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Indoor Aeroallergen Sensitization and Associated Factors in Hospitalized Children with Asthma Exacerbations

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ABSTRACT

Background: Allergic asthma represents the most popular phenotype of childhood asthma and is characterized by eosinophilic airway inflammation associated with specific immunoglobulin E (IgE) antibodies sensitization to various allergens, as evidenced by serology or skin prick test.[2] Sensitization to indoor aeroallergens is associated with severe asthma and severe asthma exacerbations. **Objective**: This study aimed to identify the prevalence of aeroallergen sensitization and its associated factors in children with an asthma exacerbation in Vietnam. **Methods:** A cross-sectional study was conducted at Children's Hospital 1, Ho Chi Minh City (HCMC). Children who were aged 3 to 15 and admitted to the hospital with moderate or severe asthma exacerbation were recruited to the study. Data was collected from interviews and medical records. SPT was used to identify aeroallergen sensitization. The association between school-age, living area, and passive smoking with the odds of aeroallergen sensitization was assessed using a multivariable logistic regression. **Results**: The prevalence of aeroallergen sensitization was 82.6% and this figure in school-age children was higher than that in preschool-age ones (93.8% vs 72.1%, p=0.001). School-age, living in HCMC, and passive smoking significantly increased the odds of aeroallergen sensitization in asthmatic children with adjusted OR [95%CI] as 6.9 [2.1-23.3], 4.1 [1.5-11.5], and 2.9 [1.0-8.4], respectively. Asthmatic children with aeroallergen sensitization required more hours to resolve an asthma exacerbation than those without (22.4 vs 15.2, p=0.006). **Conclusion**: Aeroallergen sensitization was common in hospitalized children with moderate or severe asthma exacerbation. It is necessary to establish environmental policy and screening practices of aeroallergen sensitization to improve the quality of asthma management for Vietnamese children.

Keywords: aeroallergen sensitization, pediatric asthma exacerbation, skin prick test..

1. BACKGROUND

Asthma is a major noncommunicable disease, causing a global health burden, and is the most common chronic disease among children. Asthma causes 5.1 million disability-adjusted life years among children aged 1-19 globally (1). Allergic asthma represents the most popular phenotype of childhood asthma and is characterized by eosinophilic airway inflammation associated with specific immunoglobulin E (IgE) antibodies sensitization to various allergens, as evidenced by serology or skin prick test (2). Sensitization to indoor aeroallergens is associated with severe asthma and severe asthma exacerbations (3, 4). Although allergen avoidance is challenging in clinical practice but there is mounting evidence that, if achieved, reduced exposure to allergens in sensitized patients may have tangible clinical benefits. They include reduced number of days with asthmatic symptoms, number of hospitalizations and fewer unscheduled asthma-related visits to the emergency department or clinic (5). However, most asthmatic patients are not investigated for their underlying aeroallergen sensitizations (6).

A survey was conducted among 1176 patients with asthma aged 5 to 65 years in the US from March 16, 2009, to May 1, 2014 found that only 2% had documented allergy test results (7). Allergy testing also has not been given enough attention in management of Vietnamese asthmatic children.

2. OBJECTIVE

Therefore, the study was conducted to identify the prevalence of aeroallergen sensitization and its associated factors in hospitalized children with an asthma exacerbation in Vietnam.

3. MATERIALS AND METHODS

Study population

Our cross-sectional study was conducted from July 2020 to April 2021 at Children's Hospital 1, a tertiary pediatric hospital, located in Ho Chi Minh City (HCMC). HCMC is the biggest city in the south of Vietnam and is classified as a moderately polluted city in the South East Asia (8), The study was approved by the Ethics Committee of University of Medicine and Pharmacy at Ho Chi Minh City, Vietnam (Ref: 218/HĐĐĐ-ĐHYD, dated March 24, 2020). Medical records of children were screened for eligibility at the time of admission. Parents of eligible children were approached and explained the purpose of the study. Signed consent forms were collected from all parents who allowed their children to join the study before data was collected.

Children were included if they were between 3 and 15 years old, admitted to the hospital due to a moderate or severe asthma exacerbation, and their parents allowed them to join the study. They were scheduled for a skin prick test (SPT) after discharge. An asthma exacerbation was identified based on a history of significant acute wheezing (at least 2 episodes of wheezing within previous 12 months were applied to under-6-year-old children) related to airflow obstruction which responded well to rescue medication without other causes of wheezing (9, 10). According to the Global Initiative for Asthma 2010 guideline, 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% (11). 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). Children with neurologic, metabolic, or genetic diseases, chronic pulmonary diseases other than asthma, cardiopathy, or immuno-suppression were excluded from the study.

Data collection and tool

Data including age (in years), gender (boy, girl), passive smoking (yes, no), parental history of asthma (yes, no), individual history of eczema (yes, no) or confirmed asthma (yes, no), and recent using asthma controller (yes, no) was collected from interviews and cross-checked with medical records. For the sake of clarification, passive smoking was yes if a child inhaled smoke from family members daily (12). Personal eczema was yes if the parents confirmed that their child was diagnosed by a physician. Parental asthma was yes if the parents confirmed that they were diagnosed with asthma by a physician. The recent use of asthma controller was yes if the parents confirmed that the child was still taking the prescribed asthma controller prior to the exacerbation. SPT was performed by qualified nurses following the standard procedures (13). The duration required to relieve an exacerbation was recorded from the moment the patient was treated with the first dose of an inhaled short-acting beta-2 agonist (Salbutamol) until when the child stopped wheezing.

Detection of aeroallergen sensitization

SPT was employed to diagnose children's aeroallergen sensitization. SPT is a simple and cheap but safe, and valid and reliable test. Its specificity and sensitivity were 70%-95% and 80%-97%, respectively (14). The participant's history and physical examination were taken prior to the procedure. The children were eligible for SPT if they had stable asthma and stopped using antihistamines or systemic corticosteroids one week before performing SPT, but inhaled corticosteroids (ICSs) were continued. In the case of those who were using long-acting antihistamines, SPT was conducted after 4 weeks of discontinuation of the medication. The five common indoor allergen extracts of Lofarma Allergeni (Milan, Italy), which included *Dermatophagoides pteronyssinus* (Dp), *Dermatophagoides farinae* (Df), cockroach, cat, and dog dander, were used in the SPT. SPT was conducted by putting a drop of every tested allergen extract on the healthy skin over the anterior forearm with a gap of approximately 4cm between the drops. A shallow prick through the allergen drop to the skin was made by using a specially designed "lancet". Reading was interpreted after 15-20 minutes. Skin reactivity was assessed by calculating the mean diameter of a wheal with a ruler. To establish test validity, positive control needed to be at least 3mm more than the negative control. Any reaction with normal saline more than 3mm was considered invalid. An allergen was positive if its wheal diameter was larger than 3 mm compared to that of the negative control (13).

Statistical analysis

Data were entered using Microsoft Excel 2010 (Redmond, WA, USA) and analyzed using IBM SPSS Statistics 24.0 (Armonk, NY, USA). Age, interval between onset and admission, time required to resolve an exacerbation, and length of hospitalization were described as mean ± standard deviation (SD). Gender, personal eczema, parental asthma, passive smoking, known asthma, or aeroallergen sensitization were described as frequency and percentage.

T-tests with equal or unequal variance were used to compare the average days from onset to admission, hours to resolve an asthma exacerbation, and days of hospitalization between children with and without receiving SPT, and across aeroallergen sensitization (yes, no).

Chi-square tests were used to compare the age group, gender, individual history of eczema, parental history of asthma, living areas, passive smoking, known asthma, recent using asthma controller, severe asthma exacerbations between children with and without receiving SPT, and across aeroallergen sensitization (yes, no).

Model 1, a binary logistic regression, was used to measure the associations between variables including school-age, gender, personal eczema, personal histo-

ry of asthma, parental asthma, living in HCMC, passive smoking with the odds of positive SPT. Odds Ratio (OR) and its 95% confidence interval (CI) were calculated to measure the strength of associations. A p-value of 0.20 was used to select potential variables for a multivariable logistic regression in model 2 (15). A p-value of 0.05 was considered statistically significant.

4. RESULTS

There were 224 children who satisfied inclusion criteria, including 37 severe and 187 moderate asthma exacerbations. The mean age of these children was 5.9 years (SD 2.6), ranging from 3 to 13.6 years old. Boy represented 60.7% and school-age asthmatics represented 40.6% of the sample. Of these participants, 160 (71.4%) lived in HCMC and 120 (53.6%) were exposed to smoke daily.

It was remarkable that 53.1% of these patients had been diagnosed with asthma for several months before this admission. Among 24 asthmatic children prescribed with asthma controllers, only 10 children had been using their medications until admission. Also, 56/119 (47.1%) children with a history of asthma were 6 years or older but there were only three patients who have recently used daily asthma controller.

Only 132 participants had results of SPT. The patients who took the SPT were older than those who did not take it with mean age of 6.3 versus 5.5 (p=0.024, t-test). The percentage of school-age asthmatics who took the SPT was higher than that of children who did not take the SPT (48.5% vs 29.3%, chi-squared test, p=0.004). Additionally, there were significant differences in the interval between onset and admission as well as the length of hospitalization between these two groups. Meanwhile, there was no difference in the proportions of severe asthma exacerbations, gender, children living in HCMC and those with passive smoking between the group of children with SPT and the group of those without.

Characteristics	Total (N=224)	Receiving Skin Prick Test		p-value
		Yes (N=132)	No (N=92)	
Age, years (Mean ± SD)*	5.9 ± 2.6	6.3 ± 2.6	5.5 ± 2.5	0.024
Age group; n (%)				
Preschool (<6 years old)	133 (59.4)	68 (51.5)	65 (70.7)	0.004
School-age (≥6 years old)	91 (40.6)	64 (48.5)	27 (29.3)	
Gender; n (%)				
Girl	88 (39.3)	50 (37.9)	38 (41.3)	0.606
Boy	136 (60.7)	82 (62.1)	54 (58.7)	
Individual history of eczema; n (%)				
No	182 (81.2)	107 (81.1)	75 (81.5)	0.931
Yes	42 (18.8)	25 (18.9)	17 (18.5)	
Parental history of asthma; n (%)				
No	202 (90.2)	120 (90.9)	82 (89.1)	0.660
Yes	22 (9.8)	12 (9.1)	10 (10.9)	
Living in HCMC; n (%)				
No	64 (28.6)	37 (28.0)	27 (29.3)	0.830
Yes	160 (71.4)	95 (72.0)	65 (70.7)	
Passive smoking; n (%)				
No	104 (46.4)	67 (50.8)	37 (40.2)	0.120
Yes	120 (53.6)	65 (49.2)	55 (59.8)	
Known asthma; n (%)				
No	105 (46.9)	60 (45.5)	45 (48.9)	0.610
Yes	119 (53.1)	72 (54.5)	47 (51.1)	
Recent using asthma controller; n (%)				
No	214 (95.5)	126 (95.5)	88 (95.7)	0.944
Yes	10 (4.5)	6 (4.5)	4 (4.3)	
Severe asthma exacerbations; n (%)				
No	187 (83.4)	109 (82.6)	78 (84.8)	0.662
Yes	37 (16.5)	23 (17.4)	14 (15.2)	
The interval between onset and admission; days (Mean ± SD)*	2.3 ± 1.0	2.2 ± 1.0	2.4 ± 0.8	0.199
Time to resolve an asthma exacerbation; hours (Mean ± SD)*	22.5 ± 18.7	21.2 ± 16.0	24.5 ± 22.0	0.182

Table 1. Epidemiologic and clinical characteristics of the study population (N=224). SD: Standard deviation.All used Chi-squared test, except stated others.*T-test with equal variance was used; †T-test with unequal variance was used. *Chi-squared test was used to compare the percentages of aeroallergen sensitization between preschool age and school age children. A p-value of <0.05 is statistically significant.

Allergic sensitization to common indoor allergens

Of the patients who took the SPT, 109 (82.6%) showed sensitization to at least one of the 5 tested aeroallergens. House dust mites were the most frequent allergens (75.8% for *Dermatophagoides farinae* and 73.5% for *Dermatophagoides pteronyssinus*), followed by cockroach (24.2%), cat dander (9.8%) and dog dander (9.8%). Sensitization to at least two allergens occurred in 70.5% of those with SPT performing and in 85.3% of allergic asthmatics. There was no difference in the rate of severe asthma exacerbations between children with multiallergen sensitization and those with monoallergen sensitization (18.3% vs 18.8%; chi-squared test, p=0.964).

Older children were more likely to sensitize to indoor aeroallergens. The percentage of positive SPT in school-age asthmatic patients was significantly higher than that in pre-school children (93.8% vs 72.1%; chi-squared test, p=0.001). However, there was no difference in the rates of specific sensitizations between pre-school and school-age children.

Characteristics	Aeroallergen sensitization		Model 1			Model 2		
	Yes (n=109) N (%)	**No (n=23)** N (%)	OR	95%CI	p-value	aOR	95%CI	p-value
Age group								
< 6 years old	49 (45.0)	19 (82.6)						
≥ 6 years old	60 (55.0)	4 (17.4)	5.8	1.9 - 18.2	0.003	6.9	2.1 - 23.30	0.002
Gender								
Girl	39 (35.8)	11 (47.8)						
Boy	70 (64.2)	12 (52.2)	1.6	0.7 - 4.1	0.282			
Personal eczema								
No	89 (81.7)	18 (78.3)						
Yes	20 (18.3)	5 (21.7)	0.8	0.3 - 2.4	0.706			
Parental asthma								
No	100 (91.7)	20 (87.0)						
Yes	9 (8.3)	3 (13.0)	0.6	0.1 - 2.4	0.472			
Living area								
Other provinces	25 (22.9)	12 (52.2)						
Ho Chi Minh City	84 (77.1)	11 (47.8)	3.7	1.4 - 9.3	0.006	4.1	1.5 - 11.5	0.007
Passive smoking								
No	51 (46.8)	16 (69.6)						
Yes	58 (53.2)	7 (30.4)	2.6	1.0 - 6.8	0.052	2.9	1.0 - 8.4	0.047
Known asthma								
No	50 (45.9)	10 (43.5)						
Yes	59 (54.1)	13 (56.5)	0.9	0.4 - 2.2	0.834			

Table 2. Characteristics of children with allergic and non-allergic asthmatics (N=132). OR: Odds Ratio; aOR: adjusted Odds Ration; 95%CI: 95% Confidence Interval. Model 1: Binary logistic regression assessed the association between characteristics of children with the odds of aeroallergen sensitization. Model 2: Multiple logistic regression assessed the association of combination of school-age, living area, and passive smoking with the odds of aeroallergen sensitization.

Factors associated with aeroallergen sensitization

A binary logistic regression in Table 2 showed that a combination of school-age, living in HCMC and passive smoking significantly increased the risk of aeroallergen sensitization in asthmatic children with respective adjusted OR [95%CI] as 6.9 [2.1–23.3] for school-age, 4.1 [1.5–11.5] for living in HCMC, and 2.9 [1.0–8.4] for passive smoking.

Outcomes of asthma exacerbations	All sample (N=132) Mean ± SD	Aeroallergen sensitization		P-value
		Yes (n=109) Mean ± SD	No (n=23) Mean ± SD	
The interval between onset and admission (days)	2.2 ± 1.0	2.1 ± 0.9	2.7 ± 1.4	0.049*
Duration to resolve an asthma exacerbation (hours)	21.2 ± 16.0	22.4 ± 16.8	15.2 ± 9.2	0.006*
Length of hospitalization (days)	3.4 ± 1.8	3.2 ± 1.7	4.0 ± 2.0	0.052†

Table 3. Difference in average number of days between onset and admission, number of hours to resolve an asthma exacerbation, number of days in hospital between children with and without aeroallergen sensitization (N=132).

Additionally, asthmatic children who had aeroallergen sensitization required more time to resolve an asthma exacerbation than those without aeroallergen sensitization with mean duration of 22.4h versus 15.2h (t-test, p=0.006). Also, the allergic asthmatic children had shorter interval between onset and admission than the non-allergic ones with mean duration of 2.1 days versus 2.7 days (t-test, p=0.049).

5. DISCUSSION

This study found that the prevalence of aeroallergen sensitization determined by SPT among asthmatic children hospitalized with moderate or severe asthma exacerbation was 82.6%. House dust mites were the most popular allergens of allergic asthmatic children, which is compatible with the literature and other studies (4, 11, 16-19). Additionally, school-age asthma accounted for 40.6% of the sample and 48.5% of the children taking SPT. Although there was no difference in the percentages of sensitizations to specific aeroallergens, the percentage of overall aeroallergen sensitization was higher in school-age children than in younger ones (93.8% vs 72.1%, p=0.001), which is similar to previous studies (16, 18). It may be related to dynamic of IgE levels by age. It was observed that IgE antibody levels to aeroallergens in atopic children typically fluctuate over time ('cycling') during early childhood. However, from age two onwards, this cycling is replaced by a pattern of upwardly trending

IgE production, progressing to clinical sensitization by age five (20). So, a repeat SPT at school-age should be considered if SPT was negative in preschool-age.

Daily exposure to allergen for a long time causes persistent allergic inflammation, resulting in structural and functional changes that lead to chronic asthma symptoms later in sensitized individuals (21). Sensitization to multiple aeroallergens and sensitization combined with indoor perennial exposure in childhood predict asthma persistence, exacerbation, and lung dysfunction in adulthood (22). Aeroallergen sensitization testing increases the ability to predict asthma development, drug response, and risk for future asthma exacerbations (23). Therefore, allergen testing and avoidance in childhood may be considered fundamental to reducing the clinical symptoms of allergies or reducing the risk of developing persistent asthma in adulthood (5).

However, it is noted that only 2/119 (1.7%) patients, aged 8.9 and 11, who had been diagnosed with asthma prior to joining the study were investigated for aeroallergen sensitization, which is consistent to the previous study in the US (7). Among 224 participants, 131 (58.5%) children including the boy aged 8.9 came back to the hospital after discharge to receive SPT. His SPT result was unchanged the second time. The percentage of the participants taking SPT in the preschool-age group was lower than that in the school-age group (51.1% vs 70.3%, chi-squared test, p=0.004). It may be explained that their parents did not believe in the diagnosis of pre-school asthma as well as the relevance of evaluating aeroallergen sensitization in asthmatic patients. Therefore, it is necessary to promote patient/parent education in management of childhood asthma. Also, medical courses on testing underlying aeroallergen sensitization for asthmatic children should be organized to improve quality of pediatric asthma management. A tangible result of SPT may strengthen education for asthmatic children's families in lowering exposure to allergens by methods of environmental hygiene to get clinical benefits.

Futhermore, school-age, passive smoking and living in a polluted city such as HCMC increased the odds of aeroallergen sensitization in children. This was consistent with previous evidence (24, 25). Recent studies have suggested that pollutant air plays a crucial role in inception and exacerbation of allergy (26). An enhanced IgE-mediated response to aeroallergens and enhanced airway inflammation favoured by air pollution could account for the increasing prevalence of allergic respiratory diseases in urban areas (25). Air pollutants can facilitate sensitization to aeroallergens by a direct effect on airway epithelium. They increase airway epithelial barrier permeability, inhibit mucociliary clearance, and induce alveolar epithelial cells to secrete an array of inflammatory mediators such as chemokines, cytokines, eicosanoids, and adhesion molecules that recruit and activate dendritic cells (DCs), type 2 innate lymphoid cells (ILC2s), and basophils, thus contributing to Th2-type immunity. Moreover, diesel exhaust particles upregulate the messenger ribonucleic acid (mRNA) levels of thymic stromal lymphopoietin (TSLP), which can promote maturation of myeloid DCs that support Th2-type polarization. Another mechanism is that air pollutants such as particulate matter (PM) and diesel exhaust particles interact with allergens, thus acting as carriers and adjuvants that modify the features of allergens, which in turn enhance the immune response to them (26, 27). Additionally, studies have shown that tobacco smoke both increases the permeability of epithelium, which are susceptible to direct toxic activity of the chemicals in tobacco smoke, and weakens mucociliary clearance. This effect facilitates allergen penetration across the epithelium and augments release of histamine from subepithelial sensitized basophils. Furthermore, tobacco smoke exposure increases secretion of the proallergic cytokine, TSLP, a cytokine which influences development of Th2 cells, resulting in development of allergic asthma (28).

Sensitization to indoor aeroallergens is associated with severe asthma and severe asthma exacerbations (3, 4). However, there was no difference in the percentages of severe exacerbations between children with aeroallergen sensitization and those without aeroallergen sensitization in our study (18.3% vs 13%, chi-squared test, p=0.542). Among the allergic asthmatic patients who had aeroallergen sensitization, 93 (85.3%) were sensitized to at least two allergens but there was no difference in the percentage of severe asthma exacerbations between children with multiallergen sensitization and those sensitized to monoallergen (18.3% vs 18.8%; chi-squared test, p=0.964). Sensitization to many allergens is considered as a dependent risk of asthma exacerbations (29). However, this feature was not confirmed in this study. It is conceivable that our patient's asthma exacerbations were triggered by anything other than their sensitized allergens.

In addition, although the percentage of severe asthma exacerbations was not different between allergic and non-allergic asthmatic children, allergic asthmatic children had a shorter interval between onset and admission and needed more time to resolve their asthma exacerbation. It may be explained that pre-existing allergic inflammation induced airway hyper-responsiveness was worsened during asthma exacerbation in allergic asthmatics. It was documented that aeroallergen sensitization was associated with increased airway responsiveness in children (30).

Our study was conducted at one hospital with a small sample size. So, findings should be cautiously extrapolated to a more general population. However, the study found the important role of screening of aeroallergen sensitization in asthmatic children living in HCMC and reminds the Government to have better policies in environmental protection and healthcare.

6. CONCLUSION

In conclusion, a very high percentage of aeroallergen sensitization was found amongst asthmatic children, especially in school-age children, with a severe or moderate asthma exacerbation admitted to the Children's Hospital 1 in Ho Chi Minh City, Vietnam. House dust mites were the most popular airborne allergens of all ages. The

odds of aeroallergen sensitization was four times higher in children living in HCMC, a polluted city, compared to the others. Passive smoking also increased the odds of aeroallergen sensitization in school-age children living in HCMC. As a result, allergic asthmatic children were more likely to be admitted to the hospital due to moderate – severe asthma exacerbation and poorly respond to asthma rescue therapy. The policies of air environmental protection should be considered. Moreover, it is necessary to encourage the quality of education on asthma self-management by early screening for underlying aeroallergen sensitization among asthmatic children, especially school-age children.

- **Data Sharing Statement**: The datasets generated and/or analysed during the current study are not publicly available due to privacy concerns but are available from the corresponding author on reasonable request.
- **Ethical Approval**: The Ethics Committee of University of Medicine and Pharmacy at Ho Chi Minh City approved our study (Ref: Ref: 218/HĐĐĐ-ĐHYD, dated March 24, 2020).
- **Informed Consent**: Signed consent forms were collected from all parents who allowed their children to join the study before data was collected. In cases of children 12 years older, their signatures were also requested at the same time.
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