

Association of Aeroallergen Sensitization with Asthma Severity and Treatment

Jasmeet Kaur, DCH, DNB,¹ Sushil Kumar Kabra, MD,² Rakesh Lodha, MD,²
Mahendra Kumar Agarwal, PhD,³ and Mani Kalaivani, MSc⁴

Relationship between atopy and asthma is complex. Studies evaluating association between markers of atopy with asthma severity or lung function tests have failed to yield consistent results. A prospective cohort study was done at the Pediatric Chest Clinic at tertiary care university hospital, Delhi, India. Children with physician diagnosed, moderate to severe persistent asthma, between 5 and 15 years of age, were enrolled from May 2007 to June 2009. Sensitization to aeroallergens was assessed by the skin prick test using 12 common aeroallergens. Asthma was managed according to the National Asthma Education and Prevention Program–Expert Panel Report 3 guidelines and children were followed up as a cohort every 2 months for 6 months. Correlation between aeroallergen sensitization, atopic markers with asthma severity, and treatment outcome was studied. Seventy-eight (57 boys) patients with mean age of 109 ± 27 months were subjected to the skin prick test. Forty-nine (62.8%) children were sensitized to at least one aeroallergen. Common aeroallergens to which children were sensitized: cockroach (37%), rice dust (31%), mosquito (29%), housefly (29%). Sensitized patients had a higher rate of breathlessness, seasonal symptoms, and atopic dermatitis than those who were nonsensitized, ($P < 0.05$). Children with high absolute eosinophil count had decreased spirometry parameters after 6 month of follow up, ($P = 0.04$). Sensitization rates were independently associated with children having breathlessness ($P = 0.04$) and seasonal symptoms ($P = 0.01$). No significant association was found between sensitization, asthma severity, and treatment outcome. Aeroallergen sensitization was found in two-third patients. The most common aeroallergens were insects and rice dust. Sensitization was neither related to asthma severity nor to asthma control.

Introduction

ATOPY IS AN important risk factor for allergic diseases such as asthma, rhinitis, and eczema in children. The relationship between the intensity of allergic sensitization and asthma severity is not clear.^{1,2} Few studies showed a linear relationship between aeroallergen sensitization with asthma severity^{3–5} and few did not.^{2,6} There are studies that showed sensitization of indoor allergens such as house dust mite with increasing asthma severity and sensitization to outdoor allergens such as pollens with moderate to severe allergic rhinitis in children.^{7–9} There are few studies^{10,11} that demonstrated sensitization of children with aero or food allergens in India, but none has related it with asthma severity. We carried out this study with the primary aim to determine sensitization to common aeroallergens in children with

moderate to severe persistent asthma and a secondary aim to determine its association with asthma severity, pulmonary function test, and outcome of pharmacological treatment.

Materials and Methods

The prospective cohort study was carried out at the Pediatric chest clinic at tertiary care university hospital, All India Institute of Medical Sciences, New Delhi, and Vallabhbhai Patel Chest Institute, Delhi, India. Newly diagnosed, untreated children between ages 5 and 15 years presenting to the Pediatric Chest Clinic with asthma between May 2007 and June 2009 were screened for study inclusion. The inclusion criteria included newly diagnosed untreated children with asthma attending the clinic. The exclusion criteria included children having acute exacerbation of

¹Division of Pediatric Pulmonology, Asthma, Allergy, Department of Pediatrics, Dr. B.L. Kapur Super Speciality Hospital, New Delhi, India. Formerly as Senior Research Associate, Division of Pediatric Pulmonology, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India.

²Division of Pediatric Pulmonology and Intensive Care, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India.

³Department of Respiratory Allergy and Immunology, Metro Center for Respiratory Diseases, Metro Group of Hospitals, Noida, India. Formerly Professor and Head, Department of Respiratory Allergy and Applied Immunology, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, India.

⁴Department of Biostatistics, All India Institute of Medical Sciences, New Delhi, India.

asthma, history of anaphylaxis to aeroallergens, and those who were not willing to come for follow-up due to distant places. Seventy-eight patients fulfilling the inclusion criteria were enrolled in the study. The diagnosis of asthma was clinical, based on the National Asthma Education and Prevention Program–Expert Panel Report 3 (NAEPP-EPR3) guidelines.¹² Standardized forms were used throughout the study for recording detailed history regarding asthma symptoms, risk factors, associated illness, parasitic infestation, control of symptoms, episodes of acute exacerbation, compliance and technique of taking inhalation medicines, treatment details, physical examination, and results of spirometry tests at enrollment and at each visit. Spirometry was performed in accordance with the American Thoracic Society/ERS guidelines¹³ using Ponygraphic spirometer, Vitalograph 2012, at enrollment and at every visit. Appropriate flow volume loops (graphs) were obtained in a standing position. The peak expiratory flow rates (PEFR), forced expiratory volume in one second (FEV1), forced vital capacity, forced expiratory ratio (FEV1/FVC – FEV1 × 100/FVC), and forced midexpiratory flow (FEF 25%–75%) were obtained and best of the three maneuvers recorded. Children were categorized into groups based on normal percentage predicted values of FEV1 according to age, sex, and ethnicity.¹² Skin prick tests were performed with the 12 most common aeroallergens selected according to the geographical areas of the study subjects.¹⁴ Allergen extracts were obtained from a licensed commercial vendor. Twelve common aeroallergens used for assessing sensitization were rice dust, *Dermatophagoides farinae* (house dust mite), pollens—*Cynodon dactylon* (doob grass), *Prosopis juliflora* (vilayti keekar), fungi—*Holoptelea* sp, *Aspergillus tamarii*, *Alternaria* sp, *Curvularia* sp, Insects—*Periplaneta americana* mixed (cockroach), *Musca domestica* (housefly), *Culex* sp (mosquito), and dog dander. Approximately 2–3 mL of blood sample was collected from each subject at enrollment for estimating the absolute eosinophil count (AEC) and total immunoglobulin E (IgE) level. The study was approved by the Human Ethics Committees of the two Institutions. Written informed consent was obtained from parents.

Antihistamines were discontinued for 72 h before skin testing. The procedure involved cleaning of the child's forearm with an alcohol swab. A small drop of allergen extract (1:20 w/v in 50% glycerinated buffer saline) was applied by a sterile applicator at an appropriate distance on the forearm. The wheal size (mean of maximum dimensions in two axis) was measured and recorded with a measuring scale in millimeter after 15 min. Fifty percentage glycerinated buffer saline and histamine solution (10 mg/mL) were used as negative and positive controls, respectively. The reactions were graded by comparing the average wheal diameter of allergen extract to that of the positive control, that is, histamine as 2+, if more than that as 3+, 4+ using the standard criteria.¹⁵ Total IgE estimation was done by standardized ELISA reader Carbotech, Inc. The values were measured in IU/mL, according to the age group (60–108 months – ≥ 60 IU/mL, 109–180 months – ≥ 120 IU/mL) using standard criteria¹⁶ and calculated as mean $\pm$ SD for the analysis. Asthma treatment was in accordance with evidence-based guidelines provided in EPR-3.¹² Children were followed every 2 months for a total of 6 months.

Those who were skin prick test positive ($\geq 2+$ grade) to any of the aeroallergens were grouped as sensitized children

and others who had ($<2+$ grade) were labeled as non-sensitized children. On the basis of control of asthma symptoms,¹² children were assessed as controlled, partly controlled, and uncontrolled patients. Treatment plans were reevaluated at each visit.¹² The demographics, medical profile, associated allergic diseases, precipitating risk factors, family history of asthma, past history of acute exacerbation, details of treatment were studied between the sensitized and nonsensitized group. The association between aeroallergen sensitization, marker of atopy (AEC ≥ 500 mm³ and mean total serum IgE levels) with asthma severity, and outcome of treatment was assessed. Asthma severity was determined based on the impairment and future risk of asthma symptoms, that is, symptoms (moderate/severe), episodes of acute exacerbations, decline in lung function test and treatment response according to the NAEPP-EPR3 guidelines.¹²

Statistics

To detect the sensitization rate of 60% with 12% precision and 95% confidence, a sample size of 67 children was required. Data were analyzed using Stata software (Stata Corp.). Demographic and medical characteristics were tabulated between sensitized and nonsensitized patients. Correlation was studied between younger (60–108 months) and older age children (109–180 months) with aeroallergen sensitization and atopic markers. The chi-squared test/Fisher's exact test was applied to assess the statistical significance for categorical variables. The Student's *t*-test and one-way ANOVA were used for continuous variables. The Pearson's correlation coefficient (*r*) was calculated to assess the correlation between the age and AEC/IgE level. Logistic regression analysis was carried out to find the significant factors associated with sensitization. Results were assessed at 5% level of significance ($P < 0.05$).

Results

Among the 700 screened patients attending the clinic during the study period, there were 350 eligible children. None had a history of anaphylaxis, 10 had a history of acute exacerbation at enrollment, and 262 declined to participate. Seventy-eight patients were enrolled in the study. The mean age of study subjects was 109 ± 27 (range: 60–180 months) with 57 (73%) boys. There were 40 (51%) children in the younger age group (60–108 months) and 38 (49%) in the older age group (109–180 months). The main clinical characteristics of enrolled subjects were cough 78 (100%), wheezing 71 (90%), and breathlessness 72 (92%). Atopic dermatitis was found in 21 (27%) children, allergic rhinitis in 38 (48%), and vernal conjunctivitis in 29 (37%) patients. Sensitization to at least one aeroallergen was documented in 49 (62.8%) children. Monosensitization was found in 17 children (21.8%) and polysensitization in 32 children (41%). The most common aeroallergens to which patients were sensitized, cockroach (37%), rice dust (31%), mosquito (29%), and housefly (29%), as shown in Table 1. Demographic, medical details, precipitating factors, and associated illness among sensitized and nonsensitized patients are highlighted in Table 2. The sensitization rates in both age groups were similar (51% vs. 49%). We found that sensitized children had higher rates of breathlessness, seasonal symptoms, and atopic dermatitis than those who were nonsensitized ($P < 0.05$).

TABLE 1. SENSITIZATION RATES OF PATIENTS TO VARIOUS AEROALLERGENS

S. no.	Aeroallergens	Sensitized asthmatics n (%)
1	Cockroach (<i>Periplaneta americana</i>)	29 (37)
2	Rice dust	24 (31)
3	Mosquito (<i>Culex</i> sp)	23 (29)
4	Housefly (<i>Musca domestica</i>)	23 (29)
5	House dust mite (<i>Dermatophagoides farinae</i>)	17 (22)
6	Vilayati keekar (<i>Prosopis juliflora</i>)	15 (19)
7	Doob grass (<i>Cynodon dactylon</i>)	14 (18)
8	<i>Holoptelea</i> sp	14 (18)
9	<i>Alternaria</i> sp	11 (14)
10	<i>Curvularia</i> sp	9 (11.5)
11	<i>Aspergillus tamarii</i>	8 (10)
12	Dog dander	7 (9)

On multivariate analysis, breathlessness ($P=0.04$) and seasonal symptoms ($P=0.01$) were independently associated with sensitization (Table 2). Among 78 enrolled subjects, 75 completed the study: one was lost to follow up and two withdrew from the study.

Among 75 patients, there were 32 (42.6%) children with high AEC and 47 (60.2%) with high total IgE level. We did not find significant correlation among children with high AEC and IgE levels between the sensitized and non-sensitized group with age (Table 3). Out of 32 (42.6%) children with high AEC, 8 (25%) showed decline in spirometry parameters as compared to 3 (9.4%) children having low AEC ($P=0.04$), (Table 4). There was a trend toward a higher rate of acute exacerbations, poor control, and increased frequency of step-up therapy in the sensitized group, but none reached statistical significance (Table 4). The use of oral antihistamines [15 (30.6), 5 (17.2); $P=0.28$], nasal spray [13 (26.5), 7 (24.1); $P=1.0$], and oral corticosteroids [6 (12.3), 3 (10.3); $P=1.0$] was higher in the sensitized group as compared to nonsensitized children. The use of oral

TABLE 2. DEMOGRAPHIC, MEDICAL CHARACTERISTICS, PRECIPITATING FACTORS AMONG SENSITIZED AND NONSENSITIZED PATIENTS

Variable	Sensitized 49 (%)	Nonsensitized 29 (%)	Unadjusted OR (CI)	P-value	Adjusted OR (CI)	P-value
Age (mean $\pm$ SD)	110 $\pm$ 27	108 $\pm$ 26	0.48 (0.41–2.5)	0.72	–	–
Sex (M:F)	2.9:1	2.6:1	1.05 (0.37, 2.9)	0.91	–	–
Moderate persistent	35 (71)	20 (69)	1.10 (0.45, 2.8)	0.81	–	–
Severe persistent	14 (28)	9 (31)				
Duration of illness (m) median (range)	72 (6–154)	72 (18–144)	0.86 (0.95–1.0)	0.88	–	–
Age at onset of illness (m) median (range)	12 (1–120)	24 (1–108)	0.99 (0.98–1.01)	0.82	–	–
Duration of episode of each illness (days) median (range)	7 (2–15)	7 (2–15)	0.98 (0.86–1.1)	0.75	–	–
Clinical Symptoms						
Cough	49 (100)	29 (100)	–	–	–	–
Wheezing	45 (92)	26 (89.6)	1.3 (0.26, 6.2)	0.74	–	–
Breathlessness	48 (97.9)	24 (82.7)	9.9 (1.10, 90)	0.04	10.9 (1.0, 114.3)	0.04
Sneezing	39 (79.5)	21 (72)	1.5 (0.41, 4.3)	0.46	–	–
Rhinorrhea	43 (88)	24 (82.7)	1.5 (0.40, 5.4)	0.54	–	–
Skin rash	13 (26.5)	6 (20.6)	1.3 (0.46, 4.1)	0.56	–	–
Allergic rhinitis	26 (53)	12 (41.3)	1.1 (0.40, 3)	0.80	–	–
Vernal conjunctivitis	20 (40.8)	9 (31)	1.5 (0.6, 0.04)	0.38	–	–
Atopic dermatitis	18 (36.7)	3 (10)	5 (1.3, 19)	0.017	3.5 (0.8, 14.3)	0.07
Gastroesophageal reflux	1 (2)	1 (3.4)	0.6 (0.03, 9.6)	0.77	–	–
Precipitating factors						
Upper respiratory tract infection	44 (89.8)	26 (89.8)	1 (0.2, 4.6)	0.98	–	–
Exercise	45 (91.8)	24 (82.7)	2.3 (0.6, 9.5)	0.23	–	–
Smoke	39 (79.5)	21 (72.4)	1.5 (0.5, 4.3)	0.47	–	–
Dust	40 (81.6)	20 (68.9)	2 (0.7, 5.8)	0.2	–	–
Cold air	42 (85.7)	23 (79.3)	1.5 (0.5, 5.2)	0.46	–	–
Exposure to pets	7 (14.2)	5 (17.2)	3.9 (0.8, 19)	0.09	–	–
Emotional stress	20 (40.8)	15 (51.7)	0.64 (0.25, 1.6)	0.35	–	–
Cold food	43 (87.7)	24 (82.7)	1.5 (0.4, 5.4)	0.54	–	–
Head bath	28 (57.1)	18 (62)	0.8 (0.3, 2.08)	0.66	–	–
Change place of living	21 (42.8)	15 (51.7)	0.7 (0.2, 1.7)	0.44	–	–
Past h/o hospitalization (last 1 year)	12 (49)	17 (65)	1.2 (0.1, 14)	0.41	–	–
Perennial and seasonal symptoms	22 (45) 22 (45)	22 (76) 7 (24)	0.25 (0.09, 0.7)	0.009	0.2 (0.07, 0.72)	0.01
Urban:rural living	30:19	19:10	0.8 (0.3, 2.1)	0.7	–	–
Industrial:residential	13 (26)	8 (27)	0.9 (0.33, 2.6)	0.9	–	–
Family h/o smoking	22 (45)	11 (38)	1.3 (0.52, 3.4)	0.91	–	–
Family h/o asthma	40 (81)	23 (79)	1.1 (0.36, 3.6)	0.8	–	–

OR, odds ratio; CI, confidence interval; SD, standard deviation; M:F, male:female; m, months; h/o, history of.

TABLE 3. CORRELATION BETWEEN TOTAL IgE LEVELS, AEC AMONG SENSITIZED AND NONSENSITIZED CHILDREN WITH AGE

Variable	Sensitized (49)	Nonsensitized (29)
IgE (IU/mL)	$r=0.03, P=0.83$	$r=-0.02, P=0.93$
AEC (mm ³)	$r=-0.17, P=0.24$	$r=0.20, P=0.29$

r , Pearson's correlation coefficient; IgE, immunoglobulin E; AEC, absolute eosinophil count.

corticosteroids was higher in children with severe persistent asthma 4 (17.4%) when compared to those with moderate persistent asthma 6 (11%), ($P=0.04$). None of the children had parasitic infections.

We did not find any significant relation in aeroallergen sensitization or those with high IgE levels with decline in spirometry values, control of asthma (clinical parameters), or need for stepping up of treatment ($P>0.05$), (Tables 4 and 5).

Discussion

Aeroallergen sensitization depends on the age, geographical area, and allergen exposure. There is scarcity of data from the northern part of India; therefore, we performed this study to identify the rate of aeroallergen sensitization, its association with asthma severity, and outcome of pharmacological treatment.

We observed the prevalence of aeroallergen sensitization in 5–15-year-old asthma patients as 62.8%. Similar results

have been reported^{4,5} from industrialized countries with a sensitization rate of 45%–90%. Our results were concordant with the Indian study by Roy et al.,¹⁷ who studied 90 children between 5 and 10 years of age and found a sensitization rate of 58.9% using various allergens tested by the skin prick test. Another study by Prasad et al.¹⁸ found higher sensitization rates (89.2%) on performing 2,800 skin prick tests with 60 aeroallergens in 12–45-year-old patients with nasobronchial allergy.

We found higher rates of aeroallergen sensitization with insects [cockroach (37%), mosquito (29%), housefly (29%)], rice dust (31%), house dust mite (22%), and lowest with dog dander (9%). The study by Prasad et al.¹⁸ from the same geographical region recorded higher sensitization to insects (21.2%) followed by dust (11.9%) and pollens (7.8%). Another Indian study by Lal et al.¹⁹ found a high sensitization rate with house dust (75.2%), cotton dust (67.9%), and insects (18.4%). Mahesh et al.²⁰ found high sensitization to cockroach extract (53%) among young patients (<21 year) with asthma and allergic rhinitis in different geographical areas. In contrast, studies^{21–23} done in western and south Asian countries reported an increased sensitization rate of children with house dust mite—*D. farinae* (80%–82%), animal dander (17%–38%), and *Aspergillus* sp. (17%). This suggests that aeroallergen sensitization to insects and dust are more common in developing countries as compared to sensitization to house dust mite, fungus, and animal dander in western or developed countries. This variation may be because of differences in the environment and ethnicity.

TABLE 4. ASSOCIATION OF SENSITIZATION, AEC, TOTAL IgE LEVELS WITH SPIROMETRY VALUES AT SIXTH MONTH OF FOLLOW UP

Variable	Sensitized 46 (%)	Non sensitized 29 (%)	P- value	AEC (≥500) 32 (%)	AEC (<500) 43 (%)	P- value	IgE 75 (mean ± SD)	P- value
PEFR								
≥80% predicted	3 (6.6)	4 (13.8)	0.53	5 (15.6)	2 (4.7)	0.57	7 (67 ± 28)	0.85
60%–79% predicted	8 (17.4)	4 (13.8)		4 (12.5)	8 (18.6)		12 (82 ± 26)	
40%–59% predicted	6 (13)	4 (13.8)		3 (9.4)	7 (16.3)		10 (95 ± 18)	
<40% predicted	29 (63)	17 (58.6)		20 (62.5)	26 (60.4)		46 (77 ± 26)	
FEV1								
≥80% predicted	19 (41.3)	15 (51.8)	0.15	12 (37.5)	22 (51.2)	0.10	34 (80 ± 25)	0.85
60%–79% predicted	6 (13)	5 (17.2)		3 (9.4)	8 (18.6)		12 (77 ± 24)	
40%–59% predicted	6 (13)	4 (13.8)		5 (15.6)	4 (9.3)		9 (78 ± 33)	
<40% predicted	15 (32.7)	5 (17.2)		12 (37.5)	9 (20.9)		20 (83 ± 26)	
FVC								
≥80% predicted	22 (44.8)	13 (44.8)	0.89	11 (34.3)	24 (53.4)	0.04	35 (80 ± 25)	0.25
60%–79% predicted	9 (27.8)	8 (27.6)		9 (28.1)	8 (18.6)		17 (79 ± 27)	
40%–59% predicted	8 (13.8)	4 (13.8)		4 (12.5)	8 (18.6)		12 (71 ± 25)	
<40% predicted	7 (13.6)	4 (13.8)		8 (25.1)	3 (9.4)		11 (87 ± 22)	
FEV1/FVC								
≥80% predicted	42 (91.3)	26 (92.8)	0.94	27 (84.4)	41 (95)	0.05	68 (78 ± 26)	0.25
60%–79% predicted	1 (2.2)	1 (3.6)		1 (3.2)	2 (5)		3 (84 ± 10)	
40%–59% predicted	3 (6.5)	0 (0)		3 (9.2)	0		3 (94 ± 7)	
<40% predicted	0 (0)	1 (3.6)		1 (3.2)	0		1 (105 ± 0)	
FEF25–75								
≥80% predicted	6 (13.1)	3 (10.3)	0.96	4 (12.5)	5 (11.6)	0.35	9 (69 ± 28)	0.42
60%–79% predicted	4 (8.7)	4 (13.8)		2 (6.3)	6 (13.9)		8 (82 ± 25)	
40%–59% predicted	10 (21.7)	6 (20.7)		5 (15.6)	11 (25.6)		16 (79 ± 81)	
<40% predicted	26 (56.5)	16 (55.2)		21 (65.6)	21 (48.9)		42 (81 ± 22)	

PEFR, peak expiratory flow rate; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; FEF25–75, forced midexpiratory flow.

TABLE 5. ASSOCIATION OF SENSITIZATION, AEC, TOTAL IgE LEVELS WITH EPISODES OF ACUTE EXACERBATIONS, RESPONSE, AND OUTCOME OF TREATMENT AT SIXTH MONTH OF FOLLOW UP

<i>Patients (75)</i>	<i>Sensitized 46 (%)</i>	<i>Non sensitized 29 (%)</i>	<i>P- value</i>	<i>AEC (≥500) 32 (%)</i>	<i>AEC (<500) 43 (%)</i>	<i>P- value</i>	<i>IgE (mean ± SD)</i>	<i>P- value</i>
No. of acute exacerbations								
Nil	16 (34.7)	8 (27.6)	0.81	9 (28.1)	15 (35)	0.87	24 (74 ± 29)	0.85
≤2	19 (41.3)	16 (55.2)		15 (46.9)	20 (46.5)		35 (79 ± 27)	
≥3	11 (24)	5 (17.2)		8 (25)	8 (18.5)		16 (89 ± 16)	
Response to treatment								
Controlled	18 (39.1)	11 (37.9)	0.68	11 (34.4)	18 (41.8)	0.66	29 (72 ± 27)	0.84
Partly controlled	19 (41.4)	14 (48.2)		16 (50)	17 (39.5)		33 (83 ± 26)	
Uncontrolled	9 (19.5)	4 (13.9)		5 (15.6)	8 (18.6)		13 (88 ± 16)	
Outcome of treatment								
Same	26 (56.5)	19 (65.5)	0.74	18 (56.3)	27 (62.7)	0.68	45 (81 ± 25)	0.85
Step up	5 (10.9)	2 (6.9)		4 (12.5)	3 (7.1)		7 (80 ± 31)	
Step down	15 (32.6)	8 (27.6)		10 (31.2)	13 (30.2)		23 (76 ± 26)	

In our study, patients with atopic dermatitis and those having seasonal symptoms had higher sensitization rates than those who had no atopic dermatitis and perennial symptoms. Our results are in concordance with other studies^{24,25} done on children having asthma and associated atopic dermatitis showing a high sensitization rate with aeroallergens—house dust mite and food allergens—prawns, seafood, peanuts, and milk.

The association between atopic markers (AEC, total IgE level) and asthma severity has been variable. We observed that asthmatics with high AEC showed decline in spirometry parameters after 6 months of adequate treatment. In contrast, studies^{7,8} have reported the association of asthma severity with an increased total IgE level and not to blood eosinophil count. Carroll et al.² found an association of the total IgE level with asthma severity score and not with sensitization and wheal sizes.

Our results were similar to that reported by Siroux et al.⁶ who did not find any association of allergen sensitization with asthma severity. However, there are studies^{8,9} that showed the linear relationship of aeroallergen sensitization with asthma severity and increased hospital admissions.

Our study suggests that children having asthma are highly sensitized to aeroallergens, predominantly insects and rice dust. The sensitization rate was higher in children with seasonal variation of asthma symptoms and associated atopic dermatitis. Children with high AEC showed decline in spirometry parameters despite adequate pharmacological treatment. We observed a trend that a higher proportion of sensitized children who had uncontrolled symptoms required stepping up of treatment.

The limitations of our study includes a small sample size, low power to detect the association between markers of atopy (AEC and serum IgE level) with severity of asthma and treatment. There was a higher proportion of boys in the enrolled children; this may reflect gender bias in seeking healthcare in the country. More studies are needed in this geographical area to determine the complex relationship between atopy and asthma severity.

We conclude that almost two third of our patients were sensitized to at least one of the aeroallergens. Most common aeroallergens included insects and rice dust. There was no relation between aeroallergen sensitization with asthma severity or treatment outcome.

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Address correspondence to:

Jasmeet Kaur, DCH, DNB

Division of Pediatric Pulmonology, Asthma, Allergy

Department of Pediatrics

Dr. B.L. Kapur Super Speciality Hospital

New Delhi 110005

India

E-mail: drjasmeet47@gmail.com

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