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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Research Paper

Neurological Complications in Children Hospitalized With Seizures and Respiratory Infections: A Comparison Between SARS-CoV-2 and Other Respiratory Infections

Grace Gombolay, MD a,b,∗, Monique Anderson, MD, PhD c, Yijin Xiang, MPH d, Shasha Bai, PhD d, Christina A. Rostad, MD e, William Tyor, MD c, f

a Division of Neurology, Department of Pediatrics, Emory University School of Medicine, Atlanta Georgia
b Division of Pediatric Neurology, Children’s Healthcare of Atlanta, Atlanta Georgia
c Department of Neurology, Emory University School of Medicine, Atlanta, Georgia
d Emory University School of Medicine, Pediatric Biostatistics Core, Atlanta, Georgia
e Division of Infectious Diseases, and Center for Childhood Infections and Vaccines, Department of Pediatrics, Emory University School of Medicine, Children’s Healthcare of Atlanta and Emory University School of Medicine, Atlanta, Georgia
f Atlanta VA Medical Center, Decatur, Georgia

Article history:
Received 14 March 2022
Accepted 17 July 2022
Available online 30 July 2022

Keywords:
SARS-CoV-2
COVID-19
Other coronaviruses
Influenza
Stroke
Pediatric
Respiratory viruses
Parainfluenza

ABSTRACT

Background: Children with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can experience neurological symptoms, but limited data are available on neurological symptoms associated with other respiratory infections. We compared proportions of neurological symptoms in children hospitalized with seizures and respiratory infections, including SARS-CoV-2, influenza, and endemic coronaviruses.

Methods: A retrospective cohort study was performed on children admitted for seizures who had positive respiratory polymerase chain reactions for SARS-CoV-2, coronavirus NL63, coronavirus OC34, influenza (A and B), adenovirus, Mycoplasma pneumoniae, or parainfluenza 3 or 4. Primary outcomes were rates of new neurological diagnoses and mortality.

Results: A total of 883 children were included. Mortality rates ranged from 0% with M. pneumoniae to 4.9% with parainfluenza 4. Strokes were observed with all infections except for coronavirus OC43 and M. pneumoniae, with the highest rates in parainfluenza 4 (4.9%) and SARS-CoV-2 (5.9%). Compared with other infections, children with SARS-CoV-2 were older, had higher rates of stroke, and lower rates of intubation. The most common brain magnetic resonance imaging (MRI) abnormality was diffusion restriction. Abnormal MRI rates were lower in SARS-CoV-2, compared with patients with other coronavirus (OC). However, rates of stroke, encephalopathy, hypoxic-ischemic encephalopathy, and meningoencephalitis were similar between SARS-CoV-2 and influenza cohorts.

Conclusions: In children hospitalized with seizures, higher rates of stroke were observed in SARS-CoV-2 versus OC. Similar rates of neurological symptoms were observed in patients with SARS-CoV-2 and those with influenza. Strokes can occur in children with these viral infections, particularly SARS-CoV-2.

© 2022 Elsevier Inc. All rights reserved.
Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) results in coronavirus disease 2019 (COVID-19) and can cause neurological symptoms in children, including seizures, meningoencephalitis, Guillain-Barré syndrome, stroke, and demyelinating syndromes. Neurological symptoms are also reported in children with influenza. However, limited information is known about the rates of neurological sequelae in children with other respiratory infections including other coronaviruses (OCs). In addition, neurological symptoms such as seizures are associated with severe COVID-19 in hospitalized children, but limited studies are available in children regarding seizures and the risk for other neurological symptoms associated with respiratory infections. In this study, we examine neurological symptoms in children hospitalized with seizures and positive respiratory infection testing for SARS-CoV-2, OCs (coronavirus NL63 and coronavirus OC34), influenza (A and B), adenovirus, Mycoplasma pneumoniae, and parainfluenza 3 or 4.

Methods

Institutional review board approval was obtained (STUDY0000008555). Data on children aged between zero and 21 years who were admitted with new-onset seizures to Egleston Children’s Hospital, a single quaternary referral free-standing children’s hospital in Atlanta, Georgia, were compiled from January 2014 to August 2021 using electronic medical records. Patients were grouped by positive nasopharyngeal real-time polymerase chain reaction respiratory panel testing (BioFire), which was obtained at the clinician’s discretion. SARS-CoV-2 testing was captured either separately or on the BioFire Respiratory Panel 2.1, which added SARS-CoV-2, which was utilized starting November 12, 2020. Neurological diagnoses were identified using International Classification of Diseases-10 codes or key words including seizure, stroke, meningitis, encephalitis, encephalopathy, and demyelinating disease. Patients with prior seizure diagnoses and febrile seizures were excluded.

Patient characteristics including age, race, sex, ethnicity, hospital length of stay (LOS), intensive care unit (ICU) admission, intubation, chest radiograph results, brain magnetic resonance imaging (MRI), and mortality were abstracted from the medical record. Brain MRI features and chest x-rays were classified as abnormal or normal based on reports. Incidental findings on MRI were defined by structural abnormalities or prior abnormalities that were not new during the admission for infection.

Statistical analysis

Summary statistics were presented using counts and percent-ages or medians and quartiles. Differences in demographics and clinical characteristics between the patients with different infections were tested using parametric (chi-square) and nonparametric (Fisher exact and Wilcoxon rank sums) tests. Statistical significance was set at \( P < 0.05 \), and all \( P \) values were two-sided. Statistical analyses were performed with the R version 4.0.2 software (R Foundation for Statistical Computing).

Results

Baseline clinical characteristics

Clinical characteristics among the different infections in 883 children are presented in Table and Supplemental Table 1. The infections included adenovirus, OCs (coronavirus NL63 and OC43), influenza A and B, M. pneumoniae, parainfluenza 3 and 4, and SARS-CoV-2, with 20 to 214 children in each group. Median LOS for the overall admission was 3 to 4 days except for M. pneumoniae (median 7 days, interquartile range [IQR] 3.8 to 16.5). Mortality occurred in association with each infection except for M. pneumoniae, with the highest percentage observed with parainfluenza 4.

As for neurological diagnoses (Supplemental Figure 1), up to 15.6% had encephalopathy with up to 10.4% hypoxic-ischemic encephalopathy (HIE). Hypoxic-ischemic encephalopathy was new and observed in 46% of patients with cardiac arrest versus 7% of patients without cardiac arrest (\( P < 0.0001 \)). Strokes were observed in association with all infections except for coronavirus OC43 and M. pneumoniae, with 4.9% in parainfluenza 4 and 5.9% in SARS-CoV-2. Meningoencephalitis was observed in all infections except for coronavirus OC43, parainfluenza 4, and SARS-CoV-2. In those patients with brain MRIs (\( N = 124 \)), abnormal MRIs ranged from 43% to 100%. The most common MRI abnormality was diffusion restriction. Cerebrospinal fluid (CSF) pleocytosis was noted in 0% to 33% of patients with no lumbar punctures performed in SARS-CoV-2 (Supplemental Table 1).

SARS-CoV-2 versus other infections

SARS-CoV-2 (\( N = 68 \)) was compared with all other respiratory infections combined (Figure, Table). Children with SARS-CoV-2 were older (median 11.3 years, IQR 4.4 to 15.6) than those with other infections (median 4.0 years, IQR 1.9 to 8.0, \( P < 0.001 \)). Differences were observed in ICU admission rates (SARS-CoV-2 50.0% versus others 38.5%, \( P = 0.008 \)) and intubation rates (SARS-CoV-2 19% versus 33% in others, \( P = 0.021 \)), and rates of strokes were higher in those with SARS-CoV-2 (5.9%) than those with other infections (1.6%, \( P = 0.036 \)). Median white blood cell counts were different between patients with SARS-CoV-2 versus those with other infections (Table).

SARS-CoV-2 versus OCs, influenza, and adenovirus

Since respiratory infections have different clinical presentations, subanalyses were performed comparing SARS-CoV-2 with other pathogens: OCs (coronavirus NL63 and OC43, \( N = 187 \)), influenza (A and B, \( N = 232 \)), and adenovirus (\( N = 214 \) (Table). Patients with SARS-CoV-2 were older than those with OCs (\( P < 0.001 \)), influenza (\( P < 0.001 \)), and adenovirus (\( P < 0.001 \)). No differences in race were observed, but the proportion of Hispanic/Latino patients was higher in SARS-CoV-2 (32.4%) than OC (19.4%, \( P = 0.042 \)).

Patients with SARS-CoV-2 had lower ICU admission rates (\( P = 0.008 \)) and lower intubation rates than those with OC (\( P = 0.021 \)) and adenovirus (\( P = 0.015 \) and \( P = 0.001 \), respectively). Stroke rates were higher in SARS-CoV-2 versus OC (6% versus 0.5%, \( P = 0.019 \)) and adenovirus (1.9% \( P = 0.009 \)). Proportions of abnormal MRI were similar among the groups. The rate of abnormal MRI was lower in patients with SARS-CoV-2 than those with OCs (57% versus 82%) with a medium to large effect size (standard mean difference) of 0.55. However, similar characteristics were observed between SARS-CoV-2 and influenza cohorts in LOS, ICU admission/intubation rates, and proportions of neurological diagnoses including stroke, abnormal MRI rates, and mortality (Table).

Discussion

We compared rates of neurological complications in children hospitalized with seizures and positive respiratory polymerase chain reactions for SARS-CoV-2 versus other respiratory pathogens. Children with SARS-CoV-2 had higher rates of stroke and lower...
rates of intubation. Moreover, higher stroke rates and lower ICU admission/intubation rates were observed in SARS-CoV-2 when compared with OC or adenovirus. Interestingly, influenza had similar rates of neurological complications as SARS-CoV-2, highlighting that influenza can cause neurological sequelae and death similarly to COVID-19. M. pneumoniae was included in this study due to its association with encephalitis in children, but meningoencephalitis was infrequent in our cohort. Also, children with SARS-CoV-2 were older than children with other infections. Age may be a confounding variable. However, seizures usually affect younger children; thus, investigating the reasons behind why older patients were more likely to be hospitalized with seizures could shed insight into the mechanisms leading to neurological symptoms related to SARS-CoV-2.

The pathophysiologic mechanisms for neurological manifestations have been reported to include inflammatory cytokines,
endothelial complications, and direct viral invasion.\(^7\)\(^8\) Systemic proinflammatory cytokines are elicited by influenza and SARS-CoV-2 infections,\(^9\) and children with neuropsychiatric symptoms in SARS-CoV-2 have increased CSF cytokines.\(^10\) Central nervous system-specific antibody-mediated inflammation is uncommon. Infections are a risk factor for stroke in children and adults,\(^11\) and in adults, SARS-CoV-2 has increased risk for stroke when compared with influenza.\(^12\) Stroke was also observed in parainfluenza in our cohort. Although parainfluenza is associated with increased mortality in adults, association of stroke with parainfluenza is unknown. Nonetheless, parainfluenza can infect endothelial cells, leading to an increased stroke risk.\(^13\) Neurological symptoms were associated with adenovirus, which has been observed in other children.\(^14\) In a pediatric cohort with adenovirus infection, a subset (1.5%, 21 of 1360) had evidence of encephalitis, encephalopathy, or meningitis. In this subset, 100% (21 of 21) had encephalopathy, with seizures (9.5%, three of 21), weakness (9.5%, three of 21), and gait disturbance (5%, one of 21), and one patient (5%) died.\(^14\) One study using a mouse model with adenoviral infection may shed some light on a potential pathophysiologic mechanism for how adenovirus can cause neurological symptoms. This mouse model of neuroinflammation related to adenoviral infection demonstrates hemorrhagic encephalomyelitis, with microglial activation and blood-brain barrier dysfunction.\(^15\)

Limitations of our study include a single quaternary referral center and that this was a retrospective study. Moreover, complications in children without seizures were not included. Imaging findings were limited to reports, and diagnoses were also limited by billing codes. Another limitation was that CSF studies, including viral testing, were not performed in many patients.

In conclusion, we observed differences in clinical outcomes of SARS-CoV-2 versus OCs, including higher rates of stroke, but lower rates of ICU admission and intubation in hospitalized children with seizures. Strokes were observed in association with many respiratory pathogens. Similar rates of neurological symptoms were observed in association with SARS-CoV-2 and influenza. Acute neurological sequelae are common in children with respiratory viral infections and new-onset seizures.

Data statement

Data will be available to researchers upon reasonable request.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pediatrneurol.2022.07.010.

References

1. Fink EL, Robertson CL, Wainwright MS, et al. Prevalence and risk factors of neurologic manifestations in hospitalized children diagnosed with acute SARS-CoV-2 or MIS-C. Pediatr Neurol. 2022;128:33–44.
2. LaToove KL, Hirosse 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;78:536–547.
3. Ekstrand JJ. Neurologic complications of influenza. Semin Pediatr Neurol. 2012;19:96–100.
4. Frankl S, Coffin SE, Harrison JB, Swami SK, McGuire JL. Influenza-associated neurologic complications in hospitalized children. J Pediatr. 2021;239:24–31.e1.
5. Drouin O, Hepburn CM, Farrar DS, et al. Characteristics of children admitted to hospital with acute SARS-CoV-2 infection in Canada in 2020. CMAJ. 2021;193:E1483–E1493.
6. Britton PN, Dale RC, Blyth CC, et al. Causes and clinical features of childhood encephalitis: a multicenter, prospective cohort study. Clin Infect Dis. 2020;70:2517–2526.
7. Lin JE, Asfour A, Sewell TB, et al. Neurological issues in children with COVID-19. Neurosci Lett. 2021;743, 135567.
8. Song E, Zhang C, Israelow B, et al. Neuroinvasion of SARS-CoV-2 in human and mouse brain. J Exp Med. 2021;218, e20202135.
9. Bohmwald K, Andrade CA, Karagiannis AM. Contribution of pro-inflammatory molecules induced by respiratory virus infections to neurological disorders. Pharmaceuticals (Basel). 2021;14:340.
10. Ngo B, Lapp SA, Siegel B, et al. Cerebrospinal fluid cytokine, chemokine, and SARS-CoV-2 antibody profiles in children with neuropsychiatric symptoms associated with COVID-19. Mult Scler Relat Disord. 2021;55, 103169.
11. Elkind MSV, Boehme AK, Smith CJ, Meisel A, Buckwalter MS. Infection as a stroke risk factor and determinant of outcome after stroke. Stroke. 2020;51:3156–3168.
12. Stein LK, Mayman NA, Dhamoon MS, Fifi JT. The emerging association between COVID-19 and acute stroke. Trends Neurosci. 2021:44:527–537.
13. Bahouth MN, Venkatesan A. Acute viral illnesses and ischemic stroke: pathological considerations in the era of the COVID-19 pandemic. Stroke. 2021;52:1885–1894.
14. Zhang XF, Tan CB, Yao ZX, Jiang L, Hong SQ. Adenovirus infection-associated central nervous system disease in children. Pediatr Infect Dis J. 2021;40:205–208.
15. Guida JD, Pejer G, Pirofski LA, Bronson CF, Horwitz MS. Mouse adenovirus type 1 causes a fatal hemorrhagic encephalomyelitis in adult C57BL/6 but not BALB/c mice. J Virol. 1995;69:7674–7681.