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Research Paper

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

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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.

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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.[1,2] Neurological symptoms are also reported in children with influenza.[3,4] 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.[5] 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 (STUDY000000855). 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 percentages 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

TABLE.
Comparison of Hospitalized Pediatric Patients With Seizures and SARS-CoV-2 Versus Those With All Other Infections (Adenovirus, Other Coronaviruses, Influenza A/B, *Mycoplasma pneumoniae*, Parainfluenza 3 and 4), and Then SARS-CoV-2 Versus Other Coronaviruses (NL63 and OC63) and Influenza (A and B)

Characteristic	SARS-CoV-2	Other Infections	*P* Value	Other Coronavirus	*P* Value	Influenza	*P* Value	Adenovirus	*P* Value
No.	68	815		187		232		214	
Sex M:F (%)	59:41	53:47	0.376	56:44	0.671	49:51	0.17	59:41	0.332
Age, years (median [IQR])	11.3 [4.4, 15.6]	4.0 [1.9, 8.0]	**<0.001**	4.9 [2.3, 7.8]	**<0.001**	6.2 [3.4, 11.2]	**<0.001**	2.9 [1.2, 5.1]	**<0.001**
Ethnicity, No. (%)					**0.042**		0.107		0.05
Hispanic or Latino	22 (32.4)	179 (22.0)	0.07	36 (19.4)		51 (22.1)		44 (20.6)	
Race, No. (%)			0.51		0.68		0.076		0.356
Black or African American	23 (33.8)	330 (40.5)		71 (38.0)		104 (44.8)		93 (43.5)	
Other	12 (17.6)	142 (17.4)		26 (13.9)		51 (22.0)		34 (15.9)	
White	33 (48.5)	343 (42.1)		90 (48.1)		77 (33.2)		120 (42.6)	
ICU admit (%)	34 (50.0)	314 (38.5)	0.071	129 (69.0)	**0.008**	116 (50.0)	1	143 (66.8)	**0.015**
Admission LOS, days (median [IQR])	4.00 [1.00, 9.50]	4.00 [2.00, 9.00]	0.459	4.00 [2.00, 8.00]	**0.876**	3.50 [2.00, 9.00]	0.832	4.00 [2.00, 10.00]	0.319
ICU LOS, days (median [IQR])	4.00 [2.00, 15.00]	4.00 [2.00, 9.00]	0.977	3.00 [1.00, 8.00]	**0.401**	4.50 [2.00, 10.25]	0.797	4.00 [2.00, 15.00]	0.934
Intubation, No. (%)	13 (19.1)	279 (33.1)	**0.021**	65 (34.8)	**0.021**	58 (25.0)	0.417	89 (41.6)	**0.001**
Death, No. (%)	2 (2.9)	17 (2.1)	0.652	4 (2.1%)	0.659	4 (1.7)	0.621	5 (2.3)	0.676
Neurological diagnoses, No. (%)									
Stroke	4 (5.9)	13 (1.6)	**0.036**	1 (0.5)	**0.019**	5 (2.2)	0.122	4 (1.9)	**0.099**
Encephalopathy	6 (8.8)	76 (9.3)	1	24 (12.8)	0.51	17 (7.3)	0.615	23 (10.7)	0.82
HIE	3 (4.4)	67 (8.2)	0.352	16 (8.6)	0.418	13 (5.6)	1	22 (10.3)	0.218
Meningoencephalitis	0 (0.0)	16 (2.0)	0.627	3 (1.6)	0.567	2 (0.9)	1	7 (3.3)	0.202
Polyneuropathy	1 (1.5)	5 (0.6)	0.383	3 (1.6)	1	0 (0.0)	0.227	2 (0.9)	0.564
ADEM	0 (0.0)	1 (0.1)	1	0 (0.0)	NA	1 (0.4)	1	0	NA
Other demyelinating diseases	0 (0.0)	3 (0.4)	1	3 (1.6)	0.567	0 (0.0)	NA	NA	NA
CXR total No.	41	618	0.42	149		155		164	
Abnormal No. (%)	23 (56.1)	299 (48.4)		73 (49.0)	0.482	73 (47.1)	0.38	76 (46.3)	0.297
WBC, 1000/μL (median [IQR])	7.32 [6.05, 11.07]	9.64 [6.62, 13.31]	**0.016**	10.66 [7.61, 14.26]	**0.001**	7.40 [5.25, 10.35]	0.632	11.85 [8.63, 16.20]	<0.001
Lumbar puncture, No.	0	41	NA	8	NA	11	NA	16	NA
CSF pleocytosis, No. (%)	ND	6 (14.6)		1 (12.5)		3 (27.3)		1 (6.2)	
CSF WBC, cells/μL (median [IQR])	ND	1.0 [1.0, 3.0]	NA	1.0 [0.0, 1.0]	NA	1.0 [1.0, 7.0]	NA	1.0 [1.0, 2.0]	NA
Brain MRI No.	7	117		27		26		43	1
Abnormal, No. (%)	4 (57.1)	75 (64.1)	0.704	22 (81.5)	0.315	12 (46.2)	0.688	27 (62.8)	
Brain MRI findings, No. (%)			0.102		0.116		0.294		**0.022**
Normal	3 (42.9)	42 (35.9)		5 (18.5)		14 (53.8)		16 (37.2)	
DWI changes	0 (0.0)	29 (24.8)		6 (22.2)		5 (19.2)		12 (27.9)	
Demyelination	1 (14.3)	4 (3.4)		2 (7.4)		2 (7.7)		0 (0.0)	
Hydrocephalus	1 (14.3)	1 (0.9)		0 (0.0)		1 (3.8)		0 (0.00	
Atrophy	1 (14.3)	8 (6.8)		3 (11.1)		0 (0.0)		3 (7.0)	
Cortical edema alone	0 (0.0)	1 (0.9)		0 (0.0)		1 (3.8)		0 (0)	
Incidental	1 (14.3)	30 (25.6)		11 (40.7)		3 (11.5)		12 (27.9)	
Brain MRI enhancement, No. (%)			1		1		1		1
None	2 (25.0)	29 (23.4)	1	8 (27.6)		8 (28.6)		10 (21.7)	
Parenchymal	0 (0.0)	4 (3.2)		1 (3.4)		0 (0.0)		3 (6.5)	
Leptomeningeal	0 (0.0)	12 (9.7)		2 (6.9)		3 (10.7)		3 (6.5)	
ND	6 (75.0)	78 (62.9)		18 (62.1)		17 (60.7)		29 (63.0)	

Abbreviations:
CSF = Cerebrospinal fluid
CXR = Chest x-ray
DWI = Diffusion-weighted imaging
F = Female
HIE = Hypoxic-ischemic encephalopathy
ICU = Intensive care unit
IQR = Interquartile range
LOS = Length of stay
M = Male
MRI = Magnetic resonance imaging
NA = Not applicable
ND = Not done
SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2
WBC = White blood cell
P values indicate comparison with SARS-CoV-2.
Bold values are for $P < 0.05$.

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.[3] *M. pneumoniae* was included in this study due to its association with encephalitis in children,[6] 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,

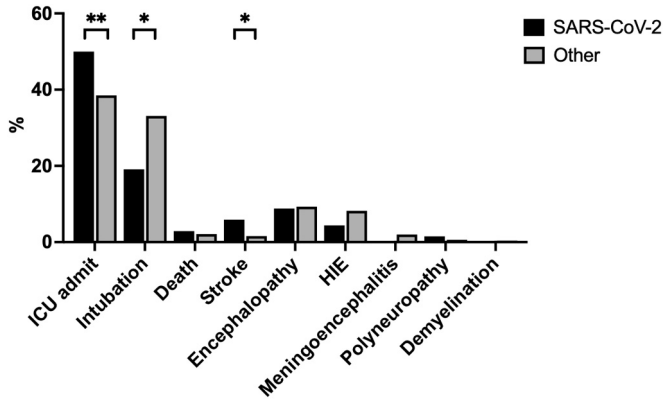

FIGURE. Proportions of neurological symptoms in hospitalized patients for seizures comparing SARS-CoV-2 versus other infections. HIE, hypoxic-ischemic encephalopathy; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. *$P < 0.05$, **$P < 0.01$.

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.

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