

Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma

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Background: Few studies have characterized the atopic profile of toddler-aged children with recurrent wheezing at high risk of the development of persistent asthma.

Objective: We sought to determine the atopic profile of toddler-aged children with frequent wheeze at high risk for the development of persistent asthma who either had a parental history of asthma, a personal history of atopic dermatitis, or both.

Methods: Participants enrolled in the Prevention of Early Asthma in Kids study (n = 285) on the basis of a modified Asthma Predictive Index were characterized on the basis of allergy and asthma questionnaire responses and allergy skin puncture test results.

Results: The majority of the children (60.7%, n = 148) were sensitized to either food or aeroallergens. Male children were significantly more likely to be sensitized to aeroallergens ($P = .03$) and to have a blood eosinophil level of 4% or greater ($P = .03$) and a total serum IgE level of greater than 100 IU/mL ($P = .0004$). Additionally, eosinophilia and total serum IgE level had the strongest correlation with aeroallergen sensitization.

Conclusion: The high prevalence of aeroallergen sensitization in this high-risk cohort suggests that aeroallergens might have an important role in the early development of asthma. As such, the Prevention of Early Asthma in Kids cohort appears to be an appropriate cohort in which to test whether early intervention with an inhaled corticosteroid can significantly attenuate, or perhaps even prevent, the allergic march from the initial stages of allergic sensitization to the subsequent development of asthma in toddlers with episodic wheezing. (*J Allergy Clin Immunol* 2004;114:1282-7.)

Key words: Allergens, aeroallergen and food sensitization, asthma predictive index, atopy, clinical trials, early childhood asthma, fluticasone, glucocorticoids, intermittent wheezing, prevention of asthma, research network, skin prick test

Asthma remains a significant public health problem in the United States in the pediatric age group.¹ Not only is the prevalence of the disease increasing, especially during the early school years, but studies of the natural history of the disease have demonstrated that in most cases of persistent asthma the initial asthma-like symptoms occur during the first several years of life.² Thus it is important to understand the clinical features of very young children who might be at risk for the development of persistent asthma. In addition, few studies exist that characterize the atopic profile of toddler-aged children with frequent recurrent wheezing and the events that follow in terms of the so-called allergic march. We describe the atopic profile of a large number of high-risk toddler-aged children identified by using a modified Asthma Predictive Index (mAPI)³ who were enrolled in a long-term secondary asthma prevention study. Our hypothesis is that the majority of toddler-aged children who are at high risk for the development of asthma will be sensitized to aeroallergens and that this sensitization might be modified by sex and ethnicity.

METHODS

Subjects

Children 2 and 3 years of age with frequent intermittent wheezing at high risk of persistent asthma but without persistent symptoms were identified by meeting the criteria for a positive mAPI result and enrolled in the Prevention of Early Asthma in Kids (PEAK) Trial. The cohort is population based and identified by primary care physicians within the cities of the 5 clinical centers (listed in the Appendix in the Journal's Online Repository at www.mosby.com/jaci) on the basis of identification of children with recurrent wheeze. Children were then screened for eligibility for enrollment on the basis of the study inclusion and exclusion criteria that have been published in more detail elsewhere.⁴

The original Asthma Predictive Index (API) was based on data from the Tucson Children's Respiratory Study (TCRS), a large and

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TABLE I. mAPI* versus original API (Castro-Rodriguez et al³)

1. The child must have a history of 4 or more wheezing episodes with at least one physician diagnosis.	
2. In addition, the child must have a history of 4 or more wheezing episodes with at least 1 confirmed by a physician.	
mAPI: Major criteria • Parental history of asthma • Physician-diagnosed atopic dermatitis • Allergic sensitization to ≥1 aeroallergen	Original API: Major criteria • Parental history of asthma • Physician-diagnosed atopic dermatitis
mAPI: Minor criteria • Allergic sensitization to milk, egg, or peanuts • Wheezing unrelated to colds • Blood eosinophils ≥4%	Original API: Minor criteria • Physician-diagnosed allergic rhinitis • Wheezing unrelated to colds • Blood eosinophils ≥4%

*Differences in indices are in bold.

Abbreviations used
API: Asthma Predictive Index
CAMP: Childhood Asthma Management Program
CARE: Childhood Asthma Research and Education Network
mAPI: Modified Asthma Predictive Index
NHLBI: National Heart, Lung, and Blood Institute
OR: Odds ratio
PEAK: Prevention of Early Asthma in Kids
SPT: Skin prick test
TCRS: Tucson Children’s Respiratory Study

longitudinal assessment of respiratory illnesses in more than 1200 children.^{5,6} The API included frequent wheezing in the first 3 years of life and either one major risk factor (parental history of asthma or personal history of atopic dermatitis) or 2 of 3 minor risk factors (eosinophilia, wheezing without colds, and allergic rhinitis; Table I).³ The API had a positive predictive value for active asthma of 47.5% to 51.5% between the ages of 6 and 13 years. Conversely, only 5% of children with a negative API result had active asthma between the ages of 6 and 13 years. Therefore children with a positive API result are likely to go on to have persistent asthma. The PEAK trial modified the published API to include 2-year-old children because PEAK is an asthma prevention study directed at early intervention in high-risk children.⁴ The 2-year-old children in PEAK possessed similar API characteristics as the 3-year-old children, including wheezing burden and sensitization. Although it was not evaluated during the Tucson study, allergic sensitization to aeroallergens and allergic sensitization to milk, eggs, or peanuts during the first years of life have been reported as risk factors for the subsequent development of persistent asthma in the literature.⁷⁻¹² Because allergic rhinitis can be difficult to diagnose in young children, the published API was also modified (Table I) for use in the PEAK study to include allergic sensitization to aeroallergens and to foods and was used in its place with the expectation of at least a similar positive predictive value for asthma. Because food sensitization^{10,11} and not definitive food intolerance caused by allergy has been used for asthma prediction, food challenges to confirm food allergy in those participants with food sensitization were not performed as part of PEAK.

To focus on the API major criteria revealed in the TCRS cohort³ in this analysis, we examined the atopic profile of a subset of toddler-aged children enrolled in the PEAK study with frequent wheeze at high risk for the development of asthma who either had a parental history of asthma, a personal history of atopic dermatitis, or both.

Study design

PEAK is a multicenter, double-blind, randomized, placebo-controlled, parallel-group comparison of inhaled fluticasone propionate with placebo in children. It is a long-term trial developed by the National Heart, Lung, and Blood Institute (NHLBI)–sponsored Childhood Asthma Research and Education (CARE) Network (see the Appendix in the Journal’s Online Repository). During the enrollment and randomization study visits, data were collected on family and personal medical history, environmental history, medication use, and quality of life on the basis of questionnaire results, physical examination findings, lung function testing, eosinophil counts, IgE, and allergy skin prick tests (SPTs). A detailed description of the screening, recruitment, design, and statistical analysis for the PEAK study is reported elsewhere.⁴ The primary outcome of this ongoing study is to assess whether chronic and early therapy with inhaled corticosteroids initiated in children 2 and 3 years of age at high risk of asthma can prevent the development of persistent asthma at 4 to 6 years of age. It is currently being conducted in accordance with the principles of the Declaration of Helsinki and has been approved by the NHLBI, the CARE Network Steering Committee, the CARE Network Protocol Review Committee, the CARE Network Data Safety Monitoring Board, and the local institutional review boards at all participating centers. Parents provided informed consent.

Procedures

All of the PEAK participants (n = 285) were evaluated for the presence of allergic sensitization by means of SPT or specific IgE assessment (Pharmacia CAP system [CAP FEIA]; Pharmacia, Uppsala, Sweden) techniques.⁴ If a child was suspected to have had an anaphylactic reaction to any tested allergen, a CAP FEIA test was performed instead of skin testing; a level of 0.35 IU/mL or greater was considered positive, as specified by the manufacturer and other studies.¹³ Two hundred fifty-seven children were evaluated by means of skin testing alone, 15 by means of CAP FEIA alone, and 13 by means of both methods.

The atopic profile was further characterized with peripheral blood eosinophil percentages by means of automated assay at each center in 198 children. An eosinophil count of 4% or greater was considered increased. This is greater than the 90th percentile of the normal value in a birth cohort of 900 nine-month-old infants (unpublished data from the Tucson Children’s Respiratory Study). Total serum IgE (Pharmacia CAP system) levels were measured at each clinical center on serum from blood clotted at room temperature for 226 children. SPTs were performed by PEAK-certified personnel in accordance with a study-specific protocol on the basis of that used in the Childhood Asthma Management Program (CAMP) study and the National Cooperative Inner-City Asthma Study.^{14,15} Allergy skin

TABLE II. Demographics and asthma characteristics of the PEAK cohort

Characteristic	Mean $\pm$ SD or n (%), n = 244
Age, mo	35.9 $\pm$ 7.0
Race or ethnic group no. (%)	
Non-Hispanic white	130 (53.3)
Non-Hispanic black	29 (11.9)
Hispanic	53 (21.7)
Other	32 (13.1)
Sex, no. (%)	
Female	96 (39.3)
Male	148 (60.7)
Parental history of asthma, no. (%)	
Maternal history	111 (45.5)
Paternal history	91 (37.3)
Both	20 (8.2)
Parental history of atopy, no. (%)	
Maternal history	105 (43.0)
Paternal history	83 (34.0)
Both	44 (18.0)
Cigarette exposure first 2 years of life, no. (%)	
Maternal smoking	37 (15.2)
Paternal smoking	53 (21.7)
Other household member smoking	43 (17.6)
Age of first asthma diagnosis by a physician, mo	16.0 $\pm$ 9.9
Children with pets in house, no. (%)	143 (58.6)
Hospitalizations for asthma in year before enrollment, no./100 person-years	6.7 $\pm$ 0.64
Recordings during enrollment month (average days per week)	
Albuterol use	1.0 $\pm$ 1.2
Night awakenings	0.5 $\pm$ 0.7

tests were performed to 8 common aeroallergens at all the clinical centers (mixtures for house dust mite [*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*], cockroach [American and German], dog [mixed breeds], cat [standardized], mold [mix no. 1], grass [standardized Southern mix], tree [eastern 8 tree mix], and weed [national mix] and 3 foods [cow's milk, chicken and whole egg, and peanut; Greer Laboratories, Lenoir, NC] by using the Multi-test II (Lincoln Diagnostics, Decatur, Ill) prick technique. The St Louis center tested the following additional allergens: red oak, *Aspergillus fumigatus*, and short ragweed (Greer Laboratories). A test response was considered positive if the prick test resulted in a wheal with a mean diameter (mean of maximum and 90° midpoint diameters) that was at least 3 mm greater than that produced by a saline control.⁴ Questionnaire data were collected at the time of enrollment from the child's parents regarding baseline medical, demographic, and atopic history.

Data analysis

Double data entry was used, with both the clinical center entering the data in real time by using a Web-based database and second entry from data at the data-coordinating center to ensure accuracy. Discrepant values were resolved by the clinical centers. All analyses were carried out with version 8.2 of the SAS statistical software

system (SAS Institute Inc, Cary, NC). Descriptive statistics, including mean, median, SD for continuous variables, and frequency tables for discrete variables, were generated. Associations between demographic factors and allergic sensitization were characterized by using contingency table analysis. Significance levels were determined by using the Pearson χ^2 statistic and confirmed by using the Fisher exact test in the case of sparsely populated tables. Multivariable logistic regression was used to assess associations between allergic sensitization and predictor variables, including atopic dermatitis, eosinophil percentages, serum total IgE levels, clinical center, age, sex, race, and parental history of asthma. Both *P* values corresponding to the contingency table analysis (unadjusted *P* value) and the multivariable analysis (adjusted *P* value) were reported in any instance in which they differed. The total serum IgE level was converted to an ordinal scale and classified according to the quartiles of the total serum IgE levels on the continuous scale. Associations between eosinophil percentages and IgE and demographic factors were characterized by means of ANOVA, and significance levels were determined by using the *F* statistic and confirmed with nonparametric Kruskal-Wallis tests in the case of maldistribution. Two-sided *P* values of less than .05 were considered statistically significant.

RESULTS

PEAK cohort demographics

Complete data were available for 244 participants with either a parental history of asthma, a personal history of atopic dermatitis, or both randomized to the PEAK study (Table II). Participants were children with a mean $\pm$ SD age of 36 $\pm$ 7 months who were predominately male (60.7%) and non-Hispanic white (53.3%), with an age of physician diagnosis of asthma of 16.0 $\pm$ 9.9 months in 86% of participants who had received this diagnosis and experienced 6.7 $\pm$ 0.64 hospitalizations for wheezing per 100 person-years (Table II). All participants had at least 4 episodes of wheezing lasting at least 24 hours in the 12 months before enrollment. The participants experienced a mean and standard deviation per week of 1.0 $\pm$ 1.2 days of albuterol use and 0.5 $\pm$ 0.7 night awakenings as recorded on daily diary cards during the month of study run-in, during which they received no medications except albuterol as needed. No significant associations (*P* > .05) were appreciated for food and aeroallergen sensitization and the number of hospitalizations, use of albuterol, or number of nocturnal awakenings recorded during the enrollment month.

Modified API characteristics

Of the 244 participants, 90.3% met the mAPI criteria on the basis of a history of either a positive parental history or personal history of atopic dermatitis. All 3 major mAPI criteria (parental history of asthma, personal history of atopic dermatitis, and ≥ 1 positive aeroallergen skin test response) were satisfied by 19% of the cohort. Two hundred forty-four subjects were either tested for allergen sensitization by means of SPT (91.7%) or CAP FEIA (8.3%). Of these, 60.7% (*n* = 148) demonstrated allergen sensitization. Of this cohort, 6.6% (*n* = 16) had food sensitization alone, 28.3% (*n* = 69) had aeroallergen

sensitization alone, and 25.8% ($n = 63$) had sensitization to both (Fig 1; Table E1 in the Journal's Online Repository at www.mosby.com/jaci).

Male children were significantly more likely to be sensitized to any allergen (66.2%, $n = 98$, adjusted $P = .03$) and sensitized to an aeroallergen specifically (59.5%, $n = 88$, adjusted $P = .04$). Younger children 24 to 36 months of age had a similar rate of allergic sensitization to children older than 36 months of age.

Sensitization to any allergen was higher in the group that had a personal history of atopic dermatitis with or without parental history of asthma compared with in the group that had a parental history of asthma alone (66.1% vs 51%, $P = .04$). In children who met the mAPI criteria on the basis of a parental history of asthma alone, sensitization to any allergen was higher in the older compared with the younger participants (63.8% and 40.0%, respectively; $P = .02$). Children given a physician diagnosis of allergic rhinitis (20.3%, $n = 30$) were more likely to be sensitized to either a food allergen or aeroallergen ($P = .012$). Children with history of at least daily asthma-like symptoms, such as cough, wheeze, shortness of breath, and chest tightness (8.1%, $n = 12$), were not more likely to be sensitized to any allergen than children with less-frequent symptoms ($P = .32$).

Children who had a pet in their home were more likely to be sensitized to any aeroallergen than those who did not live with a pet ($P = .015$, Table E2 in the Journal's Online Repository at www.mosby.com/jaci). However, children who lived with pets were just as likely to be allergic to cats and dogs as those children who did not (58% [$n = 87$] vs 59.3% [$n = 54$], respectively; $P = .84$). Children who had environmental tobacco smoke exposure in the first 2 years of life were not more likely to be sensitized than children who did not have such exposure (Table E2 in the Journal's Online Repository). Parental history of asthma was not a significant predictor of sensitization (odds ratio [OR], 1.6; 95% CI, 0.35-7.23) in multivariate logistic regression. Those children who had a maternal history of asthma were not more likely to be sensitized to an aeroallergen or food allergen than those with a paternal history (30% [$n = 33$] vs 25% [$n = 27$], respectively; $P = .39$).

Children had a mean eosinophil percentage of $4.1\% \pm 3.04\%$ (range, 0% to 23%). Male participants were also more likely to have an eosinophil percentage of 4% or greater compared with female participants (48.3% vs 35.1%, respectively; adjusted $P = .05$; Table E1 in the Journal's Online Repository). Children 36 months or older were more likely to have increased eosinophil counts when compared with those younger than 36 months of age (48.7% vs 37.5%, respectively; $P < .05$). An eosinophil percentage of 4% or greater (OR, 2.3; 95% CI, 1.1-4.5) and a total serum IgE level of greater than 100 IU (<10 IU vs >100 IU [OR, 5.7; 95% CI, 2.1-15.9], 10-40 IU vs >100 IU [OR, 3.5; 95% CI, 1.3-9.9], and 41-100 IU vs >100 IU [OR, 2.8; 95% CI, 1.1-7.5]) were the only significant predictors of aeroallergen sensitization among demographic, parental history, and atopic risk factors in a multivariate logistic regression. However, a total serum

Sensitization by Allergen Class

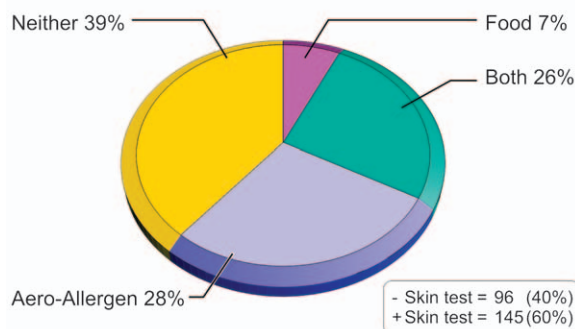


FIG 1. Distribution of allergic sensitization by SPT or CAP FEIA in the PEAK cohort.

IgE level of greater than 100 IU (<10 IU vs >100 IU [OR, 4.5; 95% CI, 1.6-12.5], 10-40 IU vs >100 IU [OR, 3.5; 95% CI, 1.4-8.8], and not eosinophil percentage [OR, 1.1; 95% CI, 0.5-2.2]) was a significant predictor of food allergen sensitization.

Male participants (81.4%, $n = 48$) were more likely than female participant to have a total IgE level of 100 IU or more ($P = .0004$). No significant differences in total IgE levels were found between age groups on the basis of history of physician-diagnosed allergic rhinitis.

Those children with a family-reported ethnic background of African American were more likely to be sensitized to either at least one food allergen (55.2%, $n = 16$; $P = .01$; adjusted $P = .10$) or aeroallergen (79.3%, $n = 23$; unadjusted $P = .01$; adjusted $P = .05$) than participants who reported other ethnic origins. No differences were seen in peripheral eosinophil percentages or total IgE levels between subjects with varying family-reported ethnic backgrounds ($P = .13$). The difference between the unadjusted and adjusted P values corresponding to the association between ethnicity and allergic sensitization is due to a confounding between ethnicity and clinical center. In particular, one clinical center had a significantly lower rate of participant sensitization and also had a lower percentage of minority ethnic participation. Because the apparent ethnic differences in sensitization might actually be due to geographic differences in sensitization, these results must be considered to be inconclusive.

DISCUSSION

PEAK is the first clinical trial to enroll participants on the basis of a high-risk index known as the API.³ Children with a positive API have been shown to be likely to go on to have persistent asthma.³ PEAK therefore has the potential to examine the atopic and asthmatic characteristics of a high-risk cohort with frequent intermittent wheezing episodes who are likely to have persistent asthma.

In this analysis we examined a young group of children with frequent wheezing and at least one of the 2 major criteria of the API.³ This study finds that toddlers

at high risk of development of persistent asthma are frequently sensitized in early life to allergens, particularly aeroallergens. Two thirds of this high-risk cohort of 2- and 3-year-old children were sensitized to either aeroallergens, food allergens, or both. This degree of allergic sensitization is higher than the 23% to 50% prevalence reported in cohorts of similarly aged wheezing children selected on the basis of a history of only personal intermittent wheezing¹⁶⁻¹⁸ or only a parental history of atopy (unpublished data from R. F. Lemanske).^{10,20,21} It is, however, more comparable with the degree of sensitization observed in cohorts of young children with frequent wheezing responsive to asthma medication (51% to 58%).^{6,19}

There appears to be early activation of the immune system involved with allergic inflammation, with demonstrable IgE antibody formation to both food allergens and aeroallergens. The high frequency of aeroallergen sensitization suggests that aeroallergens might have an important role in the early developmental stages of asthma. Children who had a personal history of atopic dermatitis had higher sensitization rates compared with those who had only a parental history of asthma. Allergic sensitization to foods alone was uncommon (7% of the cohort), and the prevalence of sensitization did not differ between the 2- and 3-year-old age groups. Thus sensitization to aeroallergens appears to begin early in life in these high-risk children, a process that might initiate or perpetuate allergic inflammatory responses within the airways and contribute to asthma pathogenesis and the so-called allergic march. This has implications for the management of these high-risk children and the potential prevention of persistent asthma through early intervention with asthma medications or environmental control.

Similar to previous reports, male children and those with a family-reported African American background demonstrated increased allergen sensitization, reaching nearly 80% by 4 years in the latter.^{20,21} Increasing rates of hospitalizations and mortality have been described in African American asthmatic patients,^{22,23} which potentially could be a result of increased allergic sensitization and chronic exposure to those allergens. However, significant differences in sensitization were seen between clinical centers, with a range of between 45% and 82%. This might be due in part to the ethnic differences between the populations of both cities, with St Louis having a greater percentage of persons reported as having African American background and also performing a greater number of skin tests. This confounding variable, clinical center, does not allow us to definitively characterize differences in sensitization across ethnic groups. Another explanation might be the differences in aeroallergen composition between these 2 cities, with Denver reporting a lower rate of dust mite sensitization.²⁴ However, it should be noted that similar rates of sensitization to different allergens have been reported in environments with varying rates of dust mite sensitization.²⁵⁻²⁸

Personal atopic dermatitis is more predictive of sensitization in younger children than a parental history of

asthma. Unlike a previous report,⁶ a maternal history of asthma did not confer a higher risk of sensitization in the PEAK cohort that might be overshadowed by selection of a high-risk cohort identified by an API. This suggests that atopic dermatitis is a more powerful surrogate for sensitization than parental history because it is evidence of established personal atopy. Parental history of asthma appears to be a more important factor in the older child without established personal atopic dermatitis. In fact, maternal history is important in univariate analysis as a risk factor for asthma, but once allergic rhinitis and atopy covariates are added to a multivariate model for asthma, parental history becomes nonsignificant (unpublished data from the TCRS).

Children who lived with pets were more likely to be sensitized to any aeroallergen than those who did not live with a pet. The protective effect of living with a pet early in life was not seen in these 2- and 3-year-old children. However, previous reports suggest that the exposure might be protective if it occurs within the first year of life²⁹⁻³¹ and might be detrimental if it occurs after the child is sensitized.³²⁻³⁴ We did not obtain data if the pet was present in the home at birth and therefore cannot address this issue. The PEAK study also selected a group of children at high risk for the development of atopy and for which exposure to pets might not have a significant protective effect. An additional finding was that those children living with a cat or dog were not more likely to be sensitized to pet dander than those who did not. Recent reports have indicated that pet ownership is not necessarily required for sensitization to pet dander^{35,36} because exposure to allergen found in schools and other non-domiciliary settings³⁷ might be sufficient to lead to sensitization. In addition, children in the PEAK study who were exposed to parental cigarette smoke in the first 2 years of life were not more likely to be sensitized than children who were not. This is not supportive of previous findings that found that children exposed to cigarette smoke in early life are more likely to become atopic.³⁴⁻³⁹ However, PEAK does not possess the power of a large and longitudinal study to detect such a difference.

Eosinophils and IgE levels, biomarkers of atopy, were significantly increased in male participants. No ethnic differences were observed in blood eosinophil counts or IgE levels, but as noted earlier, the data on ethnicity is limited by confounding by clinical center.

Many similarities can be drawn between the cohorts in the PEAK and CAMP trials. CAMP was a study of more than 1000 older children, 5 to 12 years of age, with documented persistent asthma.³⁸ Both the PEAK and CAMP cohorts evidenced a male predominance, a high degree of allergen sensitization and eosinophilia, a strong family history of asthma and atopy, and a majority of home environments with cats and dogs.^{22,39} The cohorts differed in asthma severity, with PEAK and CAMP consisting, respectively, of intermittent wheezers and mild-to-moderate persistent asthmatic children. It is reasonable to speculate that the PEAK cohort represents a cohort similar to the CAMP cohort but before persistent asthma has

developed. As such, the PEAK cohort appears to be an appropriate group to attempt secondary asthma prevention with inhaled corticosteroids.

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