

PEDIATRIC ASTHMA

Clinical Features Cannot Distinguish Allergic from Non-allergic Asthma in Children

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Objective. Environmental allergens are a major trigger of asthma, but not all asthmatics are allergic. This study was designed to review clinical characteristics in children with allergic and non-allergic asthma, based on responsiveness to allergy skin tests, in order to identify a combination of features that could distinguish allergic from non-allergic asthma in children. **Methods.** Medical records of 321 children who had allergy skin testing were reviewed, and demographic and clinical data were compared between allergic and non-allergic patients. **Results.** Approximately two-thirds of the asthmatic children had at least one positive skin test. These allergic patients were more likely to have a history of eczema or Medicaid insurance, but these findings had poor predictive value. There was no difference between allergic patients and non-allergic patients in terms of family history of atopy or asthma, home tobacco smoke exposure, age of onset of asthma, gender, rate of obesity, or asthma severity. Among the allergic asthma patients, neither the number of positive skin tests nor specific individual allergic sensitivities correlated with age of onset of asthma or asthma severity. **Conclusions.** This study failed to identify any combination of features that could reliably distinguish allergic from non-allergic asthma in children. Thus, all children with asthma should undergo allergy testing in order to identify potential allergic triggers in allergic patients and to avoid the institution of unnecessary environmental control measures in non-allergic patients.

Keywords allergy skin tests, asthma severity, atopy, child, eczema

INTRODUCTION

Environmental allergens are a key trigger of asthma. The effects of allergen exposure may be immediately demonstrable, with the acute onset of sneezing, rhinorrhea, wheeze, or cough upon exposure to an offending antigen. The results of allergen exposure may also be insidious, particularly for sensitized persons chronically exposed to perennial antigens, resulting in chronic symptoms or inadequate asthma control. Thus, the National Asthma Education and Prevention Program (NAEPP) Expert Panel recommends that patients who have asthma at any level of severity should, if possible, reduce exposure to those allergens to which they are sensitized and exposed (1). To accomplish this, the NAEPP Expert Panel advises a three-step approach for patients with persistent asthma: (1) evaluation for a potential role of allergens, particularly indoor aeroallergens, using the patient's medical history to identify allergen exposures that may worsen the patient's asthma; (2) determination of sensitivity to perennial indoor aeroallergens by skin testing or *in vitro* testing; and (3) assessment of the significance of positive tests in the context of the patient's medical history (1).

Not all asthmatics are allergic, however. This is particularly true for young children who wheeze in infancy and the preschool period (2). Among children

continuing to wheeze at six years of age, approximately 60% are allergic and about 40% are non-allergic (3). The percentage of allergic asthma increases through later childhood, such that by age 16 years, approximately 80% of asthmatic children are allergic (4). Healthcare providers often cannot assess a patient's sensitivity to perennial indoor allergens based on medical history alone (5). In part, this inability reflects the fact that sensitized patients chronically exposed to perennial antigens may not experience acute symptoms and therefore may be unaware of the role of allergen exposure in their asthma control.

This study was designed to review clinical characteristics in children with allergic and non-allergic asthma, based on responsiveness to skin prick tests. We hoped to determine if a predictable combination of features could reliably distinguish allergic from non-allergic asthma in children and identify a group of children needing allergy testing. Based on what is known about allergic and non-allergic asthma, we hypothesized that, relative to non-allergic patients, allergic asthmatics would have later age of onset of disease (3), increased likelihood of a family history of atopy, higher incidences of eczema and chronic rhinitis, and greater asthma severity (6–9).

METHODS

We retrospectively examined the medical records of 321 asthmatic children who were followed by the Pulmonary Division and had allergy skin testing performed between January 2004 and December 2007 at the Connecticut Children's Medical Center. Patients were identified from

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an existing database of skin test patients that is maintained by the Pulmonary Division for quality improvement purposes. Children with chronic medical conditions other than asthma were excluded, as were children who received skin testing but did not have asthma or were not followed by the Division. The study was approved by the Institutional Review Board at Connecticut Children's Medical Center. The requirement for informed consent was waived due to its retrospective nature.

Skin Prick Testing

Skin prick tests were carried out using a panel of 14 aeroallergens (Greer Laboratories, Lenoir, NC, USA), consisting of house dust mite (*Dermatophagoides farinae*), dust mix, cockroach, cat and dog dander, feathers, three types of mold (*Aspergillus*, *Alternaria*, *Penicillium*), two weed pollens (mugwort/sage and ragweed), and three pollen mixes (tree, grass, and weed). Positive and negative controls were histamine dihydrochloride (10 mg/ml solution diluted in 50% glycerine) and saline (diluted in 50% glycerine and 0.5% phenol), respectively. The allergens were applied to the skin using two Multi-Test applicators (Lincoln Diagnostics, Decatur, IL, USA), usually on the forearms but occasionally on the backs of younger children, according to standard practice (10). The tests were read after 20 minutes, with measurement of the greatest diameter of the wheal responses. Tests that had no wheal response to histamine were considered noninformative, and these patients were not included in the study database. Wheals of at least 3 mm diameter larger than that of the negative control were regarded as positive. Subjects with positive histamine responses but negative responses to all 14 allergens were considered to be non-allergic, and those having one or more tests with positive wheal responses were considered to be allergic. The skin test responses were entered into a study database, and the patients' clinic records were reviewed for demographic and clinical data.

Statistical Analysis

Relationships between allergic status and outcomes were assessed using χ^2 -tests for nominal variables and *t*-tests for continuous variables. Linear and logistic regression was used to evaluate the association between factors and allergic status. Data were analyzed using Stat-View statistical software (version 4.5; SAS Institute, Cary, NC, USA) and were reported as frequencies or as mean $\pm$ SD. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported as appropriate.

A power calculation was performed prior to data collection. Based on studies in other pediatric populations, we expected that about twice as many asthmatic children would be allergic as would be non-allergic. If so, then at a power of 85%, the study would need at least 270 patients to detect a 20% difference in incidence of a parameter between allergic and non-allergic patients – a change that we felt would be clinically significant. Based on this *a priori* analysis, we had sufficient power to examine our hypothesis.

RESULTS

Characteristics of Allergic and Non-allergic Asthmatic Patients

Of the 321 patients, 207 (64.5%) had at least one positive skin test (besides the histamine control) and 114 (35.5%) had no positive tests. As shown in Table 1, allergic patients were more likely than non-allergic patients to have or have had eczema (OR = 1.94; 95% CI = 1.14–3.32), but the two groups were identical in their incidence of rhinitis symptoms. Demographically, allergic patients were more likely to be non-Caucasian than Caucasian (OR = 1.78; 95% CI = 1.06–2.99) and to be covered with Medicaid rather than private insurance (OR = 2.07; 95% CI = 1.30–3.30). Urban residence tended to be higher in the allergic patients, without reaching statistical significance (95% CI = 0.91–3.00). On multiple logistic regression, only the presence of eczema and Medicaid insurance correlated significantly with the presence of allergy (eczema: *p* = .0093, OR = 2.32, 95% CI = 1.23–4.39; Medicaid: *p* = .033, OR = 1.86, 95% CI = 1.05–3.30). Ethnicity and urban residence did not (non-Caucasian: *p* = .49; 95% CI = 0.63–2.58; urban: *p* = .92; 95% CI = 0.44–2.47).

As further shown in Table 1, there was no difference between allergic patients and non-allergic patients in terms of family history of atopy or asthma, or of specific maternal history of asthma. The incidence of home tobacco smoke exposure was similar in the two groups. There was no difference between allergic and non-allergic patients in terms of age of onset of asthma, mean age at

TABLE 1.—Characteristics of allergic and non-allergic patients.

Trait	Allergic patients (<i>n</i> = 207)	Non-allergic patients (<i>n</i> = 114)	<i>P</i> -value
Age at testing (years)	8.4 $\pm$ 3.2	8.7 $\pm$ 3.5	.48
Gender (%M:%F)	56.5:43.5	50.9:49.1	.35
Race			.18
Caucasian (%)	60.4	73.1	.031
African-American (%)	14.1	10.6	.47
Hispanic (%)	24.5	15.4	.075
Weight (percentile)	68.6 $\pm$ 27.9	69.6 $\pm$ 24.4	.77
Obese (%)	19.2	19.4	.99
Residence (% urban)	23.7	15.8	.11
Medicaid (%)	57.5	39.5	.0024
Fam Hx asthma (%)	85.4	86.8	.85
Mat Hx asthma (%)	31.3	31.2	.99
Fam Hx atopy (%)	73.8	77.0	.74
ETS exposure (%)	39.1	33.9	.39
History of eczema (%)	34.1	21.1	.015
History of rhinitis (%)	87.6	79.6	.094
Age of onset of asthma (years)	3.7 $\pm$ 3.0	4.2 $\pm$ 3.9	.26
Cough as main symptom (%)	41.1	37.7	.63
Asthma severity			.86
Moderate-severe (%)	56.5	54.4	.73
ICS dose (mcg)	369 $\pm$ 272	357 $\pm$ 245	.72
FEV ₁ (% predicted)	92.1 $\pm$ 22.1	92.2 $\pm$ 27.7	.99

Note: Data represent percentages or mean $\pm$ SD values. ICS, inhaled corticosteroid; ETS, Environmental tobacco smoke; FEV₁, forced expiratory volume in 1 second.

allergy skin testing, gender, average weight percentiles, or obesity rates (defined by weight above 95th percentile for age).

Asthma severity [classified by NAEPP criteria, mean daily inhaled corticosteroid (ICS) dose, or mean forced expiratory volume in 1 second (FEV₁)] and symptoms (cough, wheeze, shortness of breath, chest pain/tightness) were similar between the two groups, as was the finding of cough as the primary symptom. Although increased mean daily ICS dosing was associated with a lower FEV₁ ($p < .0001$; Figure 1), the presence or absence of allergy did not alter this relationship (allergic patients: $FEV_1 = 100.3 - 0.020 \times ICS$; non-allergic patients: $FEV_1 = 100.7 - 0.023 \times ICS$; $p = .89$ by analysis of covariance).

Characteristics of Allergic Patients

Among the allergic asthma patients, the median number of positive skin tests was 2, with a range of 1–8 per patient and an effective mean $\pm$ SD of 2.7 ± 2.0 per patient. The number of positive skin tests did not correlate with age of onset of asthma (Figure 2) or with asthma severity (Figure 3, *top*), but it was noted that persistent allergic asthmatics (mild, moderate, and severe) had a younger age of onset of asthma symptoms than intermittent allergic asthmatics (Figure 3, *bottom*; $p < .0001$). A trend for younger age of onset in persistent versus intermittent asthmatics was also seen in the non-allergic subjects, but it did not reach statistical significance ($p = .23$). There was also no correlation between asthma severity and individual specific allergic responses (i.e., to dust mite, cockroach antigen, cat or dog dander, mold antigen, or pollens). Moreover, logistic regression analysis showed no correlation between combinations of allergic responses and asthma severity.

In comparing allergic patients having moderate to severe asthma ($n = 117$) with allergic patients having intermittent to mild persistent asthma ($n = 90$; Table 2),

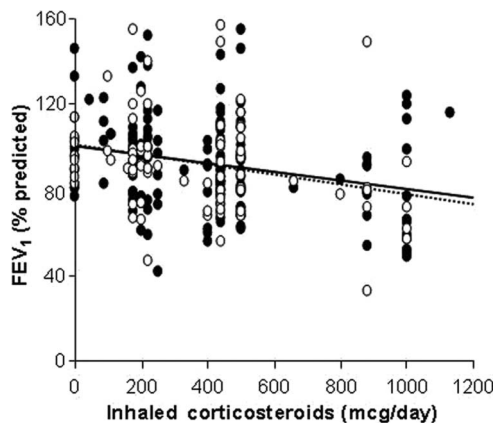


FIGURE 1.—Plot of FEV₁ versus inhaled corticosteroid (ICS) dose. The FEV₁ decreased and daily ICS dose increased with escalating asthma severity, such that an inverse relationship existed between the two parameters. The relationship did not differ between allergic patients (open symbols and dashed line) and non-allergic patients (filled symbols and solid line).

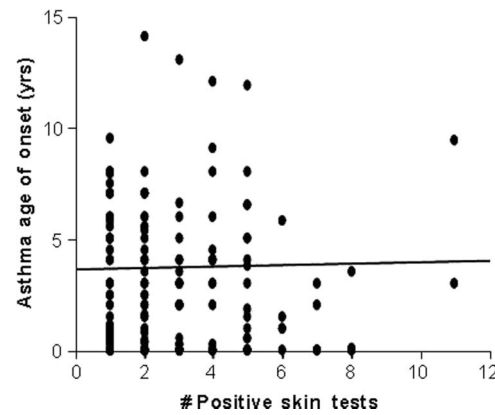


FIGURE 2.—Plot of age of asthma onset versus number of positive allergy skin tests. There was no association between the number of positive skin tests in children with allergic asthma and the age of onset of their asthma symptoms. Points represent individual subjects; line of regression was $age = 3.59 + 0.33 \times tests$; $r = 0.02$; $p = .79$.

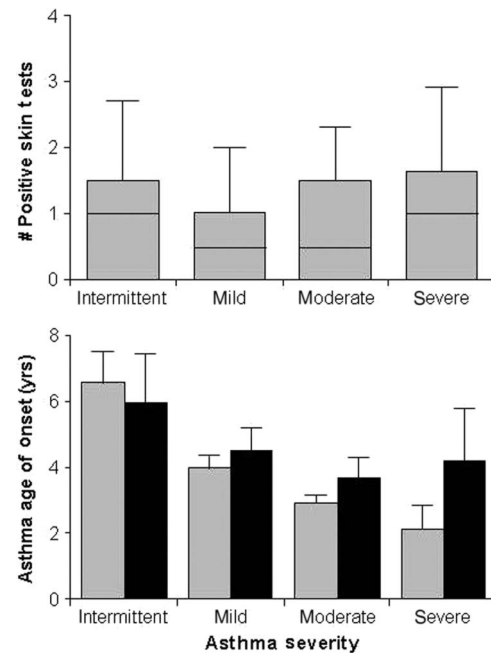


FIGURE 3.—(*Top panel*) Box plot of number of positive skin tests versus asthma severity. The number of positive skin tests did not correlate with asthma severity. Middle bars depict median values, shaded areas 25th and 75th percentiles, and upper lines the 90th percentiles; $p = .54$ by Kruskal–Wallis test. (*Bottom panel*) Bar graph of age of onset of asthma versus asthma severity. For allergic patients (gray bars), more severe asthma was associated with an earlier onset of asthma symptoms ($p < .0001$); this association was not seen in non-allergic patients (black bars; $p = .23$). Data represent mean + SEM values.

the moderate to severe allergic asthmatics had a younger age of onset of asthma symptoms than intermittent to mild allergic asthmatics and were more likely to be of Hispanic ethnicity (OR = 2.88; 95% CI = 1.38–5.98). On the other hand, neither urban residence nor Medicaid status varied with asthma severity. The prevalence of eczema tended to be greater in the moderate to severe allergic asthmatics, but the difference did not reach statistical significance (OR = 1.67; 95% CI = 0.92–3.03). There were no significant differences in mean age at testing,

TABLE 2.—Characteristics of allergic patients.

Trait	Mild asthma (<i>n</i> = 90)	Moderate– severe asthma (<i>n</i> = 117)	<i>P</i> -value
Age at testing (years)	8.1 ± 3.1	8.7 ± 3.3	.16
Gender (%M:%F)	56.7:43.3	56.4:43.6	.99
Race			.0074
Caucasian	73.8	50.0	.0010
African-American	10.7	16.7	.30
Hispanic	14.3	32.4	.0040
Weight (percentile)	68.2 ± 28.1	69.0 ± 27.9	.84
Obese (%)	18.0	20.2	.72
Residence (% urban)	20.0	26.5	.32
Medicaid (%)	54.4	59.8	.48
Fam Hx asthma (%)	81.3	88.8	.19
Mat Hx asthma (%)	17.6	42.7	.0007
Fam Hx atopy (%)	71.8	76.4	.68
ETS exposure (%)	45.1	34.5	.18
History of eczema (%)	27.7	39.1	.10
History of rhinitis (%)	87.5	87.6	.99
Age of onset of asthma (years)	4.6 ± 3.4	2.8 ± 2.2	.0002
Cough as main symptom	45.6	38.6	.39
ICS dose (mcg)	204 ± 181	485 ± 267	<.0001
FEV ₁ (% pred)	98.0 ± 19.2	87.6 ± 23.0	.0011
Number of positive skin tests	2.7 ± 2.0	2.8 ± 1.9	.85
+ dust mite	55.6	59.0	.67
+ cockroach	7.8	12.8	.27
+ cat dander	51.1	57.3	.40
+ dog dander	11.1	17.1	.24
+ mold	21.1	12.0	.086
+ pollens	47.8	52.1	.58

Note: Data represent percentages or mean ± SD values. ICS, inhaled corticosteroid; ETS, Environmental tobacco smoke; FEV₁, forced expiratory volume in 1 second.

gender, weight percentiles or obesity rates, or home tobacco smoke exposure. Of interest, while maternal history of asthma was not associated with allergic asthma (Table 1), it did significantly increase the risk of a child having moderate to severe asthma (OR = 3.50; 95% CI = 1.68–7.26).

DISCUSSION

This study compared clinical characteristics in children with allergic and non-allergic asthma, based on responsiveness to aeroallergen skin prick testing. Approximately one-third of our asthmatic patients tested negative for any aeroallergen. This rate is similar to other studies of allergic prevalence, which have noted percentages of non-allergic asthma ranging between 18% (9) and 38% (11).

While we had hoped to find a constellation of clinical, historical, and demographic findings that could alert a healthcare provider to the presence of inhaled allergies in an asthmatic child, we were unable to do so. Allergic subjects did show a greater presence of eczema than non-allergic subjects; however, the predictive value of the presence of eczema was poor, in that its presence correctly predicted positive skin test findings in 75% of our asthmatic

patients and its absence correctly predicted the absence of positive skin tests in only 37%. The addition of Medicaid insurance did not change the predictive power, resulting in a positive predictive value of 80% and a negative predictive value of 36%. Relative to adults with allergic asthma, adult patients with non-allergic asthma are more likely to be female and to have cough as the predominant symptom, and they are less likely to have symptoms of rhinitis (6). In our study, allergic and non-allergic children did not differ in gender, cough, or rhinitis symptoms. There was also no difference in family history of atopy between the two groups. Previous studies have reported conflicting results in this regard, with some showing a parental history of asthma or atopy to be a strong predictor of asthma in their children (7, 12–14), and others demonstrating no association between parental atopy and asthma in their children (15, 16). In contrast to our hypothesis and the findings of Morgan et al. (4), allergic asthmatic children had a similar (rather than older) age of asthma onset when compared with non-allergic patients.

In addition, asthma severity did not differ significantly between allergic and non-allergic asthma patients, as determined by the presence of symptoms, mean FEV₁ values, mean ICS doses, and NAEPP criteria. There is a reported correlation between severe asthma and the non-atopic condition in pediatric patients (17). We combined our moderate and severe persistent asthmatics because we had relatively few children with severe asthma (*n* = 23). When the subjects with severe asthma were analyzed separately, they were as often allergic (70% allergic) as children with moderate (64% allergic; *p* = .66) or intermittent/mild asthma (63% allergic; *p* = .64). In addition, the presence of inhalant allergies did not affect the ICS dose or the relationship between FEV₁ and ICS doses in our patients. If the presence of allergies worsened asthma, one would expect to see either increased ICS doses in the allergic patients, or lower FEV₁ values for the same ICS dose. Similarly, the presence of atopy (as determined by skin prick testing or total serum immunoglobulin E (IgE) levels) does not influence bronchial reactivity to methacholine in children with asthma (18).

There was also no association between the number of positive skin tests and asthma severity, ICS dose, or baseline FEV₁ values, although this study may not have been adequately powered to determine a difference in these outcomes. This finding differs from observations by Zimmerman et al. (9), who reported increasing numbers of positive skin tests and increased prevalence of animal sensitivity with increasing severity of asthma. The discrepancy may be explained by different populations studied and different ways of assessing asthma severity in the two studies. In a different study using NAEPP-determined asthma severity, there was a significant positive association between increasing asthma severity and total number of allergen sensitivities per subject in adults, but there was no correlation between asthma severity and total number of allergen sensitivities or specific allergen sensitization in children (19).

There are several important limitations to our study. First, we defined the presence of allergy by positive skin prick tests to aeroallergens rather than by serum total IgE or antigen-specific IgE levels. Some studies comparing the two test methods have found skin prick tests to be more sensitive (i.e., lower false-negative rate) and serum IgE tests to be more specific (i.e., lower false-positive rate) (20, 21). We also did not examine food allergen sensitivity in this study. Food allergen sensitivity in asthmatic children has been reported to be 3.5–8% (22, 23), far lower than the prevalence of aeroallergen sensitivity. Thus, the exclusion of food allergy testing was not likely to have made a significant difference in our identification of allergic patients. The retrospective nature of our study did not allow us to assess for other factors associated with the development of non-allergic asthma, such as early-life infections (15), pet exposure during the first year of life (15, 24), and indoor dampness (15, 25). In addition, we compared allergen sensitization with asthma severity but not asthma control, and we did not perform an in-home environmental assessment for allergen exposures. Accordingly, while in this study sensitization to cockroach antigen was not associated with increased asthma severity, we could not determine whether exposure to high cockroach allergen concentrations was associated with poorer asthma control, as has been reported in previous studies of urban asthmatic children (8, 26, 27). Finally, while children with allergic sensitization are at increased risk for developing asthma (28), this study was not designed to assess the future development of asthma in non-asthmatic children with aeroallergen sensitivities.

CONCLUSIONS

Although clinical and demographic data are important parameters for determining asthma risk, severity, and treatment, as demonstrated in this study, there was no identifiable feature or group of features that could distinguish allergic from non-allergic asthma. Thus, this study suggests that all children with asthma should undergo allergy testing in order to identify potential allergic triggers in allergic patients and to avoid the institution of unnecessary environmental control measures in non-allergic patients.

DECLARATION OF INTEREST

No author has financial or other potential conflicts of interest in the subject of this manuscript. The authors alone are responsible for the content and writing of the paper.

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