Virus-induced asthma exacerbations in Vietnamese preschoolers

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ABSTRACT

The health burden of asthma is mainly related to asthma exacerbation, whose most common trigger is viral infection. Additionally, preschool children experience the highest rate of morbidity from asthma. The objective of this cross-sectional study was to find out the prevalence of virus-induced asthma exacerbations among hospitalized preschoolers in the south of Vietnam with tropical weather. A total of 133 children aged 3-5 years admitted to the Children's Hospital 1 with asthma exacerbations were enrolled. Within 24 hours of admission, nasopharyngeal swabs were tested for popular respiratory viruses by multiplex real-time polymerase chain reaction, and the genotype of human rhinovirus (HRV) was subsequently determined by Sanger sequences. Virus infections accounted for 48.9% of hospitalized preschoolers with moderate or severe asthma exacerbations. HRV was the most common pathogen (55.4%), with more than half of the cases being HRV-C (58.3%). The group of HRV-induced asthma exacerbations was older than the other group (4.3±0.9 compared to 3.7±0.7 years old, p=0.01). Also, the length of stay (LOS) was shorter in the patients with HRV-induced asthma exacerbations compared to the patients with other virus-induced exacerbations (3.2±1.5 compared to 4.4±2.7 days, p=0.04). To conclude, HRV-C was the most popular agent among hospitalized virus-induced asthma exacerbations in Vietnamese preschoolers. Compared to hospitalized asthmatic patients infected by other viruses, patients with HRV infection were older and had shorter LOS.

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Introduction

Asthma is a chronic respiratory disease, affecting about 14% of children in the world with rising prevalence.[1] A birth cohort study, followed by a 6-year follow-up survey on 1202 children at a provincial hospital in Nha Trang, Vietnam, shows that the proportion of asthmatic children is 5.1%.[2] Preschool children experience the highest rate of morbidity of asthma.[3] Asthma might cause death, especially during severe asthma exacerbations.[4] Respiratory viral infection, especially human rhinovirus (HRV) infection, is the most common trigger of asthma exacerbations among both adults and children, accounting for 60 to 95% of asthma exacerbations in countries with temperate climates.[5,6] Due to the synergy of viral infection and allergic inflammation, allergic asthmatic patients are more likely to have severe virus-induced asthma exacerbations.[7,8] In Vietnam, a tropical country, about 60% of patients with acute respiratory infection are positive for viruses,[9] but research on virus-induced asthma exacerbations in preschool children has been lacking.

Materials and Methods

A cross-sectional study was approved by the Research Ethics Committee of the University of Medicine and Pharmacy at Ho Chi Minh City (HCMC), Vietnam (approval number: 218/IRB-VN01002 dated March 24, 2020).

The study recruited 133 preschool children who were admitted to Children's Hospital 1, HCMC, Vietnam, from July 2020 to April 2021 with asthma exacerbations. The children had a pediatrician's diagnosis of asthma based on the history of at least two episodes of wheezing related to airflow obstruction, which responded well to asthma medication without other causes of wheezing.[3] Asthma exacerbations were confirmed based on the need for systemic corticosteroids, urgent unscheduled care, and hospitalizations for asthma.[10] According to the Global Initiative for Asthma 2010, a severe asthma exacerbation was determined if a patient had at least two of the following signs, including breathless at rest, talking in words, severe retractions of accessory muscles and peripheral oxygen saturation (SpO_2) <92%; a moderate asthma exacerbation was determined if a patient had two of the following signs including breathless at talking, talking in phrases, moderate retractions of accessory muscles and SpO_2 92-95%.[11] All the participants had a current medical history of up to 5 days before admission and had never been diagnosed with heart diseases, neurologic disorders, immunodeficiency, or other chronic lung diseases. Parents of eligible children were explained the purpose of the study and asked to sign the consent forms before data were collected.

Within 24 hours of admission, a nasopharyngeal swab was standardly obtained with a sterile cotton tampon right after study inclusion, placed in a dedicated tube, and stored in the fridge not over 24 hours before being transferred to Nam Khoa Biotek Laboratory (HCMC, Vietnam) for detection of respiratory viruses. Nam Khoa Biotek Laboratory is a highly qualified microbiology lab getting certification of ISO 17025.[12] The adenovirus, respiratory syncytial virus, influenzavirus (A, B, C), parainfluenzavirus (1, 2, 3), human metapneumovirus (hMPV), enterovirus, human coronavirus (hCOV), bocavirus and HRV were investigated by using a validated multiplex real-time polymerase chain reaction (MPL-rPCR). To meet the correlation to clinical symptoms, we chose a cut-off of 10^4 copies/mL to get a positive result of viral infection.[13] The specimens that tested positive for any virus were coded as "pathogen positive". Coinfection was defined as the positive for ≥2 pathogens in one specimen. All HRV-positive samples were further subjected to Sanger sequencing with specific primers to determine the A, B, or C genotype of the HRV detected.

Additionally, a skin prick test (SPT) was performed to investigate the participant's sensitization to common indoor aeroallergen extracts (Lofarma Allergeni, Milan, Italy) such as *Dermatophagoides pteronyssinus* (Dp), *Dermatophagoides farina* (Df), cockroach, cat and dog dander.[14] The patient's asthma condition was assessed and should be stable before the procedure. Any allergen showing a wheal size of at least 3 mm larger than the negative control would be considered positive.[15] Participants with positive SPT results were identified as preschoolers with allergic asthma.[16]

Age, gender (male/female), residence (HCMC, others), passive smoking (yes/no), individual history of known asthma and atopic dermatitis (yes/no), as well as a history of parental asthma (yes/no) were collected from interviews and cross-checked with medical records. Passive smoking was yes if a child inhaled smoke from family members daily.[17] The individual history of known asthma or atopic dermatitis was yes if the child was diagnosed by a physician. The history of parental asthma was yes if the diagnosis was done by a physician. Length of present history refers to the days of acute illness prior to admission. Length of stay (LOS) was calculated by subtracting the day of admission from the day of discharge. Results of MPL-rPCR and SPT were reported by qualified microbiologists and allergists.

Data were entered using Microsoft Excel 2010 (Redmond, WA, USA) and analyzed using IBM SPSS Statistics 24.0 (Armonk, NY, USA). Age, length of present history, and LOS were described as mean and standard deviation. Gender, residence, passive smoking, individual history of known asthma and atopic dermatitis, history of parental asthma, viral infection, and allergic asthma were described as frequency and percentage. The chi-squared test was performed to compare the distribution of a categorical variable in one group with the distribution in another one. The student's *t*-test was done to compare the means between the two groups. A p-value <0.05 was considered statistically significant.

Results

Demographic characteristics of the study population

The study enrolled 133 participants aged 4.1±0.9 years with 20 severe and 113 moderate cases of asthma exacerbations. More than half of the study population were male (59.4%) and had been exposed to passive smoke (54.9%). Most of the participants (69.9%) have been living at HCMC. Out of 133 children, 70 (52.6%) had not been previously diagnosed with asthma. The percentage of atopic dermatitis was 17.3%, and history of parental asthma accounted for 10.5%. There were no significant differences in epidemiological characteristics between the two groups of severe and moderate asthma exacerbations (Table 1).

Characteristics of allergic asthmatic preschoolers

Only 68 patients got SPT and there was no significant difference in the percentages of taking SPT between the two groups of severe and moderate asthma exacerbations (50% *vs.* 51.3%; p=0.91). It was found that 49/68 (72.1%) children had allergic asthma, and house dust mite was the most common indoor aeroallergen (70.6%). The percentages of allergic asthma in the groups of severe and moderate cases were the same (70% *vs*. 72.4%, p=0.88). The percentages of aeroallergens to which allergic asthma patients were sensitized were dust mite Df (69.1%), dust mite Dp (66.2%), cockroach (22.1%), followed by dog (10.3%), and cat (7.4%).

Furthermore, the percentage of multiallergen sensitization was 67.6% (46/68 cases). Also, these percentages were not significantly different between the severe cases and the moderate ones (70% *vs.* 67.2%, p=0.86). There were no significant differences in the percentages of viral infection between the two groups of allergic and non-allergic asthma (42.9% *vs.*42.1%; p=0.96) as well as between the group of multial-

lergen sensitization and the other one (45.7% *vs*.36.4%; p=0.47).

Characteristics of virus-induced asthma exacerbations

The study found that 48.9% of the 224 nasopharyngeal swabs were positive for at least one respiratory virus. Among them, 57 cases were infected with one virus, and 8 were coinfected with two viruses. HRV type C was the most prevalent in causing HRV-induced asthma exacerbations (Table 2). No one was infected by hMPV, enterovirus, or hCOV.

Compared to non-passive smokers, passive smokers had no significant difference in the percentage of viral infection (50.7% *vs.* 46.7%; p=0.65). Also, there was no significant difference in the percentage of viral infection between the two groups of severe and moderate cases (55% *vs*.47.8%; p=0.55) in the study population.

Among the patients with virus-induced asthma exacerbations, the group of HRV-induced asthma exacerbations was older than the other one. Meanwhile, other demographic characteristics were not significantly different between these two groups (Table 3). In addition to that, the children with HRV-induced asthma exacerbations had shorter length of present history as well as LOS than the children with exacerbations related to other viruses (Table 4). Furthermore, the percentage of taking parenteral antibiotics was 40% and this figure in the group of HRV infection was significantly lower than that in

Table 1. Demographic characteristics of the study population (n=133).

Variables	Asthma exacerbations		p
	Moderate (n=113)	Severe (n=20)	
Age (mean±SD)	4.1±0.9	4.1±0.8	0.93*
Gender, n (%)			
Male	71 (62.8)	8 (40)	0.06**
Female	42 (37.2)	12 (60)	
Residence, n (%)			
Ho Chi Minh City	78 (69)	15 (75)	0.59**
Others	35 (31)	5 (25)	
Passive smoking, n (%)			
Yes	63 (55.8)	10 (50)	0.63**
No	50 (44.2)	10 (50)	
Atopic dermatitis, n (%)			
Yes	20 (17.7)	3 (15)	0.77**
No	93 (82.3)	17 (85)	
Known asthma, n (%)			
Yes	53 (46.9)	10 (50)	0.80**
No	60 (53.1)	10 (50)	
Parental history of asthma, n (%)			
Yes	11 (9.7)	3 (15)	0.48**
No	102 (90.3)	17 (85)	

Variables are expressed as frequencies (percentages), except age. **t*-test with equal variances; **Chi-square test; SD, standard deviation.

Table 2. Distribution of pathogens in virus-induced asthma exacerbations (n=65).

Pathogens	n (%)
Human rhinovirus	36 (55.4)
C	21 (58.3)
A	7 (19.4)
Unidentified	8 (22.2)
Respiratory syncytial virus	14 (21.5)
Adenovirus	10 (15.4)
Bocavirus	9 (13.9)
Influenza virus A	2 (3.1)
Parainfluenza virus 3	2 (3.1)
Coinfection	8 (12.3)
A denovirus and HRV	3 (37.5)
Adenovirus and Bocavirus	1 (12.5)
Adenovirus and RSV	1 (12.5)
HRV and RSV	1 (12.5)
HRV and Parainfluenzae 3	1 (12.5)
Influenzae A and RSV	1 (12.5)

RSV, respiratory syncytial virus; HRV, human rhinovirus.

the other group (27.8% *vs.* 55.2%; p=0.03). Also, the percentage of patients admitted to the hospital on weekends was 14/65 and there was no significant difference in this percentage between the group of HRV infection and the other one (27.8% *vs.*13.8%; p=0.17).

Discussion and Conclusions

In this study, approximately half of the hospitalized preschoolers with moderate or severe asthma exacerbations had positive nasopharyngeal swab results for one or more respiratory viruses. Vietnamese asthmatic preschoolers in this study showed a relatively high prevalence of virus-induced asthma exacerbations, although this figure was lower than the results of other previous studies conducted in countries with temperate climates.[5,6] Our study took place during the outbreak of the COVID-19 pandemic in Vietnam. Therefore, besides the difference in geographic distribution of infection, good habits, including washing one's hands frequently, wearing masks, and keeping social distance during the pandemic, probably contributed to reducing the prevalence of acute respiratory infection.

The association between allergic inflammation and the risk of viral infection varies from one study to another. In some research, it is affected by the type of virus, the host's immunogenetics, and environmental factors.[18] In our study, there was no difference between the percentages of viral infection between the two groups of allergic and non-allergic asthma. This finding was similar to the result of a study of Canadian children admitted to the emergency room with moderate or severe asthma exacerbations.[6]

Moreover, viral infection, especially rhinovirus infection plays an important role in young children with allergic asthma.[19] More than half of the study population was infected by HRV, with HRV-C as the most prevalent pathogen. The study found no correlation between allergic asthma and the prevalence of HRV-induced asthma exacerbations. Also, there was no difference in the prevalence of severe asthma exacerbations between the children with HRV infection and those without. The number of cases of HRV-C infection in our study was not enough for further analysis. A study carried out on 958 hospitalized asthmatic Canadian children reported a high prevalence of HRV-C infection but did not find its connection with the severity of asthma exacerbation.[6] Therefore, more clinical studies are needed to clarify the role of HRV infection in asthma exacerbations.

In addition, it was found that hospitalized preschoolers with HRV-induced asthma exacerbations were older than

Table 3. Demographic characteristics of children with virus-induced asthma exacerbations.

Outcome\Variables	Virus-induced asthma exacerbations		p
	HRV (n=36)	Another virus (n=29)	
Age, mean±SD (n=65)	4.3±0.9	3.7±0.7	0.01*
Gender, n (%)			
Male (n=41)	22 (53.7)	19 (46.3)	0.71**
Female (n=24)	14 (58.3)	10 (41.7)	
Residence, n (%)			
Ho Chi Minh City (n=45)	28 (62.2)	17 (37.8)	0.10**
Others (n=20)	8 (40)	12 (60)	
Passive smoking, n (%)			
Yes (n=37)	19 (51.4)	18 (48.6)	0.45**
No (n=28)	17 (60.7)	11 (39.3)	
Atopic dermatitis, n (%)			
Yes (n=12)	6 (50.0)	6 (50.0)	0.68**
No (n=53)	30 (56.6)	23 (43.4)	
Known asthma, n (%)			
Yes (n=33)	22 (66.7)	11 (33.3)	0.06**
No (n=32)	14 (43.8)	18 (56.3)	
Allergic asthma***, n (%)			
Yes (n=21)	15 (71.4)	6 (28.6)	0.09**
No (n=8)	3 (37.5)	5 (62.5)	

Variables are expressed as frequencies (percentages), except age.**t*-test with unequal variances; **Chi-square test; ***only 29 cases taking skin prick test; HRV, human rhinovirus; SD, standard deviation.

Table 4. Clinical features of virus-induced asthma exacerbations (n=65).

Clinical features of asthma exacerbations	Virus-induced asthma exacerbations		p
	HRV (n=36)	Another virus (n=29)	
Severe exacerbations; n (%)	7 (19.4)	4 (13.8)	0.55**
Length of present history; mean±SD	2.1±0.7	2.6±1.0	0.03*
Length of stay; mean±SD	3.2±1.5	4.4±2.7	0.04*

**t*-test with unequal variances; **Chi-square test. HRV, human rhinovirus; SD, standard deviation.

those with asthma exacerbations related to other viruses. A profile analysis of respiratory virus in children also reported a higher frequency of rhinovirus infection in children aged 4 years and older among preschoolers.[20] The patients with HRV-induced asthma exacerbations had a shorter length of present history compared to the others. This may be explained by prolonged chronic inflammation in older children, enhancing their inflammatory responses. As a result, they need earlier urgent healthcare due to their airway hyperresponsiveness happening more severely and rapidly. Besides, older age, female gender, and weekend admissions were associated with longer LOS for pediatric asthma hospitalizations.[21] However, our study found that the group of HRV-induced asthma exacerbations with shorter LOS was older and had no difference in gender or weekend admissions compared to the other one. Also, antibiotic treatment, especially intravenous antibiotic treatment, was associated with increased LOS.[22] In our study, the percentage of parenteral antibiotics was lower in the children with HRV infection compared to the children without.

Furthermore, it is presumed that small airways are the major sites of inflammation and airway remodeling in all severities of asthma patients.[23] Chronic allergic inflammation may worsen small airway dysfunction in preschool children with already smaller airways. In our study, it found that 72.1% of asthmatic preschoolers had allergic asthma, but no correlation was found between allergy and severe asthma exacerbations.

Nevertheless, there are some limitations in our study. Firstly, it is a cross-sectional study with a small sample size in one hospital and being conducted during a limited period. Secondly, a few patients had SPT due to social distancing and the parents' fear of going to the hospital during the COVID-19 pandemic. Finally, some HRV-positive pharyngeal specimens could not be genotype identified because the amount of the detected HRV was not enough for sequencing polymerase chain reaction, so we could not have the genotype result of these samples.

In conclusion, our data revealed that more than half of virus-induced asthma exacerbations in Vietnamese preschoolers are caused by HRV, with HRV-C being the majority. Additionally, children with HRV-induced asthma exacerbations were older and had shorter LOS than the other ones.

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