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COVID-19-Associated Croup in Children

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Dr. Brewster conceptualized and designed the study, collected the data, carried out initial analyses, and reviewed and revised the manuscript

Dr. Parsons collected the data, carried out initial analyses, and reviewed and revised the manuscript

Dr. Laird-Gion, Dr. Hilker, Dr. Irwin and Dr. Sommerschield drafted the initial manuscript, and reviewed and revised the manuscript

Dr. Michaelis, Dr. Lam, and Dr. Parsons contributed to study design and data analysis, and reviewed and revised the manuscript

Dr. Mansbach conceptualized and designed the study, coordinated and supervised data collection and analysis, and critically reviewed the manuscript for important intellectual content

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work

Introduction

As SARS-CoV-2 has evolved, so has its effects on the pediatric population.[1] While early variants typically resulted in lower respiratory infections, the recently identified Omicron variant may exhibit a predilection for the upper airways.[2] The relatively smaller upper respiratory tract in children compared to adults has been thought to predispose them to more severe clinical presentations resembling laryngotracheobronchitis, or croup. Caused by viral-induced subglottic airway inflammation, croup is classically characterized by sudden onset "barking cough", inspiratory stridor, and respiratory distress. Endemic coronaviruses have been linked to croup, however only sparse case reports have described croup specifically associated with SARS-CoV-2 and it remains unclear if croup cases constitute a causative relationship or result of co-infection with another virus. [3–6]. To address this knowledge gap, we performed a retrospective analysis of the incidence and clinical characteristics of croup associated with SARS-CoV-2 infection at a large freestanding children's hospital.

Methods

Clinical and demographic characteristics and viral testing data were obtained from medical record data from a freestanding children's hospital in Boston, Massachusetts between 3/1/2020-1/15/2022. Inclusion criteria were a diagnosis of COVID-19 by real-time polymerase chain reaction with a recorded ICD-10 code for laryngotracheitis (J05.0, RO5, RO5.8, J38.7) during the same hospital encounter. We limited our analysis to patients treated in the emergency department and discharged ("Emergency Department") and those requiring inpatient hospitalization ("Hospitalized"). Abstracted data was corroborated with manual chart review.

We used descriptive statistics to summarize patient characteristics and outcomes. We defined the Omicron period as starting on 12/4/2021, corresponding to the first documented case of the Omicron variant in Massachusetts. Median weekly cases during the Omicron and pre-Omicron periods were compared using the Wilcoxon rank test. This study received Institutional Review Board approval.

Results

Between 3/1/2020-1/15/2022, a total of 75 children were diagnosed with COVID-19-associated croup, 81% of whom presented during the Omicron period (**Figure 1**). There was a significant difference in median weekly cases between the pre-Omicron (0 [IQR 0-0]) and Omicron periods (11 [IQR 2-17]) ($p<0.001$). Most patients were male (72%) and discharged from the emergency department (88%) (**Table 1**). All children tested for other viral infections were negative except for one with rhinovirus. Dexamethasone was administered to 97% of patients. Whereas 100% of hospitalized patients received racemic epinephrine, it was given to only 25% of patients treated in the emergency department. Among hospitalized patients, the median length of stay was 1.7 days (IQR 1.3-2.3 days) and the median number of dexamethasone and racemic epinephrine doses was 6 (IQR 4-9) and 8 (IQR 2-10), respectively. Four patients required intensive care, with one escalating to heliox and continuous positive airway pressure. No patients required invasive ventilation or died.

Discussion

This retrospective analysis of a freestanding children's hospital found that the incidence of croup co-occurring with SARS-CoV-2 infection sharply increased in December 2021, strongly correlating with emergence of the Omicron variant. Other spikes in COVID-19 were not associated with increased diagnoses of croup. Interestingly, the observed rates of hospitalization and re-dosing of croup-directed therapies may indicate a more severe phenotype compared to other viral etiologies.[7] Taken together, our preliminary findings lend compelling evidence to the hypothesis that the Omicron variant causes laryngotracheobronchitis. This tropism shift may stem from differences in protein expression between cells of the lower respiratory versus upper respiratory tract, although variant-specific mechanistic studies remain an active research area. [8–10]

This study has potential limitations. We conducted our analysis at a single center with a small sample size, potentially restricting its generalizability. Nonetheless, to our knowledge, it remains among the first and largest investigations of COVID-19-associated croup to date. An additional limitation is the absence of viral genotyping. The rapidity with which Omicron became the most dominant SARS-CoV-2 variant, however, lowers concern that there was significant local circulation of other strains. Lastly, as comprehensive viral testing was not available, we cannot entirely exclude the possibility of viral co-infection.

Two years into the COVID-19 pandemic, the pathogenicity, infectivity, and manifestations of new variants of SARS-CoV-2 have been dynamic and unique. Croup may represent yet another such novel presentation. Further research is needed to characterize the underlying mechanisms of COVID-19-associated croup, differences in clinical features from other viral etiologies, and appropriate management strategies in the SARS-CoV-2 era.

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Table 1. Characteristics of children diagnosed with COVID-19-associated croup

	Pre-Omicron (Before 12/4/2021)		Omicron (After 12/4/2021)	
	ED	**Hospitalized**	**ED**	**Hospitalized**
	n=12	n=2	n=54	n=7
Median Age (IQR)	2.6 (1.6-3.4)	1.3 (1.1-1.5)	2.4 (0.8-2.6)	1.6 (0.7-1.1)
Female Sex (%)	4 (33.3)	1 (50)	10 (18.5)	6 (85.7)
Race/Ethnicity (%) [a]				
Black, Non-Hispanic	1 (8.3)	1 (50)	8 (14.8)	0 (0)
Hispanic	4 (33.3)	0 (0)	16 (29.6)	2 (28.6)
Other [b]	6 (50)	0 (0)	20 (37)	0 (0)
White, Non-Hispanic	1 (8.3)	1 (50)	10 (18.5)	5 (71.4)
Received Viral Testing (%) [c]				
Adenovirus	1 (8.3)	1 (50)	4 (7.4)	4 (57.1)
HMPV	1 (8.3)	1 (50	3 (5.6)	4 (57.1)
Influenza A/B	6 (50)	2 (100)	40 (74.1)	6 (85.7)
Parainfluenza 1/2/3/4	1 (8.3)	1 (50)	4 (7.4)	4 (57.1)
Rhinovirus	1 (8.3)	1 (50)	3 (5.6)	4 (57.1)
RSV	6 (50)	2 (100)	36 (66.7)	6 (85.7)
Dexamethasone (%)	12 (100)	2 (100)	52 (96.3)	7 (100)
Racemic Epinephrine (%)	4 (33.3)	2 (100)	15 (27.8)	7 (100)

a) Race and ethnicity information was obtained from patient / family reported data at the time of registration documented in the electronic medical record.
b) “Other" includes Asian, American Indian, and multiracial children as well as those whose racial or ethnic identity was not recorded
c) All children tested for other viral infections were negative, except for one with rhinovirus

Figure 1. Weekly emergency department and hospitalized cases of COVID-19-associated croup in children compared to overall burden of COVID-19 in Massachusetts (Massachusetts Department of Public Health) through 1/15/2022.