arab Emirates, United Kingdom (Wales one site, England seven sites), United States (21 sites in 16 states), and Uruguay.

SARS-CoV-2 cases

In October 2020, the number of hospitalized pediatric patients 0-≤18 years who tested positive for SARS-CoV-2 between March and May 2020 was requested, and 42 of 61 sites (68.9%, denoted with * in Supplement 1) from 20 countries obtained these data. All 6 centers with strokes provided institutional numbers of hospitalized pediatric SARS-CoV-2 patients. During the first 3 months of the pandemic, 8/971 (0.82%, 95% binomial exact confidence interval 0.36%-1.62%) hospitalized with SARS-CoV-2 infection had ischemic strokes. Table 1 summarizes ischemic strokes among hospitalized SARS-CoV-2 patients from our cohort and from adult studies. Information regarding ages of SARS-CoV-2 patients and SARS-CoV-2 symptom status (including symptom severity) was not available at any center.

Institutional SARS-CoV-2 testing practices

Most centers used SARS-CoV-2 polymerase chain reaction, while some also used antibody or antigen tests. When surveyed, 13 of 57 centers that reported on neonates (22.8%) tested all neonatal hospital admissions and 40 of 57 (70.2%) only tested neonates with SARS-CoV-2 symptoms or positive contacts. Of 61 centers, 29 (47.5%) tested all hospitalized children, and 31 (50.8%) tested children with SARS-CoV-2 symptoms or positive contacts. In May 2020, neonatal stroke patients were less likely than children to be tested (20/43 [46.5%] versus 63/78 [80.8%], p=0.0001).

Ischemic stroke trends

Figure 1 shows numbers of each type of ischemic stroke case from January to May 2020. Fifty-seven centers provided data about neonatal AIS and CSVT cases, and 61 centers provided data about childhood AIS and CSVT cases. A test of trend did not reveal an increase in cases from January 2020 to May 2020 for any stroke type: neonatal AIS p= 0.18, neonatal CSVT p= 0.66, childhood AIS p= 0.22, and childhood CSVT p=0.68.

Neonatal AIS

The number of sites that tested all neonatal AIS patients for SARS-CoV-2 increased between March and May 2020 (March three sites, April 14 sites, May 18 sites). Five of 36 neonatal AIS patients were tested in March 2020 (13.9%), 13 of 38 in April 2020 (34.2%), and 16 of 34 in May 2020 (47.1%). One neonatal AIS patient from Chile tested positive for SARS-CoV-2 in May 2020. This represents 0.9% of the 108 neonatal AIS patients presenting between March and May 2020 and 2.9% of the 34 neonatal AIS patients that were tested for SARS-CoV-2 during that period.

Neonatal CSVT

The number of sites that tested all neonatal CSVT patients for SARS-CoV-2 increased between March and May 2020 (March four sites, April ten sites, May 15 sites). Three of 14 neonatal CSVT patients were tested in March 2020 (21.4%), two of ten in April 2020 (20%), four of nine in May 2020 (44.4%). None of the 33 neonatal CSVT patients presenting between March and May 2020 tested positive for SARS-CoV-2, but only seven were tested.

Childhood AIS

The number of sites that tested all childhood AIS patients for SARS-CoV-2 increased between March and May 2020 (March 13 sites, April 29 sites, May 35 sites). Twenty-two of 62 childhood AIS patients were tested in March 2020 (35.5%), 31 of 47 in April 2020 (66%), 46 of 57 in May 2020 (80.7%). Six childhood AIS patients tested positive for SARS-CoV-2. These patients included one from Egypt (May), three from France (one each in March, April, May, all from same site), and two from the United Kingdom (two different sites, one April which was previously reported [Table 2 case 6[4]], one May). This represents 3.6% of the 166 childhood AIS patients who presented between March and May 2020 and 6.1% of the 98 children with AIS tested for SARS-CoV-2 during that period. Figure 2 shows images from a

cAIS patient with SARS-CoV-2 infection and inflammatory-type focal cerebral arteriopathy. Table 2 provides clinical and radiographic details about pediatric ischemic stroke patients that tested positive for SARS-CoV-2. Supplement 2 provides reasons for hospitalization and inflammatory markers for the stroke patients with SARS-CoV-2.

Childhood CSVT

The number of sites that tested all childhood CSVT patients for SARS-CoV-2 increased between March and May 2020 (March eight sites, April 20 sites, May 28 sites). Three of 18 childhood CSVT patients were tested in March 2020 (16.7%), 13 of 15 in April 2020 (86.7%), 17 of 21 in May 2020 (81%). One childhood CSVT patient from Colombia tested positive for SARS-CoV-2 in March 2020. This represents 1.9% of 54 childhood CSVT patients who presented between March and May 2020 and 3.0% of the 33 childhood CSVT patients tested for SARS-CoV-2 during that period.

DISCUSSION

The results from this international survey of pediatric stroke subspecialists from 61 centers in 26 countries did not demonstrate an increase in pediatric ischemic strokes between January 1, 2020 and May 31, 2020 while the SARS-CoV-2 pandemic was spreading worldwide. During the first three months of the pandemic, we found that <1% of pediatric patients hospitalized with SARS-CoV-2 had ischemic strokes. While this figure may seem low, relative to the annual incidence of pediatric stroke of 1-2/100,000 per year, this proportion could be considered high.[15] Only 2.2% of 361 pediatric ischemic stroke patients tested positive for SARS-CoV-2. However, fewer than 50% of pediatric ischemic stroke patients were tested for SARS-CoV-2 during this time. Even accounting for incomplete testing for SARS-CoV-2 among pediatric stroke patients, only 4.7% of stroke patients tested had SARS-CoV-2. We are therefore cautiously hopeful that a low percentage of pediatric patients with SARS-CoV-2 will ultimately have ischemic strokes, particularly because the centers that did not provide SARS-CoV-2 hospitalization numbers did not have stroke cases positive for SARS-CoV-2 and because we likely underestimated the frequency of SARS-CoV-2 at participating institutions due to variable testing practices, variable sensitivity and specificity of the tests, and incomplete testing. Nearly all centers reported testing patients with symptoms of COVID-19 or known positive contacts, and centers that did not test patients were in regions with low numbers of cases in the underlying population. Nonetheless, some children with asymptomatic infections may not have been tested for the virus.

The majority of pediatric ischemic stroke patients who tested positive for SARS-CoV-2 infection had at least one other established risk factor for stroke. SARS-CoV-2 may be a contributing factor for stroke in children with underlying risk factors, but its contribution even in these cases, is not clear, particularly because the SARS-CoV-2 infection may be incidental given the frequency of community spread in certain regions. Whether SARS-CoV-2 is an important risk factor for ischemic stroke in children with no underlying stroke risk factors is yet undetermined. We only identified one neonate with AIS who tested positive for SARS-CoV-2, but an underestimate of virus frequency in neonatal ischemic stroke patients is likely. Many delivering mothers have asymptomatic SARS-CoV-2 infections. Among 675 mothers admitted for delivery in one New York City hospital, over 10% tested positive for SARS-CoV-2, and over 75% of these infections were asymptomatic.[16] SARS-CoV-2 may induce a thrombotic milieu, and neonatal AIS is thought to be caused by placental thrombi entering the fetal circulation[17]. Testing of mother-infant dyads for SARS-CoV-2 when a neonate is diagnosed with an ischemic stroke may be required to determine whether SARS-CoV-2 is a true risk factor for neonatal ischemic stroke.

Prior pediatric stroke studies have established inflammation and infections other than SARS-CoV-2, including asymptomatic infections, as risk factors for stroke. In this study, one child (Table 2 case 2) presented with middle cerebral artery stroke and had an inflammatory-type focal cerebral arteriopathy. This child had a varicella infection six months prior to the stroke, so it is not possible to determine whether the arteriopathy was triggered by the varicella infection, by the SARS-CoV-2 infection, or by both because varicella has been associated with arteriopathic stroke that can occur up to 12 months after acute infection.[10, 11] Other infections have also been related to pediatric arteriopathy and stroke.[8, 18, 19] From 326 childhood arterial ischemic stroke cases enrolled in the Vascular Effects of Infection in Pediatric Stroke (VIPS) study, serological evidence of acute herpesvirus infections doubled the risk of stroke, and 45% of stroke patients were positive for acute herpesvirus infections.[8] Most herpesvirus infections were subclinical which underscores the importance of considering testing all pediatric ischemic stroke patients for SARS-CoV-2 during the current pandemic, even if the patient does not have clinical symptoms associated with COVID-19. In VIPS, parvovirus B19 was detected by polymerase chain reaction in the plasma among ten of 161 AIS cases tested but was not found in controls.[18] Finally, a recent study of children with human immunodeficiency syndrome, transcranial Doppler ultrasound indices suggested abnormal intracranial vessels and hemodynamics postulated to be related to immunodeficiency and/or

concomitant infection.[19] Case reports from Iran and New York described children with basal ganglia and left middle cerebral artery infarctions, respectively, due to focal cerebral arteriopathy in the setting of COVID-19.[12, 13] The child in New York had vessel-wall imaging with enhancement, suggestive of inflammation.[13] These reports, along with case 4 in Table 2, suggest that like varicella and other viruses, SARS-CoV-2 may be a trigger for inflammation and pediatric cerebral arteriopathy that can lead to stroke. Given the lag of up to a year that can occur in the setting of varicella infection and arteriopathic stroke, serial data collection is required to determine whether SARS-CoV-2 can induce arteriopathic changes weeks to months after acute infection. This data collection should include polymerase chain reaction to identify acute SARS-CoV-2 infection and serial antibody testing to evaluate for past infection.

Our finding that <1% of pediatric patients hospitalized with SARS-CoV-2 had an ischemic stroke is similar to adult stroke estimates from several countries that range from 0.68% to 4.6% of hospitalized patients with SARS-CoV-2.[1, 20-23] A discussion of stroke mechanisms proposed in adults with COVID-19 is helpful as we begin to understand the presentations and pathophysiology of pediatric strokes in the setting of COVID-19. In a single-center retrospective analysis of 219 adult patients with COVID-19 from Wuhan, China, 4.5% developed acute ischemic stroke.[1] Patients with acute cerebrovascular disease had more severe COVID-19 symptoms, increased inflammatory markers, and greater evidence of hypercoagulable states than those without stroke. In a large hospital system in New York City, of 3,556 patients hospitalized with COVID-19, 0.9% had radiographically-proven ischemic strokes.[20] Acquired hypercoagulability was considered a potential stroke mechanism. Another series from New York City described five young adult patients aged 33 to 49 years in whom large vessel ischemic stroke was a presenting feature of COVID-19 infection, and three of these five patients had elevated D-dimer.[3] A series of three patients from Beijing, China described coagulopathy and multiple cerebral infarcts with anticardiolipin and β_2-glycoprotein I antibodies in the setting of COVID-19.[24] A series from London, United Kingdom described six patients with COVID-19 and large artery strokes with elevated D-dimer, five of whom had positive anticardiolipin antibodies.[2] In yet another series of four patients with COVID-19 who presented with acute strokes, all three tested had elevated C reactive protein, and the two in whom D-dimer was tested had elevated values.[25] Together, these studies support both inflammatory and coagulopathic mechanisms for ischemic strokes among adult patients with COVID-19.

Inflammation may also have a prominent role in pediatric stroke. In VIPS, higher concentrations of high-sensitivity C-reactive protein and myeloperoxidase were found among children with cardioembolic stroke, and higher serum amyloid A was found in children with cardioembolic and arteriopathic strokes.[26] Children with progressive arteriopathy had a higher risk of recurrent stroke and a trend toward higher high-sensitivity C-reactive protein and serum amyloid A levels than those with stable or improving arteriopathy, indicating that inflammatory biomarkers correlate with stroke cause and recurrence among those with arteriopathy. Therefore, in pediatric patients with ischemic stroke and SARS-CoV-2, testing of inflammatory markers may help elucidate pathogenesis. While ischemic stroke has not been a frequently reported clinical feature of multisystem inflammatory syndrome in children,[4-7, 14] two of eight pediatric ischemic stroke patients in this report (one previously reported)[4] had this novel inflammatory syndrome, suggesting that inflammation potentially plays a role in children with SARS-CoV-2 infection who have strokes. However, we do not have adequate information about our cases to understand fully the contribution of hypercoagulability and inflammation to the strokes.

The current study has several limitations. We were unable to obtain the number of SARS-CoV-2 cases at all participating institutions. Furthermore, the investigators that provided information on numbers with SARS-CoV-2 infection did not have access to ages of the positive patients, the reason for the SAR-CoV-2 testing, or information about the presence or absence of SARS-CoV-2 symptoms. Given the fact that many children likely have asymptomatic SARS-CoV-2 infections, the actual risk of pediatric ischemic stroke in those with SARS-CoV-2 infection is likely even lower than the point estimates we present. Also, with lack of knowledge regarding community prevalence of SARS-CoV-2 infection at each site coupled with the fact that many children with stroke had additional established stroke risk factors, it is not possible to attribute the strokes to SARS-CoV-2 infection. Due to the near shut down of research and the difficulty that many collaborators faced at the onset of the pandemic, we could not feasibly consent all patients with ischemic stroke for use of patient-level data. Therefore, comparison of stroke patients with and without SARS-CoV-2 was not possible. As noted above, we may have underestimated the prevalence of SARS-CoV-2 in all four ischemic stroke groups. Testing for SARS-CoV-2 varied by institution and was not performed in over half of stroke cases, particularly among neonates. Additionally, sensitivity and specificity of the testing can vary.[27] This study also lacked information about children with SARS-CoV-2 symptoms weeks or months prior to stroke. Arteriopathies in particular can occur or progress weeks to months after acute infection,[11] so data collected may not reflect the number of pediatric ischemic stroke cases that will eventually occur as the pandemic progresses. Also, vaccines protect against childhood AIS,[9] and a decrease in vaccination rates has occurred during the COVID-19 pandemic.[28] Furthermore, there has been a decline in

hospitalizations for adult stroke during the pandemic.[29] We therefore must interpret our finding that there was no significant change in stroke numbers from January 2020 to May 2020 carefully because we do not fully understand the effects of the pandemic on care-seeking behavior or of decreased vaccination rates on pediatric stroke incidence. Finally, we did not have participation from centers in several regions with high SARS-CoV-2 infection rates like China and New York City.

Despite this survey study's limitations, it is important to describe pediatric ischemic stroke prevalence in first few months of the novel global SARS-CoV-2 pandemic given reports of strokes in younger adults with COVID-19, parental concern, and the number of questions from physicians and parents that have been posed. Pediatric patients with SARS-CoV-2 have indeed had ischemic strokes, and known mechanisms of pediatric stroke, including arteriopathy and thromboembolism, often incited by viral infections and inflammation, offer plausible mechanisms for SARS-CoV-2 to confer stroke risk among pediatric patients. Our group will re-administer the survey throughout the pandemic and will obtain patient-level data for stroke cases with evidence of SARS-CoV-2 infection using the International Pediatric Stroke Study platform to provide additional information, including whether post-COVID-19 arteriopathies develop. A great strength of the current survey was the inclusion of sites from 26 countries, including sites from low- and middle- income countries. In a global pandemic, this worldwide collaboration will allow us to understand this pathogen's impact on pediatric neurological health.

Conclusions

The number of pediatric ischemic strokes did not appear to increase in the first three months of the global COVID-19 pandemic compared to the preceding two months. While the percentage of pediatric patients with SARS-CoV-2 who suffer stroke appears to be very low, and the number of pediatric ischemic strokes positive for SARS-CoV-2 also appears to be relatively low, conclusions cannot be made regarding the risk of ischemic stroke in children infected with SARS-CoV-2 based on these survey results alone given testing limitations. Lack of uniform testing practices around the world demonstrates the urgent need for increased SARS-CoV-2 testing among pediatric stroke patients given what is known both about stroke in adult SARS-CoV-2 patients and about viruses that trigger stroke in children, which are often either asymptomatic or remote from the stroke. Serial data collection and more robust testing are required to determine SAR-CoV-2's role in pediatric stroke and mechanisms through which this novel pathogen might cause stroke in children.

Acknowledgement: We thank our co-investigators from the International Pediatric Stroke Study and British Paediatric Neurology Association Cerebrovascular Special Interest Group (listed in Supplement 1) who contributed data which made this study possible. This study was not funded.

Author Contributions: LAB, ABL, CKF, DZ, MMD, RJF, MRF, LLL, MJN, TJB, and ND contributed to the conception and design of the study; LAB, ABL, CKF, MK, YCZZ, MHC, SMAH, SB, ML, NM, DZ, MMD, RJF, MFR, LLL, MJN, TJB, and ND contributed to the acquisition and analysis of the data; LAB, ABL, RJF, and ND contributed to drafting the text and preparing the figures.

Potential Conflicts of Interest: Nothing to report.

REFERENCES (limit to 40)

1. Li Y, Li M, Wang M, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. Stroke Vasc Neurol. 2020;5:279-284.
2. Beyrouti R, Adams ME, Benjamin L, et al. Characteristics of ischaemic stroke associated with COVID-19. J Neurol Neurosurg Psychiatry. 2020;91:889-891.
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. Riphagen S, Gomez X, Gonzalez-Martinez C, et al. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020;395:1607-1608.
5. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med. 2020;383:334-346.
6. Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ. 2020;369:m2094.
7. Cheung EW, Zachariah P, Gorelik M, et al. Multisystem inflammatory syndrome related to COVID-19 in previously healthy children and adolescents in New York City. JAMA. 2020;324:294-296.
8. Elkind MS, Hills NK, Glaser CA, et al. Herpesvirus infections and childhood arterial ischemic stroke: results of the VIPS study. Circulation. 2016;133:732-741.
9. 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.
10. Sebire G, Meyer L, Chabrier S. Varicella as a risk factor for cerebral infarction in childhood: a case-control study. Ann Neurol. 1999;45:679-680.
11. Askalan R, Laughlin S, Mayank S, et al. Chickenpox and stroke in childhood: a study of frequency and causation. Stroke. 2001;32:1257-1262.
12. Mirzaee SMM, Goncalves FG, Mohammadifard M, et al. Focal cerebral arteriopathy in a COVID-19 pediatric patient. Radiology. 2020:202197.
13. Gulko E, Overby P, Ali S, et al. Vessel wall enhancement and focal cerebral arteriopathy in a pediatric patient with acute infarct and COVID-19 infection. Am J Neuroradiol. 2020.
14. Kaushik S, Ahluwalia N, Gangadharan S, et al. ECMO support in SARS-CoV2 multisystem inflammatory syndrome in children in a child. Perfusion. 2020:267659120954386.
15. Ferriero DM, Fullerton HJ, Bernard TJ, et al. Management of stroke in neonates and children: a scientific statement from the American Heart Association/American Stroke Association. Stroke. 2019;50:e51-e96.
16. Prabhu M, Cagino K, Matthews KC, et al. Pregnancy and postpartum outcomes in a universally tested population for SARS-CoV-2 in New York City: a prospective cohort study. BJOG. 2020;127:1548-1556.
17. Dunbar M, Kirton A. Perinatal stroke. Semin Pediatr Neurol. 2019;32:100767.
18. Fullerton HJ, Luna JM, Wintermark M, et al. Parvovirus B19 infection in children with arterial ischemic stroke. Stroke. 2017;48:2875-2877.
19. Dlamini N, Pohl K, Eley B, et al. Stroke transcranial Doppler in children with human immunodeficiency virus. Dev Med Child Neurol. 2020;62:735-741.
20. Yaghi S, Ishida K, Torres J, et al. SARS-CoV-2 and stroke in a New York healthcare system. Stroke. 2020;51:2002-2011.
21. Katz JM, Libman RB, Wang JJ, et al. Cerebrovascular complications of COVID-19. Stroke. 2020;51:e227-e231.
22. Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res. 2020;191:9-14.
23. Rothstein A, Oldridge O, Schwennesen H, et al. Acute cerebrovascular events in hospitalized COVID-19 patients. Stroke. 2020;51:e219-e222.
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. Avula A, Nalleballe K, Narula N, et al. COVID-19 presenting as stroke. Brain Behav Immun. 2020;87:115-119.
26. Fullerton HJ, deVeber GA, Hills NK, et al. Inflammatory biomarkers in childhood arterial ischemic stroke: correlates of stroke cause and recurrence. Stroke. 2016;47:2221-2228.
27. Alcoba-Florez J, Gil-Campesino H, de Artola DG, et al. Sensitivity of different RT-qPCR solutions for SARS-CoV-2 detection. Int J Infect Dis. 2020;99:190-192.
28. Bramer CA, Kimmins LM, Swanson R, et al. Decline in child vaccination coverage during the COVID-19 pandemic - Michigan Care Improvement Registry, May 2016-May 2020. Am J Transplant. 2020;20:1930-1931.

29. Diegoli H, Magalhaes PSC, Martins SCO, et al. Decrease in hospital admissions for transient ischemic attack, mild, and moderate stroke during the COVID-19 era. Stroke. 2020;51:2315-2321.

FIGURE LEGENDS

Figure 1. Bar graph with pediatric ischemic strokes of each type January 2020 through May 2020
AIS=arterial ischemic stroke. CSVT=cerebral sinovenous thrombosis. Total number in bar=total number of stroke cases. Hashes=number of stroke cases tested for SARS-CoV-2. Number in box=number of strokes positive for SARS-CoV-2.

Figure 2. Focal cerebral arteriopathy and arterial stroke in a child with asymptomatic SARS-CoV-2 infection detected by serology and varicella infection 6 months prior to stroke
(A) Axial diffusion-weighted MRI with arterial ischemic stroke in the left basal ganglia. (B) Coronal time of flight MRA demonstrating focal narrowing of the left middle cerebral artery (white arrow), consistent with focal cerebral arteriopathy of childhood. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. MRI=magnetic resonance imaging. MRA=magnetic resonance angiography.

Table 1. Ischemic strokes among hospitalized SARS-CoV-2 patients

Reference	Location	Hospitalized SARS-CoV-2 patients with stroke (%)
Beslow et al.*	International Pediatric Cohort	8/971 (0.82%)
Li et al.[1]	Wuhan, China	10/219 (4.6%)
Yaghi et al.[19]	New York, New York, USA	32/3,556 (0.9%)
Katz et al.[20]	New York, New York, USA	72/10,596 (0.7%)
Lodigiani et al.[21]	Milan, Italy	9/388 (2.3%)
Rothstein et al.[22]	Philadelphia, Pennsylvania, USA	20/844 (2.4%)

*pediatric only, all other studies adult

Table 2. Clinical details of pediatric patients with SARS-CoV-2 and ischemic stroke

Stroke type	Demographics	SARS-CoV-2 tests and symptoms	Critical illness*	Stroke location	Clinician's determination of relationship between stroke and SARS-CoV-2 and other risk factors
Case 1 nAIS	F, 4 days, Chile (Native /White)	PCR+ (2 days before stroke identified); no specific symptoms	No	MRI brain: thalamo-capsular infarct	Possible; mother negative for SARS-CoV-2 but some hospital staff tested positive; perinatal
Case 2 cAIS	F, 28 months, France (White)	Serology+ (day of stroke ictus); no specific symptoms	No	MRI brain: left basal ganglia infarct MRA head: left MCA stenosis	Possible; focal cerebral arteriopathy and varicella infection 6 months prior to stroke (known risk for focal cerebral arteriopathy)
Case 3 cAIS	F, 32 months, France (White)	PCR+ for seasonal coronavirus acutely, serology+ for SARS-CoV-2 6 weeks after stroke; fever 72 hours prior to stroke	No	HCT, MRI brain: midbrain infarct	Possible; hypothesized role of coinfection with seasonal coronavirus; no known other risk factors
Case 4 cAIS	M, 10 years, Egypt (Middle Eastern)	PCR+ (7 days after stroke ictus); fever, cough, severe respiratory distress	No	HCT: bilateral PCA infarctions	Possible; iron deficiency anemia unlikely to be sole causative factor
Case 5 cAIS	M, 10 years, United Kingdom (Black)	PCR+ (7 days prior to stroke ictus) and serology+ (20 days after stroke ictus); fever, MIS-C	Yes	HCT, MRI brain: large right MCA infarct with hemorrhage and small cerebellar infarcts MRA head and neck: right internal carotid narrowing	Possible; MIS-C causing hypercoagulable state and embolic stroke from lower limb thrombosis in a child already at increased risk of stroke due to sickle cell disease
Case 6 cAIS	M, age 15 years, United Kingdom (Black)	PCR+ (8 days after stroke ictus); cough, fever, headache, diarrhea, severe respiratory distress, MIS-C	Yes	HCT: right MCA and right ACA infarction	Possible; MIS-C, ECMO, iron deficiency anemia
Case 7 cAIS	M, 16 years, France (Black)	PCR+ (9 days and 6 days prior to stroke ictus); fever, headache	Yes	HCT, MRI brain: left MCA, left ACA, right ACA infarctions MRA head: likely vasculitis	Possible; Lemierre Syndrome with Fusobacterium necrophorum sinusitis/meningitis and rapidly progressive arteriopathy consistent with vasculitis primary risk factors
Case 8 cCSVT	M, 9 years, Colombia (Native/White)	PCR+ (6 days after stroke ictus); cough, chest X-ray ground glass opacities	No	HCT, MRI brain, MRV head: right transverse sinus and right sigmoid sinus thrombus	Possible; mastoiditis primary risk factor

*Critical illness defined as intubation, septic shock, extracorporeal membrane oxygenation. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. nAIS=neonatal arterial ischemic stroke. F=female. M=male. PCR=polymerase chain reaction. CRP=C-reactive protein. nl=normal. DRRVT=dilute Russell's viper venom time. MRI=magnetic resonance imaging. cAIS= childhood arterial ischemic stroke. HCT=head computed tomography. PCA=posterior cerebral artery. MRA=magnetic resonance angiography. MCA=middle cerebral artery. ACA=anterior cerebral artery. cCSVT=childhood cerebral sinovenous thrombosis. MRV=magnetic resonance venography. MIS-C=multisystem inflammatory syndrome in children. ECMO=extracorporeal membrane oxygenation.

Supplement 1. Study Sites and Co-Investigators

Institution	Site Co-Investigator(s)
*Ain Shams University, Cairo, Egypt	
*Al Jalila Children's Hospital, Dubai, United Arab Emirates	Abdalla A Abdalla, MD
*Aristotle University of Thessaloniki, Thessaloniki, Greece	
Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Turin, Italy	Paola Saracco, MD
Bristol Royal Hospital for Children, Bristol, United Kingdom	Andrew Mallick, MB BCh, MRCPCH, PGCME, PhD
*Centro Hospitalario Pereira Rossell, Universidad de la República, Montevideo, Uruguay	Gabriel González Rabelino, MD
*Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA	Evelyn K Shih, MD, PhD Rebecca N Ichord, MD
*Children's Hospital Research Institute of Manitoba, University of Manitoba, Winnipeg Children's Hospital, Manitoba, Winnipeg, Canada	
Children's Mercy Hospital, University of Missouri Kansas City School of Medicine, Kansas City, Missouri, USA	Mukta Sharma, MD, MPH, FAAP
*Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA	Sudhakar Vadivelu, DO
Clinica Universidad de La Sabana, Bogota, Colombia	Adriana Carolina Vargas Nino, MD
*Colombia Universidad Nacional de Colombia Fundación, Hospital de la Misericordia, Bogotá, Colombia	
Cook Children's Medical Center, Fort Worth, Texas, USA	Marcela Torres, MD
Cork University Hospital, Cork, Ireland	Niamh McSweeney, MB, Bch, BAO, BmedSci, DCH FRCSP (Paeds) MD
Dell Children's Medical Center and University of Texas at Austin College of Pharmacy, Austin, Texas, USA	Collin A Hovinga, PharmD, MS, FCCP
Dr S N Medical College, Umaid Hospital for Women and Children, Jodhpur, Rajasthan, India	Manish Parakh, MD
*Evelina London Children's Hospital, Evelina Paediatric Multisystem Inflammatory Syndrome Temporarily Associated with SARS-CoV-2 (PIMS-TS), Guy's and St Thomas' NHS Trust, London, King's Health Partners Academic Health Science Centre, London, England, United Kingdom	Julia Kenny, MBBS Rahul Singh, MD Shelley Riphagen, MBBS
French Center for Pediatric Stroke, APHP University Hospital Necker-Enfants Malades, Paris, France	
Great Ormond Street Hospital and Institute of Child Health, London, United Kingdom	Vijeya Ganesan, MB, ChB
*Harvard Medical School, Boston Children's Hospital, Boston, Massachusetts, USA	Michael Rivkin, MD
Hospital Central de la Policia Nacional de Bogota, Colombia	Zulma Hernandez, MD
*Hospital de Pediatría Prof. Dr. Juan P. Garrahan, Buenos Aires, Argentina	Maria Celeste Buompadre, MD
Hospital Regional de Zipaquira – ESE Hospital Universitario de la Samaritana, Bogota, Colombia	Adriana Carolina Vargas Nino, MD
Hospital Sant Joan de Deu, University of Barcelona, Spain	Veronica Gonzalez Alvarez, MD
Indiana Hemophilia and Thrombosis Center, Indianapolis, Indiana, USA	Nihal Bakeer, MD

Inselpital University Children's Hospital, University of Bern, Bern, Switzerland	Maja Steinlin, MD Maria Regenyi, MD
*Johns Hopkins School of Medicine, Johns Hopkins University, Baltimore, Maryland, USA	Lisa R Sun, MD
*King's College Hospital, Denmark Hill, London, England, United Kingdom	Fenella Kirkham, MD Malur Sudhanva, MBBS, MD, FRCPath
LMU Munich, University Hospital, Dr. von Hauner Children's Hospital, Munich, Germany	Lucia Gerstl, MD
*Medical University of Silesia, Katowice, Poland	Ilona Kopyta, MD
Morriston Hospital, Swansea, United Kingdom	Catharine P. White, MD
*Mother and Child Health Care Institute, Belgrade, Serbia	Gordana Kovacevic, MD
*Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle University, Newcastle upon Tyne, United Kingdom	Anna Basu, MD
*Ohio State University, Nationwide Children's Hospital, Columbus Ohio, USA	Warren D Lo, MD
*Oregon Health & Science University, Portland, Oregon, USA	Jenny Wilson, MD
*Phoenix Children's Hospital, University of Arizona College of Medicine-Phoenix, Phoenix, Arizona, USA	Brian Appavu, MD
*Pontificia Universidad Catolica de Chile, Santiago, Chile	
Red Cross War Memorial Children's Hospital, University of Cape Town, Cape Town, South Africa	Alvin Ndondo, MD
*Royal Manchester Children's Hospital, Manchester, England, United Kingdom	Dipak Ram, MBBS, MRCPCH
*School of Medicine, Kenyatta University, Nairobi, Kenya	Samson Gwer, MD
Schulich School of Medicine and Dentistry, London, Ontario, Canada	Andrea Andrade, MD
*Seattle Children's Hospital, University of Washington School of Medicine, Seattle, Washington, USA	Catherine Amlie-Lefond, MD
*Stanford University School of Medicine, Stanford, California, USA	Sarah Lee, MD
*Stollery Children's Hospital, Edmonton, Alberta, Canada	Janette Mailo, MD
*Tel Aviv Sourasky Medical Center, Tel Aviv University, Tel Aviv, Israel	Moran Hausman-Kedem, MD
*The Royal Children's Hospital, Melbourne, Australia	Mark T Mackay, MD
*The University of Toronto, The Hospital for Sick Children, Toronto, Ontario, Canada	Daune McGregor, MD, MSc, MBA Gabrielle deVeber, MD Ishvinder Bhathal, NP Liza Pulcine, MD, MSC Mahendra Moharir, MD, MSc
Universidade Estadual de Campinas, Campinas, Sao Paolo, Brazil	Katia Maria Ribeira Silva Schmutzler, MD
*University Hospital Southampton NHS Foundation Trust, United Kingdom	Jaspal Singh, MD
*University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands	Niek E van der Aa, MD, PhD
University of British Columbia and BC Children's Hospital, Vancouver, BC, Canada	Bruce Bjornson, MD, FRCPC
*University of Calgary, Alberta Children's Hospital, Calgary, Alberta, Canada	Adam Kirton, MD
*University of California, San Francisco, California, USA	Hannah Glass, MD

*University of Colorado School of Medicine, Children's Hospital Colorado, Aurora, Colorado, USA	
*University of Florida College of Medicine, Gainesville, Florida, USA	Suman Ghosh, MD, MPA
University of Oklahoma Health Sciences Center, Oklahoma City	Gabriela Purcarin, MD
*University of Texas McGovern Medical School, Children's Memorial Hermann Hospital, Houston, Texas, USA	Stuart Fraser, MD
*University of Texas Southwestern Medical Center, Dallas, Texas, USA	
*University of the Philippines-Philippine General Hospital, Manila, Philippines	Marilyn Tan, MD
*Vanderbilt University Medical Center, Monroe Carell Jr. Children's Hospital at Vanderbilt, USA	Lori C Jordan, MD, PhD
*Washington University School of Medicine, St Louis Children's Hospital, St Louis, Missouri, USA	Kristin Guilliams, MD

*= Institutions provided SARS-CoV-2 positive hospitalization numbers plus ischemic stroke case numbers in those 0-≤18 years