Effects of Aeroallergen Sensitization on Symptom Severity, Pulmonary Function, and Bronchodilator Response in Children With Bronchial Asthma

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ABSTRACT

Background: Allergen sensitization, symptom severity, pulmonary function test, and bronchodilator response are important in the diagnosis and treatment of asthma. However, the relationship between these factors remains unclear.

Objective: The objective of this study was to investigate the relationship between aeroallergen sensitization and asthma severity, pulmonary function, and bronchodilator response among pediatric patients with bronchial asthma.

Methods: This was a prospective study where 155 pediatric patients aged 7–18 years old with bronchial asthma were recruited from Outpatient Clinics. Patients who met the inclusion criteria proceeded with spirometry and aeroallergen skin prick test.

Results: There was a significant degree of sensitization, wherein 100% of the patients had sensitization to one or more aeroallergens. Among these children, 106 (68%) were polysensitized. The polysensitized group had more severe and persistent asthma severity profile ($p<0.001$) and worse pulmonary function ($p<0.001$). The frequency of abnormal pre-bronchodilator lung function of the polysensitized group was higher than the monosensitized group ($p<0.001$). A positive bronchodilator response was higher among polysensitized children as compared to monosensitized children ($p<0.001$). Sensitization to *Dermatophagoides farinae, Dermatophagoides pteronyssinus* and dog correlated with impairment of both the large airways and distal small airways while sensitization to cat, cockroach, and horse correlated only with impairment of the large airways ($p<0.05$). Patients sensitized to *D. farinae, D. pteronyssinus*, cat and dog had significant bronchodilator response ($p<0.05$).

Conclusion: Polysensitized asthmatic children had a more persistent and severe asthma profile, worse pulmonary function, and higher bronchodilator reversibility compared to the monosensitized group.

Key words: asthma, aeroallergen sensitization, polysensitization, pulmonary function, bronchodilator response

INTRODUCTION

Atopy refers to the genetic predisposition to develop allergic diseases. These diseases are characterized by an exaggerated immune response to environmental allergens and are eventually associated with the production of allergen-specific immunoglobulin E (IgE).[1] Allergic asthma, the most common asthma phenotype, is characterized by IgE

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sensitization to inhalant allergens or aeroallergens, followed by asthma symptoms after exposure.[2] Atopic sensitization or allergen sensitization can be measured either in vivo by the presence of IgE-mediated inflammation to allergen extracts (skin prick test) or in vitro by allergen-specific IgE levels (blood sample) to identify whether the patient is monosensitized (sensitized to one allergen) or polysensitized (sensitized to ≥2 allergens).[3] Among all the commonly used markers of sensitization, skin prick test (SPT) correlated best with the level of lung function among symptomatic subjects.[4]

The question on how allergic sensitization and its patterns influence the development and severity of asthma, as well as its effect in pulmonary function were subjects of interest in scientific studies. However, data concerning the association between sensitization, symptom severity, and pulmonary function were conflicting.

The degree of allergen sensitization was proportional to asthma severity. In a cross sectional study among children with asthma, sensitization to indoor aeroallergens especially house dust mite (HDM) and cockroach were associated with asthma severity.[5] A retrospective review among patients aged 5 to 18 years revealed a positive association between the number of positive SPT and asthma severity in children as evaluated by FEV_1 and medication usage.[6]

There were also reports of a quantitative inverse relationship between allergen sensitization and level of lung function. Among symptomatic asthmatic children aged 6 to 12 years, sensitization to indoor aeroallergens was associated with decrements in forced expiratory volume in 1 second (FEV_1) level.[4] Sensitization and exposure to high levels of HDM, cat, and dog hair allergens in the first three years of life was associated with loss of lung function at school age.[7] Furthermore, polysensitization was predictive of impaired pulmonary function.[8]

Conversely, other studies disagree about the association between allergen sensitization, asthma severity, and pulmonary function. In the Childhood Asthma Management Program study, there was no statistically significant difference in pre-bronchodilator FEV_1 percent predicted between subjects who tested positive and those tested negative to any of the allergens examined, although there was a trend toward lower FEV_1 for children with sensitization to dog and cat and the prebronchodilator FEV_1 was lower in the groups with a positive SPT to all allergens except tree pollen.[9] Lastly, there were no consistent correlations between aeroallergen sensitization and FEV_1, percent predicted FEV_1, and FEV_1/forced vital capacity (FVC) ratio in the Asthma Clinical Research Network aeroallergen study.[10]

Although atopic children with asthma easily developed symptoms in environments with high concentrations of aeroallergens, the effect of sensitization on pulmonary function, bronchodilator response (BDR), and symptom severity was not clear. This was the first study to investigate the relationship between aeroallergen sensitization and asthma severity, pulmonary function, and BDR among Filipino children with asthma. The specific objectives were to determine the prevalence and pattern of allergic sensitization to common aeroallergens, the association of aeroallergen sensitization and asthma severity, baseline pre-bronchodilator parameters (FEV_1, FEV_1/FVC ratio, FEF_{25-75}), and BDR (FEV_1 and FEF_{25-75}), as well as to identify which aeroallergens were associated with the greatest decrements in lung function.

METHODS

This was an analytical, observational, prospective study which recruited 155 patients aged 7–18 years with bronchial asthma from the University of Santo Tomas Hospital, Outpatient Clinics for six months. These patients were physician-diagnosed asthmatics who consulted for the first time and were controller-naïve, defined as not taking any long-term controller medications.

The following patients were excluded – oral and/or inhalational corticosteroids use in the past 30 days, short-acting bronchodilator use 8 hours prior to spirometry, anatomically relevant diseases, concurrent chemotherapy or immunosuppressive therapy, severe comorbidities, including chronic lung disease and congenital heart disease affecting lung function, patients who cannot follow instructions, and patients with relative contraindications to spirometry (respiratory tract infection for the previous 4 weeks, hemoptysis, pneumothorax, aneurysm, uncontrolled hypertension, recent thoracic, abdominal or eye surgery, nausea and vomiting).

Baseline clinical assessment and information on demographic variables were recorded. The diagnosis and severity of bronchial asthma was based on the

National Asthma Education and Prevention Program's Expert Panel 3 (NAEPP EPR-3). Asthma severity was classified as intermittent, mild persistent, moderate persistent or severe persistent asthma.

Patients who met the inclusion criteria proceeded with spirometry. Spirometric maneuvers in a standing position were performed using the Spiro Lab III™ spirometer according to the American Thoracic Society guidelines for the standardization of spirometry. The following parameters were measured pre- and post-bronchodilation: FVC, forced expiratory volume in one second (FEV_1), forced expiratory flow at 25% and 75% (FEF_{25-75}), the ratio of FEV_1 to FVC (FEV_1/FVC) and peak expiratory flow (PEF). The highest of the three measurements was recorded and results were expressed as a percentage of change from baseline. Abnormal lung function was defined as FEV_1 <80% predicted, FEV_1/FVC <80%, and FEF_{25-75} <65%. Post bronchodilator, the change of FEV_1 ≥12% and FEF_{25-75} ≥30%, was positive for reversibility.[11,12]

FEV_1 and FEV_1/FVC determined large airway function while FEF_{25-75} reflected small airway function. FEF_{25-75} indirectly measured the caliber of distal airways where airflow limitation was mainly dependent on the intensity of asthma inflammatory process and not due to bronchial muscle constriction.[13] Additionally, it was a more sensitive indicator of airway obstruction in children with asthma.[11] When asthma patients have BDR values of FEV_1 ≥12% and FEF_{25-75} ≥30%, they were categorized as BDR phenotypes.[14]

Allergen sensitization was assessed using aeroallergen SPT. Patients who were not stable enough (in acute asthma exacerbation) and with the intake of montelukast for the past 24 hours, sedating antihistamine for the past 3–4 days, and non-sedating antihistamine for the past 5–7 days underwent SPT during follow-up. Using standardized diagnostic extracts, common SPT aeroallergens included kapok, house dust, dust mites (*D. pteronyssinus* and *D. farinae*), cat pelt, dog epithelium, cattle hair, horse hair, cockroach, mosquito, mixed feathers, mixed molds, Bermuda grass, *Acacia* sp., and *Candida* sp. Histamine was used as positive control and saline as negative control. A wheal diameter ≥3 mm greater than negative control was interpreted as positive. Subjects sensitized to only one category of allergens were included in the "monosensitized" group, while those sensitized to ≥2 categories of allergens were included in the "polysensitized" group.

Descriptive statistics was used to summarize the general and clinical characteristics of the participants. Frequency and proportion were used for nominal variables, median and range for ordinal variables, and mean and standard deviation for interval/ratio variables. Independent T-test, Mann-Whitney U test, and Fisher's exact/Chi-square test were used to determine the difference of mean, median, and frequency between groups, respectively. One-way ANOVA, Kruskal-Wallis test, and Fisher's exact/Chi-square test were used to determine the difference of mean, median, and frequency, respectively. Spearman's rank correlation was used to determine the association between skin test reactivity per aeroallergen to symptom severity and pulmonary function. All valid data were included in the analysis. Missing variables were neither replaced nor estimated. Null hypothesis was rejected at 0.05α-level of significance. STATA 15.0 was used for data analysis.

The study protocol was approved by the Institutional Review Board and complied with the principles outlined in the Declaration of Helsinki.

RESULTS

Demographic characteristics

The study participants (n = 155) had a median age of 11 (range 6-18) years and a balanced proportion of genders. Majority had a concomitant 2 (47%) or 1 (36%) atopic comorbidity. Seven in ten lived in an urban area. The most common environmental exposures were tobacco smoke (62%) and industrial or vehicular sources (56%) (Table 1).

There was a significant degree of sensitization to aeroallergens, wherein 100% of the patients had sensitization to one or more allergens. Among these children, 106 (68%) were polysensitized and the remaining 49 (32%) were monosensitized. Comparing these two groups, polysensitized patients had a lower proportion of males (42% vs 69%) and higher exposure to animal fur/dander (56% vs 31%). The two groups were comparable in other described aspects (Table 1).

Table 1. Baseline characteristics of children with asthma (n = 155)

	All (n = 155)	Monosensitized (n = 49)	Polysensitized (n = 106)	P-value
	Frequency (%); Median (Range)			
Age (years)	11 (7–18)	11 (7–18)	11 (7–18)	.148*
Sex				**.001** †
Male	78 (50.32)	34 (69.39)	44 (41.51)	
Female	77 (49.68)	15 (30.61)	62 (59.49)	
Anthropometrics				
Weight (kg)	39 (17–85)	39 (17–80)	38.5 (18–85)	.940*
Height (cm)	145 (114–175)	144 (115–173)	146 (114–175)	.655*
BMI (kg/m ^{2})	18.8 (12.6–33.2)	18.5 (12.6–30.4)	18.8 (13.2–33.2)	.453*
Normal	91 (58.71)	33 (67.35)	58 (54.72)	.447 †
Overweight	28 (18.06)	8 (16.33)	20 (18.87)	
Obese	20 (12.90)	5 (10.20)	15 (14.15)	
Wasted	16 (10.32)	4 (6.12)	13 (12.26)	
Personal history of atopy				
Allergic rhinitis	149 (96.13)	47 (95.92)	102 (96.23)	1.000 ‡
Atopic dermatitis	83 (53.55)	23 (46.94)	60 (56.60)	.262 †
Allergic conjunctivitis	13 (8.39)	3 (6.12)	10 (9.43)	.756 ‡
Urticaria	24 (15.48)	5 (10.20)	19 (17.92)	.217 †
Food allergy	16 (10.32)	6 (12.24)	10 (9.43)	.593 †
Drug allergy	1 (0.65)	0	1 (0.94)	1.000 ‡
Number of atopic comorbidities				.636 ‡
1	56 (36.13)	21 (42.86)	35 (33.02)	
2	73 (47.10)	22 (44.90)	51 (48.11)	
3	25 (16.13)	6 (12.24)	19 (17.92)	
4	1 (0.65)	0	1 (0.94)	
Family history of atopy				
Parent	61 (39.35)	18 (36.73)	43 (40.57)	.650 †
Siblings	48 (30.97)	16 (32.65)	32 (30.19)	.758 †
Living conditions				.238 †
Urban	108 (69.68)	31 (63.27)	77 (72.64)	
Rural	47 (30.32)	18 (36.73)	29 (27.36)	
Home environment				
Tobacco or cigarette smoke	96 (61.94)	31 (63.27)	65 (61.32)	.817 †
Industrial or automotive smoke	87 (56.13)	24 (48.98)	63 (59.43)	.223 †
Animal fur, dander or feather	74 (47.74)	15 (30.61)	59 (55.66)	**.004** †
Water damage or flood	67 (43.23)	21 (42.86)	46 (43.40)	.950 †
Mold or mildew	38 (24.52)	15 (30.61)	23 (21.70)	.230 †
Cockroach	33 (21.29)	9 (18.37)	24 (22.64)	.546 †

Statistical Tests Used: * - Mann Whitney U Test; † - Chi Square Goodness of Fit Test; ‡ - Fisher's Exact Test

Table 2. Sensitization profile of children to individual common aeroallergens

	Frequency (%)
Dermatophagoides farinae	149 (96.13)
Dermatophagoides pteronyssinus	147 (94.84)
Mosquito	85 (54.84)
Cockroach	68 (43.87)
Cat pelt	54 (34.84)
Dog epithelium	21 (13.55)
Horse hair	19 (12.26)
House dust	12 (7.74)
Mixed feathers	11 (7.10)
Cattle hair	10 (6.45)
Bermuda grass	9 (5.81)
Acacia	8 (5.16)
Candida sp.	6 (3.87)
Mixed molds	5 (3.23)

Aeroallergen sensitization

Majority of the patients were sensitized to HDM (*D. farinae*, 96.1%; *D. pteronyssinus*, 94.8%), mosquito (54.8%), cockroach (43.9%), cat (34.8%), and dog (13.6%) (Table 2).

Aeroallergen sensitization and asthma severity

Overall, 20.65% had intermittent asthma, 16.77% had mild persistent asthma, 42.58% had moderate persistent asthma, and 20% had severe persistent asthma. An intergroup comparison was performed between the monosensitized group and the polysensitized group (Table 3).

A quantitative inverse relationship was found between sensitization pattern (monosensitized vs polysensitized) and asthma severity, pulmonary function, and bronchodilator reversibility. The polysensitized group had more severe and persistent asthma severity profile ($p<0.001$) and worse pulmonary function ($p<0.001$) as demonstrated by spirometry. Furthermore, there was a significant difference in the prevalence of abnormal lung function among the polysensitized and monosensitized group. Results had shown that 93.4% of polysensitized patients had persistent asthma (mild 21.7%, moderate 44.34%, and severe 27.36%), which was much higher than the 48.98% in the monosensitized group ($p<0.001$) (Table 3).

Aeroallergen sensitization and bronchodilator response

Poorer lung function results were documented among the polysensitized group ($p<0.001$). The frequency of abnormal pre-bronchodilator lung function of the polysensitized group was higher than the monosensitized group (FEV_1 70.75% vs 38.78%; FEV_1/FVC ratio 29.25% vs 10.20%; FEF_{25-75} 51.89% vs 30.61%) (Table 3).

A quantitative direct relationship was found between sensitization pattern and BDR. Bronchodilator reversibility was higher among polysensitized children as compared to monosensitized children – FEV_1 ≥12% (99% vs 59%) and FEF_{25-75} ≥30% (75% vs 43%) ($p<0.001$) (Table 3).

Aeroallergens and impairment of lung function

The analysis of individual aeroallergens as predictors of lung function impairment showed significant inverse correlations between sensitization to HDM, pets, and cockroach, and pulmonary function. Sensitization to *D. farinae*, *D. pteronyssinus* and dog correlated with impairment of both the large airways (low FEV_1 and FEV_1/FVC) and distal small airways (low $FEF_{25–75}$) while sensitization to cat, cockroach, and horse correlated only with impairment of large airways (low level of FEV_1 and FEV_1/FVC) ($p<0.05$) (Table 4).

Further analysis of individual allergens revealed that patients sensitized to *D. farinae*, *D. pteronyssinus*, cat, and dog had significant BDR ($p<0.05$) (Table 5).

DISCUSSION

Allergen sensitization plays a critical role in the development, persistence, and severity of pediatric asthma.[15,16] This study demonstrated that the polysensitized group had a more severe and persistent asthma severity profile, worse pulmonary function, and higher bronchodilator reversibility compared to the monosensitized group.

This study reported a significant degree of sensitization to aeroallergens, wherein all (100%) patients had sensitization to one or more aeroallergens and majority were polysensitized (68%). This was supported by previous findings, wherein as many as 90% to 95% of patients with

Table 3. Asthma severity and spirometry of children with asthma

	All (n = 155)	Monosensitized (n = 49)	Polysensitized (n = 106)	P-value
	Frequency (%); Mean ± SD			
Asthma severity				<.001 †
Intermittent	32 (20.65)	25 (51.02)	7 (6.60)	
Mild persistent	26 (16.77)	3 (6.12)	23 (21.70)	
Moderate persistent	66 (42.58)	19 (38.78)	47 (44.34)	
Severe persistent	31 (20)	2 (4.08)	29 (27.36)	
Spirometry				
FEV_1/FVC ratio	90.34 ± 14.08	95.90 ± 11.93	87.76 ± 14.30	.001 §
FVC (% predicted)	83.55 ± 12.63	87.02 ± 13.13	81.94 ± 12.11	.019 §
PEF (% predicted)	71.30 ± 22.77	82.90 ± 24.01	65.75 ± 20.58	<.001 §
FEV_1 (% predicted)				
Pre-BD	75.63 ± 16.55	85.10 ± 16.13	71.25 ± 14.88	<.001 §
Post-BD	94.63 ± 12.59	100.10 ± 12.00	92.10 ± 12.10	.001 §
Change pre- to post-BD	19.09 ± 9.20	15.22 ± 7.60	20.86 ± 9.36	.001 §
	21.3 (-2.9–158.1)	13.7 (2.9–125)	23.5 (11.9–158.1)	<.001*
FEF_{25-75} (% predicted)				
Pre-BD	67.52 ± 24.67	81.16 ± 24.43	61.22 ± 22.19	<.001 §
Post-BD	93.70 ± 18.47	100.31 ± 17.84	90.65 ± 18.03	.001 §
Change pre- to post-BD	26.18 ± 11.13	19.14 ± 11.10	29.43 ± 9.57	<.001 §
	42.9 (4.3–378.6)	18.3 (4.3–78.4)	47.9 (6.1–378.6)	<.001*
Abnormal lung function				
FEV_1	94 (60.65)	19 (38.78)	75 (70.75)	<.001 †
FEV_1/FVC ratio	36 (23.23)	5 (10.20)	31 (29.25)	.010 †
FEF_{25-75}	70 (45.16)	15 (30.61)	55 (51.89)	.013 †
Positive for reversibility				
FEV_1	134 (86.45)	29 (59.18)	105 (99.06)	<.001 †
FEF_{25-75}	101 (65.16)	21 (42.86)	80 (75.47)	<.001 †

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEV_{25-75}, forced expiratory volume at 25% and 75%; PEF, peak expiratory flow.
Statistical tests used: * - Mann-Whitney U test; † - Chi Square Goodness of Fit Test; § - Independent t-test.

asthma had aeroallergen sensitization.[17] Among Chinese children, the prevalence of multiple aeroallergen sensitizations were 45.7%, 61.2%, and 66.1% in the preschool age group, in 6–11 years, and in adolescents, respectively.[15] In a study among allergic Filipino children aged 6 to 12 years, 71.81% were polysensitized.[18]

In the present study, the most common allergen sensitizations were HDM (*D. farinae*, 96% and *D. pteronyssinus*, 95%), insects (mosquito, 55% and cockroach, 44%), and pets (cat, 35% and dog, 14%). These findings were similar to other published local and international literature. In a retrospective review of inner-city children with asthma, HDM, mouse, dog, and cockroach were the most prevalent allergies in New York.[19] In 1994, Cua-Lim reported the following as the most common aeroallergens among Filipinos – HDM (87%), cockroach (41%), mold spores (37%), cat dander (36%), kapok (35%), and dog dander (32%).[20,21] In a more recent study, 97.4% of adult Filipinos exhibited polysensitization and the most common indoor allergens were *D. pteronyssinus* (97.4%), *D. farinae*, (95.8%), cockroach (80.1%), and molds (72.8%).[21] The results were a reflection of the high concentration of these aeroallergens in Filipino homes. HDM was the most common

Table 4. Skin test reactivity and pre-bronchodilator pulmonary function

	Pre-bronchodilator		
	FEV_1	FEV_1/FVC	FEF_{25-75}
	Correlation Coefficient		
Dermatophagoides farinae	-0.697*	-0.466*	-0.598*
Dermatophagoides pteronyssinus	-0.685*	-0.463*	-0.612*
Mosquito	-0.152	-0.060	-0.114
Cockroach	-0.170*	-0.059	-0.108
Cat pelt	-0.354*	-0.192*	-0.323
Dog epithelium	-0.286*	-0.223*	-0.284*
Horse hair	-0.206*	-0.122	-0.107
House dust	-0.113	-0.044	-0.043
Mixed feathers	-0.114	-0.138	-0.157
Cattle hair	-0.098	-0.069	-0.066
Bermuda grass	-0.036	-0.036	-0.078
Acacia	-0.040	-0.029	-0.038
Candida sp.	-0.083	0.033	0.034
Mixed molds	0.014	0.035	-0.013

* - p value <0.05

Table 5. Skin test reactivity and post-bronchodilator pulmonary function

	Post-bronchodilator	
	FEV_1	FEF_{25-75}
	Correlation Coefficient	
Dermatophagoides farinae	-0.550*	-0.348*
Dermatophagoides pteronyssinus	-0.566*	-0.390*
Mosquito	-0.138	-0.014
Cockroach	-0.152	-0.054
Cat pelt	-0.293*	-0.213*
Dog epithelium	-0.164*	-0.189*
Horse hair	-0.101	-0.080
House dust	-0.100	-0.057
Mixed feathers	-0.071	-0.137
Cattle hair	-0.065	-0.094
Bermuda grass	-0.021	-0.087
Acacia	-0.035	-0.0002
Candida sp	-0.089	0.090
Mixed molds	0.074	-0.009

* - p value <0.05

aeroallergen implicated in allergic individuals in Asian countries, including the Philippines. Since children were continuously exposed to these indoor perennial aeroallergens in their early years, these allergens were closely linked to asthma.[15] Continuous exposure to allergens led to chronic airway inflammation, which could upregulate airway responsiveness, enhance asthma symptoms, and diminish lung function. Sensitization to HDM and animal dander, especially cat, were strongly associated with asthma morbidity and severity in atopic Asians, particularly children. [22] In African, European, and American populations, cockroach and animal dander were also strongly associated with asthma.[22] In homes and schools without pets, significant levels of allergens brought in from outside could induce and maintain bronchial hyperresponsiveness in sensitized individuals.[6] Accordingly, pediatricians should advise avoidance of identified allergens in children with a high risk of respiratory allergy.[15]

In this study, 93.4% of polysenzitized patients had persistent asthma (mild persistent 21.7%, moderate persistent 44.34%, severe persistent 27.36%) as compared to 48.8% in the monosensitized group.

These data were consistent with other investigations which demonstrated that polysensitization was strongly associated with persistent asthma. Among children with wheezing, allergen exposure and atopic sensitization were major risk factors for persistent asthma.[8,16] Furthermore, the degree of aeroallergen sensitization was proportional to asthma severity.[5] Polysensitization, as a distinct immunological event, was characterized by more severe clinical features than monosensitized subjects. This was clinically relevant since polysensitization was associated with prognostic worsening.[23] Also, among polysensitized patients, allergic inflammation tends to be chronic, which could be persistent and severe.[24] In a cross sectional observational study, 50% of children with atopic asthma with positive SPT had moderate persistent asthma.[5] In a prospective study, 86% of children with chronic, persistent asthma had polysensitization.[23] Aeroallergen sensitization was positively associated with an earlier onset of more severe allergic airway diseases in a multicenter study in China.[15] In a retrospective review, pediatric patients aged 5 to 18 years with combined sensitivity to cat, dog, HDM, and cockroach allergens were at increased risk of more severe asthma.[6] Moderate and severe asthma also showed a significantly higher polysensitization frequency compared to mild asthma ($p<0.0001$). [25] The number of positive skin tests correlated with asthma severity, wherein sensitization to >5 allergens was associated with an 11-fold increase in the odds of having more asthma symptoms.[26] The association between polysensitization and risk for severe asthma might be related to increased duration and frequency of exposure, the magnitude of inflammation, and bronchial impairment among polysensitized individuals.[27] The immunological basis of this phenomenon could be due to a functional defect of allergen-specific T-regulatory cells (Treg), such as defective production of IL-10 and IFN-γ, which exert an antiallergic role, preventing polysensitization and its detrimental effects.[24] These results supported the hypothesis that polysensitization is a distinct clinical entity and that the underlying immunological changes could be responsible for development of more severe allergic asthma.[27]

Variable airway obstruction was a defining characteristic of asthma and diverse patterns of obstruction could have different associations with asthma severity.[28] The present study revealed that when individual spirometric parameters (FVC, FEV_1, FEV_1/FVC ratio, FEF_{25-75}) were analyzed, the frequency of abnormal pre-bronchodilator lung function of the polysensitized group was consistently higher than the monosensitized group. These children had a greater prevalence rate of abnormal FEV_1 (99%) and FEF_{25-75} (75%) of predictive value than monosensitized children ($p<0.001$). A low FEF_{25-75} was associated with increased asthma severity and may represent a risk factor for the persistence of symptoms in children with asthma.[29]

The timing (preschool age) and pattern of allergic sensitization (polysensitization) appeared to be strongly predictive of lower lung function growth of large and small airways during early childhood compared with control populations.[30] At age 7, atopic wheeze was associated with lower lung function parameters of both large and small airways. [30] In two separate cohorts, allergic sensitization to HDM, pollens, cat, and dog at ages 10 to 11 years was associated with a lower FEV_1 and FEV_1/FVC. [30] Polysensitization was significantly associated with worsening obstruction on spirometry, as measured by FEV_1/FVC, in a retrospective review of asthmatic children.[19] Clinically, these findings are important because polysensitized children could develop lower levels of lung function in both large and small airways and more severe airway reactivity at an early age, which could lead to a rapid decline in lung function in later life.

One of the unique aspects of this present study was the exploration of relationship between sensitization and BDR. The NAEPP guidelines recommended bronchodilator reversibility in all asthmatic children to provide valuable information on airway lability and airway inflammation. Some studies also suggested that assessment of airway obstruction patterns through the determination of BDR phenotype had value as a prospective marker of asthma severity.[28,31] According to the present study, there was a higher frequency of BDR among polysensitized asthmatic children, as well as those with more severe and persistent asthma ($p<0.001$).

These results were consistent with other publications. In the Asthma Phenotypes in the Inner City study, which was a prospective longitudinal study of 6- to 17-year-old children with asthma living in urban areas, the level of airway obstruction, defined by using FEV_1 percent predicted values, and its reversal with bronchodilation, contributed significantly as a risk for severe and difficult-to-control asthma associated with sensitization status.[28] In another study by the Severe Asthma Research Program among children with severe asthma and high levels of sensitization, air-trapping was exhibited that was mostly reversed with bronchodilator, compared to the non-severe asthma group with normal lung residual volume. [31] This large bronchodilator reversal of FEV_1 was mostly due to reversal of the air-trapping component. [28,31] According to previous studies, atopy and sensitization were strong predictors of BDR ≥12% in the controller-naïve subset. This finding was important because the BDR phenotype had been shown to reflect asthma severity, eosinophilic inflammation, bronchial hyperreactivity, and airway remodeling. The BDR phenotype was also a good predictor of responsiveness to inhaled corticosteroids and long-term prognosis and had been significantly related to poor asthma control and increased healthcare utilization.[32]

The present study also evaluated the association between sensitization to specific aeroallergens and baseline pulmonary function. Sensitization to *D. farinae, D. pteronyssinus* and dog correlated with impaired lung function of both the large airways and distal small airways, while sensitization to cat, cockroach, and horse correlated only with impairment of large airways. Each allergen could cause different immunological, inflammatory, functional and clinical patterns, depending on its own biological property.[33] *D. pteronyssinus* and *D. farinae* play a considerable role in reduced pulmonary function among asthmatic children, with statistically significant correlations with FEV_1 and FEF_{25-75}.[34] HDM allergens contain proteolytic enzymes, such as proteases and trypsins that could damage the airway epithelium and mediate airway inflammation through IgE activation contributing to chronic airway inflammation.[35,36] In a population-based cohort study among children, sensitization to HDM was associated with a more insidious pulmonary involvement that presented spirometrically as large and small airways disease. [36] To explain these findings, HDM allergens could become airborne via fecal particles and fragmented mite bodies in household dust. The average diameter of mite fecal pellets was 20-30 mm and those with a size between 2-6 μm could be transported into small airways, inducing an IgE response and subsequent airway inflammation. Additionally, HDM particles were important sources of microbial compounds, such as lipopolysaccharide, β-glucans and chitin, capable of eliciting strong innate immune responses.[37] Furry animals, such as cats, dogs, horses, hamsters, rabbits, and mice were also important sources of indoor aeroallergens. Allergic sensitization to cat dander at 13 years of age was associated with a lower FEV_1 level between the ages of 9 and 15.[30] Dog allergens could be readily inhaled into the lower airways and could have an immediate impact on lung function.[38] Lipocalins constitute the most important allergen protein family in furry animals. Sensitization to lipocalins had been associated with asthma in children and polysensitization towards lipocalins, kallikrein, and secretoglobin components were linked to increased bronchial inflammation in severe asthmatics. In children with severe asthma, sensitization to Can f 2 from dogs and Equ c 1 from horses were more common compared to those with controlled asthma. Furthermore, sensitization to Fel d 1 from cats, Can f 1, Can f 2, and Can f 3 and polysensitization were associated with asthma and asthma severity in adults. [37] Cockroach allergens were strong inducers of sensitization and asthma.[39] The relationship between sensitization to German cockroach and decreased pulmonary function had been reported in a study of Taiwanese children with asthma.[40] Exposure to cockroach allergen levels at home is a risk factor for accelerated decline in FEV_1.[41] Cockroach-induced asthma was described as a more severe disease, associated with perennial symptoms and high levels of total IgE.[37,39] Potential sources of cockroach allergens in the environment include whole bodies, cast skins, secretions, egg casings, and fecal material. The level of exposure for increased risk of asthma symptoms is 8 U/g of dust. However, sensitization by chronic exposure to even very low levels (1–10 μg/g of dust) of Bla g 2 was a risk factor for wheezing and asthma in children. [37] Additionally, in a study performed in Taiwan, IgE binding to Per a 2 was more frequent in patients with persistent asthma than in patients with rhinitis

only, suggesting that this allergen could be a marker for more severe airway disease.[37]

Further analysis of individual allergens in the present study had shown that patients sensitized to *D. farinae*, *D. pteronyssinus*, cat, and dog have significant BDR. This relationship was remarkable because it suggested that sensitization is supportive in evaluating airway reversibility and may serve as a marker of worse lung function and asthma severity.[38] Asthmatic children with sensitization to *D. farinae* and *D. pteronyssinus* had significantly higher prevalence rates of BDR ≥12% than their non-sensitized patients. These findings indicated that asthmatic children with sensitization may need more aggressive anti-inflammatory therapy than asthmatic children without sensitization to these aeroallergens.[14]

It is important to highlight that asthma severity and low pulmonary function in children were not simply the result of sensitization to specific aeroallergens only. Its development could have been multifactorial, involving genetic, immunologic, and environmental factors. Results of this study added to the body of literature that substantiates the need for allergic sensitization testing in the management of childhood asthma because aside from supporting the diagnosis, it may serve as a marker of asthma severity, lung function, and bronchodilator phenotype. This study also reinforced the need for increased vigilance in the measurement of pulmonary function, particularly in polysensitized children.

CONCLUSION

As a conclusion, polysensitized children had severe and persistent asthma profile, lower pulmonary function at baseline and characterized by a BDR phenotype. Documentation of aeroallergen sensitization was important due to its role in asthma pathogenesis and effect on asthma severity and pulmonary function. This could also serve as an opportunity for clinicians to identify locally prevalent allergen sensitization and recognize at-risk patients, which would be helpful in creating individualized treatment plans, such as allergen-avoidance strategies and allergen immunotherapy.

Conflict of Interest

The authors declare no conflict of interest.

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Author's Contributions

Conceptualization, G.M.M and A.G.A.; Execution, G.M.M.; Supervision, A.G.A.; Validation, G.M.M; Manuscript preparation, G.M.M.; Review and critique, A.G.A.; Manuscript editing, G.M.M.

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