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HIGH PREVALENCE OF AEROALLERGEN SENSITIZATION AMONG INFANTS OF ATOPIC PARENTS

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Abstract

Objective— To present methodology to identify atopic parents and determine the prevalence of sensitization to 15 aeroallergens in their infant offspring.

Study design— A birth cohort of infants was identified from birth records; an infant was enrolled if 1 of the parents reported allergy respiratory symptoms and had a positive skin prick test (SPT) to a common aeroallergen. At age 1 year, these infants were tested to the same aeroallergens.

Results— Of the 680 enrolled infants, 28.4% were SPT+ to 1 or more aeroallergens and/or food, and 18.0% were positive to 1 or more aeroallergens. By category of allergens, 9.7% were sensitized to pollens, 7.5% to molds, 4.3% to house dust mite and/or cockroach, and 3.4% to dog and/or cat. Of the infants who were positive to an aeroallergen, 65.7% remained positive at age 2 years.

Conclusions— Infants born to atopic parents with percutaneous sensitization to aeroallergens are at increased risk for aeroallergen sensitization during infancy, which persists to age 2 years. These findings suggest that current clinical practices, which generally avoid skin testing before age 2 years, be reassessed in this population of high-risk children.

In the Third National Health and Nutrition Examination Survey, (NHANES III), conducted in 1988–1994, 50% of children age 4 to 17 years exhibited a positive skin prick test (SPT) to at least 1 of 4 aeroallergens.[1] Over the last 2 decades, these high rates of aeroallergen sensitization have been accompanied by an estimated doubling in the incidence of allergic respiratory diseases, with an 11% gap for asthma attacks (26% vs 15%) between black and white children.[2,3] Aside from food allergies and atopic dermatitis, the potential for development of atopic respiratory disorders in infancy is often deemphasized, even though sensitization to allergens at younger ages has been shown to be more important than sensitization later in childhood for the development of wheezing symptoms and asthma.[4,5] Thus, early recognition of aeroallergen sensitization during the first and second years of life may facilitate surveillance of infants at highest risk for later expression of allergic respiratory disease.[6]

Although parental history of asthma and allergic rhinitis[7–9] are important risk factors for childhood asthma,[10–12] little is known about percutaneous sensitization profiles of infants born to parents with confirmed aeroallergen sensitization. This is due in part to the difficulties

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inherent in performing the SPT in infants as well as parents, despite the fact that this procedure can be safely performed in patients of all ages and is more sensitive than in vitro measurements of serum-specific IgE.[13] Moreover, in all but 1 birth cohort study of infants in which SPT has been performed, the number of aeroallergens evaluated was 7 or less.[14–17]

Here we report methods used to precisely identify atopic parents and successfully recruit their high-risk infants for the Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS). To better define the actual prevalence of aeroallergen sensitization among infants of parents in whom atopic status was rigorously confirmed, we present data from skin test studies performed in this cohort of high-risk infants with an expanded panel of allergens (15 aeroallergens and 2 foods). We find an unexpectedly high prevalence of positive skin tests to aeroallergens in this infant population that persists into the second year of life.

METHODS

Study Design and Family Recruitment

Newborns were identified from birth certificate records in the Cincinnati metropolitan area from October 2001 through July 2003. Eligibility for the study was determined by geocoding residential addresses from the birth certificates, as described previously.[18] Parents were informed of the study by letter; were screened by phone, mail, or personal interview at their home using an allergy symptom questionnaire (ASQ); and signed an informed consent approved by the University of Cincinnati Institutional Review Board. This study is ongoing, with annual follow-up of infants for allergic disease. The current report presents results for the parents' and infants' first SPT.

Allergy Symptoms and SPTs

To maximize the efficient identification of atopic parents, a screening ASQ identified those most likely to be sensitized to aeroallergens. Sections of the short questionnaire developed by Nielsen et al for the Glostrup Allergy Study in Denmark and the International Study of Allergies and Asthma in Childhood (ISAAC) core questionnaires were modified and pilot tested.[10,19] The final ASQ consisted of 12 symptom questions, 7 questions adapted from Nielsen et al, 4 questions adapted from the ISAAC, and 1 additional question added based on clinician feedback after pilot testing. An affirmative response to 1 symptom qualified the parent for a SPT. A positive SPT (SPT+) to 1 aeroallergen was required to enroll an infant.

The parent was considered atopic if he or she had at least 1 allergy or asthma symptom and was SPT+ to 1 of the following 15 aeroallergens: pollen (meadow fescue, timothy, white oak, maple mix, American elm, red cedar, short ragweed), mold (*Alternaria*, *Aspergillus fumigatus*, *Penicillium* mix, *Cladosporium*), pet (cat, dog), and dust (German cockroach [*Blattella germanica*], dust mite mix [*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*]).

The infants were evaluated for the same 15 aeroallergens plus cow's milk and egg. All SPTs were performed using the Accu-set tips and aeroallergen (provided by ALK-Abelló, Inc, Round Rock, TX). A positive SPT was defined as a wheal $\geq$ 3 mm larger than the saline control after 15 minutes. This criteria has a positive predictive value between 0.79 and 0.92 compared with food challenge in children under age 2 years[20] and can be interpreted without difficulty in infants older than 3 months.[21]

Data Analysis

The prevalence of positive SPTs for each allergen was calculated for parents and children. Separate multiple logistic regression analyses generated adjusted odds ratios (ORs) of a child

having a positive SPT given the parental pattern of allergic symptoms or aeroallergen sensitization; that is, all 12 parent symptoms or all 15 aeroallergens were analyzed simultaneously. Because of similarities among parent symptom questions, a cluster analysis was performed to identify groups of similar symptoms and was repeated with cluster-specific indicators of at least 1 symptom being positive in the cluster.

To obtain "true" atopic and "true" nonatopic rates, the nonsymptomatic parents completing the ASQ should have also received a SPT. But those individuals without symptoms are not generally the relevant clinical population, and they were not our relevant study population. Therefore, we evaluated the ASQ to determine which symptom was most predictive of a positive SPT for only those parents who had at least 1 symptom. Sensitivity and specificity were assessed for individual symptoms compared with all of the others. Hence, the ability of individual symptoms to predict aeroallergen SPT positivity was investigated by calculating percent sensitivity (symptom prevalence given SPT+), specificity (symptom absence given negative SPT [SPT7−]), and positive predictive values (symptom prevalence given SPT+ divided by symptom prevalence).

RESULTS

Identification, Recruitment, and Description of Atopic Parents

Of 7352 families who were sent a letter requesting their participation, 30.8% (n = 2265) completed the ASQ by phone (43.6%), mail (34.3%), or at-home visit (22.1%). The other group comprised the nonparticipants (69.2%; n = 5087), who refused to participate (19.9%), moved (7.8%), or were never reached (41.5%). Birth certificate records were compared in participants and nonparticipants to address any sources of bias. The 2 groups had similar maternal Caucasian racial status (74.3% and 70.1%), average age (28.3 [± 5.9] years and 27.7 [± 5.9] years), and Ohio residence (84.8% and 83.6%). To further assess participation bias, we asked those who refused to participate in the primary study to answer 2 brief questions; approximately half agreed to do so. Those who refused were similar to the participants in having had a previous child with asthma or allergies (13.3% vs 12.6%) but were dissimilar in reporting that they themselves had allergies or asthma (25.1% vs 53.5%). Because the purpose of the ASQ was to identify and recruit atopic parents, this latter difference does not represent a bias, because these families likely would not have been eligible to participate.

A total of 1134 parents, either themselves (911) or their spouse (223), completed the ASQ and underwent skin testing. Of these, 304 were SPT- and thus were ineligible. For these analyses, if both parents were tested (59 families), only 1 was selected, either the SPT+ parent or, if both were positive, the mother; 78.4% of those parents tested were mothers.

Enrolled parents brought their infant(s) for a SPT at age 1 year. Results were available for 680 infants and 664 parents (16 sets of twins participated) in which the parent reported at least 1 of the 12 symptoms and was SPT+ and the infant received a SPT. The mean (± 1 standard deviation) and median ages of the infant at time of their first SPT were 13.7 (± 2.6) months and 12.6 months, respectively, and 93% were under age 18 months.

Symptoms Predictive of Sensitization in Parents (n = 1134)

One goal of the study was to identify atopic parents of newborns from a general population sample using infant birth records. The wording of each question, the order in which the questions were asked, and the number and percent of parents reported to have the symptom are shown in Table I. The sensitivity, specificity, and positive predictive value for each question are shown in the Figure. Because of similarities among symptom questions, we determined which symptoms were similar and significantly predictive of a parent being atopic, and found

that 2 clusters were significant. For the first cluster, the questions included "itchy or stuffy nose or sneezing near animals" and "shortness of breath near animals." There was a 4-fold likelihood of identifying an atopic parent (ie, being SPT+) given that they reported at least 1 of these 2 symptoms (OR = 4.1; 95% confidence interval [CI] = 2.9 to 5.8). For cluster 2, the questions included "itchy or watery eyes" and "itchy or stuffy nose or sneezing near grass, trees, or flowers." There was almost a 2-fold likelihood of identifying an atopic parent given a positive response (OR = 1.9; 95% CI = 1.4 to 2.6). Thus, these 4 questions may be the most important ones for identifying allergic adults.

Symptoms and Sensitization in Parents and Infants

The first column of Table II gives the prevalence of SPT+ by individual and category of aeroallergen for all parents having at least 1 allergy symptom. Overall, 73.2% of the parents who responded "yes" to at least 1 symptom were SPT+. Of those parents whose spouse provided the symptom history, 79.8% had a SPT+; of those who self-reported symptoms, 71.6% were SPT+.

The overall rate of sensitization to any allergen in the 680 infants at their first test was 28.4% (Table II, column 3). The highest rates of sensitization, in descending order, were for egg (12.2%), milk (4.7%), dust mite (3.1%), and timothy (2.9%). The most frequent aeroallergen category included pollen (9.7%), and the least frequent included dog and/or cat allergen (3.5%). However, the pollens had a very wide difference in atopic response between adults and children in terms of allergen sensitivity (eg, 43.1% and 1.2%, respectively, for short ragweed), although the difference between parent and child was quite narrow for 2 molds, *Penicillium* (5.6% vs 1.5%) and *Aspergillus fumigatus* (7.8% vs 2.1%). For those infants who were SPT+ for aeroallergens, the highest rates were to dust mite (10.9%) and timothy (10.4%) (Table II, column 4).

The results of multiple logistic regression examining the odds of a child being SPT+ given the parental sensitivity to a specific aeroallergen showed that only *Cladosporium* was significant. It was, however, inversely (protective) associated with the child being atopic (OR = 0.6; 95% CI = 0.4 to 0.9).

Persistence of Infant Sensitization

To assess the persistence of the infant SPT results, we analyzed the results to date for those infants who have completed their second SPT (n = 589). Our results show that of these 589 infants who were tested twice, 26.7% (n = 157) were SPT+ at their first test, and 67.5% of these (n = 106) remained positive at their second. Of those who were SPT+ to an aeroallergen at their first visit, 65.7% (n = 102) remained positive, although only 39.7% (n = 31) of those who ere SPT+ to food at age 1 year (n = 78) remained positive. The overall SPT reactivity for 2-year-olds, regardless of the first-year test results, increased from 28.4% (n = 680) to 39.0% (n = 589), with 9.1% allergic to at least 1 food and 36.3% allergic to at least 1 aeroallergen (non–mutually exclusive categories).

DISCUSSION

Our study demonstrates that the prevalence of aeroallergen skin sensitization in infants born to parents in whom atopy is confirmed by skin testing is substantially higher than previously reported. The present study is unique in that no previous infant studies have undertaken SPT with so large a panel of individual aeroallergens, representing most relevant regional indoor and outdoor allergens (including tree, grass, and weed pollens), similar to that used for testing patients in allergy clinics. In clinical practice, evaluation for aeroallergen sensitization is often deferred until age 4 or 5 years, and hence assessment of potential risk for atopic disorders is

generally delayed until that time. However, we found that 28.4% of infants born to atopic parents were sensitized to 1 or more aeroallergens and/or food allergens. Furthermore, 18.0% were positive to 1 or more aeroallergens, and 13.7% were positive only to an aeroallergen. Pollens were the most common aeroallergens (9.7%). These findings have broad implications for medical practice and may warrant changes including earlier allergy evaluations for young children, especially those born to atopic parents. Further, the Third National Health and Nutrition Examination Survey (NHANES III) found that 54.3% of the US population was sensitized to at least 1 aeroallergen.[22] Therefore, our at-risk cohort has wide generalizability, because more than 50% of the US population is sensitized.

Documentation of aeroallergen skin test sensitization at age 1 has been demonstrated in a small number of birth cohort studies, but at lower prevalences than identified in the CCAAPS cohort. These differences could be related to the use of high-risk populations (eg, children of atopic parents) versus a general population-based sample or could be attributable to study differences in the numbers and types of aeroallergens tested. For example, Sandin et al[17] reported a 7% prevalence of skin test positivity at age 1 year to at least 1 of 5 allergens (egg, milk, timothy, birch, and cat) in a general population of Swedish infants. A study of 376 high-risk English infants of SPT+ parents found that 16% exhibited a positive skin test to a small allergen panel (ie, *D. pteryonyssinus*, cat, dog, grasses, egg, and milk).[14] This lower overall prevalence of sensitization compared with findings in our high-risk cohort may be due to the use of a restricted aeroallergen panel or to varying environmental or genetic influences in the background population.

Becker et al[23] reported that 21% of 545 infants born to asthmatic parents were skin-sensitized to at least 1 of a panel of allergens (ie, milk, egg white, wheat, soy, peanut, cat, dog, cockroach, and 2 mold allergens). Their panel differed from that used to skin test infants in our study by the notable absence of pollens. Becker et al noted that the frequency of allergen sensitization dropped to 14% by age 2 years, indicating that this change was due primarily to a decrease in percutaneous reactivity to food allergens.[23] Their finding contrasts with findings in the CCAAPS cohort in which the allergen sensitization rate rose from 28% during infancy to 41% in year 2, with the increase attributable to a higher prevalence of positive skin tests to aeroallergens. The lower prevalence of infantile sensitization reported by Becker et al could be related to the fact that parental atopic status was not confirmed by skin testing or that the more restricted allergen panel that excluded pollens failed to identify all sensitized subjects.

The fact that almost 10% of the infants were SPT+ to pollens raises particular concerns. Two of the 3 most prevalent aeroallergen sensitizations in the CCAAPS cohort were to outdoor allergens: timothy (2.9%) and maple mix (2.5%). This finding has important implications for skin testing in young children. Children with an atopic family history and symptoms could be evaluated by allergen skin testing even before age 1 year, including outdoor allergens. Allergists sometimes limit skin testing of young infants to foods and indoor allergens, but according to our data, this practice would miss some sensitized infants. Although the prevalence of pollen sensitization in children may indicate that the peak occurs later, the onset appears to begin earlier than previously reported.

We found no concordance between parent and child sensitization to either specific aeroallergens or categories of allergens. This lack of agreement may be because the prevalence of specific aeroallergen sensitization in infancy is relatively low compared with that in adults. Alternatively, the heredity of atopy may not be allergen-specific. Our findings support those of a multigenerational study of 100 families in which complete allergen tests were available for both parents and 2 children.[24] Their findings demonstrated that the probability that a child is sensitized to a specific allergen is independent of whether or not 1 or both of his or her parents were sensitized to the same particular allergen. In addition, we found that only 1 allergen in

the parent—*Cladosporium*—was significantly associated with their infant *not* being sensitized. Thus, we conclude that the general propensity for parental atopy (symptoms and sensitization), rather than the specific *pattern* of parent sensitization, is a high-risk factor for childhood sensitization.

Another aim of this study was to efficiently identify atopic parents from a general population cohort. Identifying key symptoms also has important clinical applications for determining which adults need allergy testing or for identifying potentially high-risk infants of atopic parents. The preciseness of the questions in the ASQ was apparent in its ability to correctly identify more than 70% of the parents who reported symptoms as atopic using 12 brief questions. As demonstrated by the cluster analysis, these 12 questions can be further reduced to 4, which can be reliably answered by either self or spouse report.

This study evaluated a large panel of aeroallergens and found a high rate of aeroallergen sensitization in infants. These findings have broad public health implications, particularly in relationship to outdoor pollen allergies, because others have shown that although dust mite and cat allergies decline with age, pollen allergies increase with age.[25] It is intriguing to speculate whether a more aggressive approach by clinicians to the early identification of, and intervention for, childhood allergies would lead to a reduction in the incidence or severity of allergic disease. For this reason, these infants are being studied prospectively to determine the significance of early sensitization to aeroallergens and the potential for future development of allergic disease.

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Glossary

ASQ
: Allergy symptom questionnaire

CCAAPS
: Cincinnati Childhood Allergy and Air Pollution Study

CI
: Confidence interval

ISAAC
: International Study of Allergies and Asthma in Childhood

NHANES

National Health and Nutrition Examination Survey

OR

Odds ratio

SPT

Skin prick test

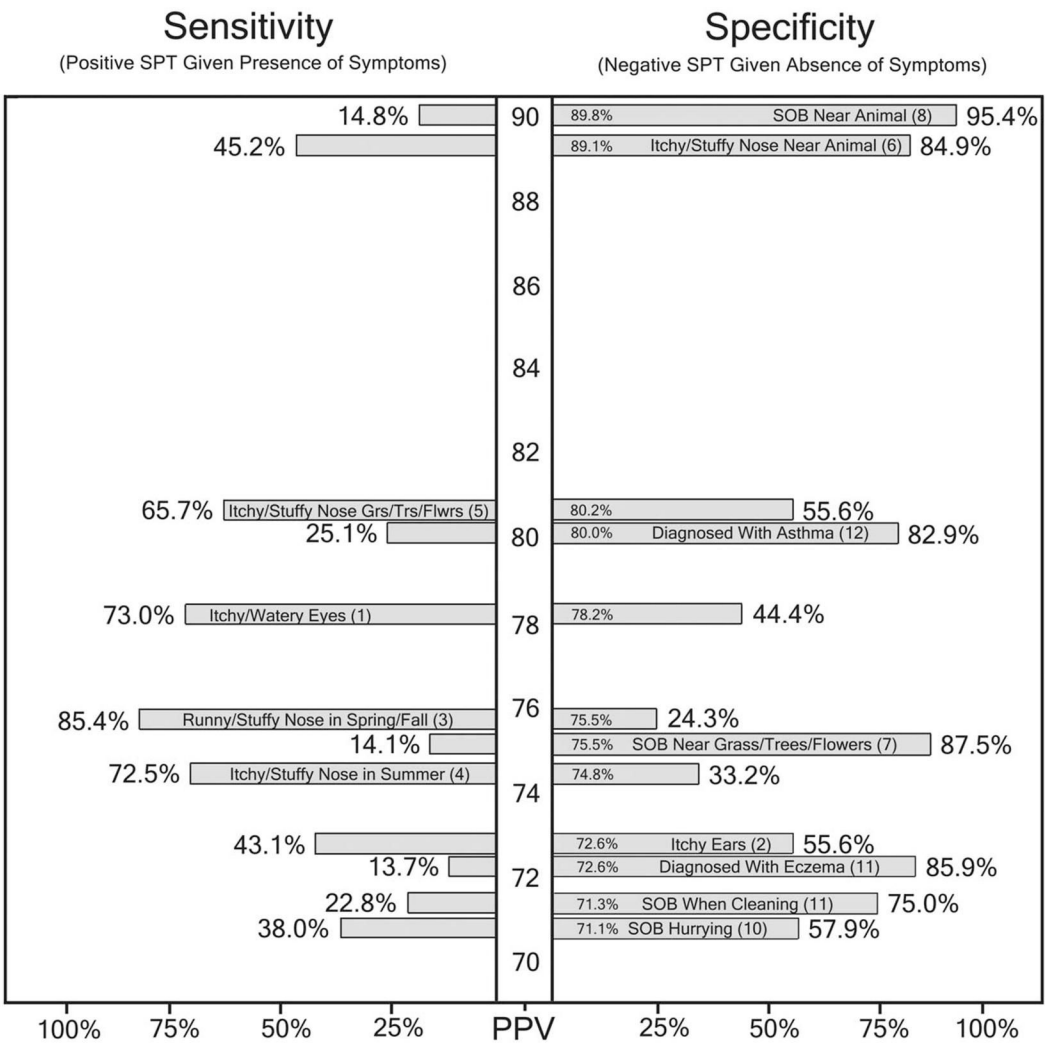

Figure.
Positive predictive value, sensitivity, and specificity of parent allergy symptoms compared with positive SPT.

Table I

Percent of tested parents (n = 1134) with reported symptom

Reported symptoms	% Reported symptom
Do you or your baby's other biological parent have problems with any of the following:	
(1) Itchy/watery eyes?[a]	68.3
(2) Itchy ears?[c]	43.5
(3)[a] Problems with sneezing or a runny, or stuffy nose without a cold or flu during the spring or fall?	82.8
(4)[b] An itchy or stuffy nose or sneezing during summer months?	71.0
(5)[b] An itchy or stuffy nose or sneezing when near grass, trees, or flowers?	60.0
(6)[b] An itchy or stuffy nose or sneezing near animals?	37.1
(7)[b] Shortness of breath when near grass, trees, or flowers?	13.7
(8)[b] Shortness of breath near animals?	12.1
(9)[b] Shortness of breath when cleaning rooms, making beds, or when in bed?	23.4
(10)[b] Shortness of breath when hurrying on level ground or walking up slight hills?	39.1
(11)[a] Ever been diagnosed with eczema?	13.8
(12)[a] Ever been diagnosed with asthma?	22.9

[a] Sources: Nielsen, et al, Glostrup Allergy Study;

[b] Asher et al, ISAAC;

[c] Clinician recommended

Table II

Prevalence of atopy by aeroallergen for all tested parents and their infants at age one[1]

Category	Individual Allergens	(1) Tested Parents With Symptoms n = 1134 %	(2) SPT+ Parents With at Least One SPT+ n = 664[2] %	(3) Tested Infants With Parent SPT+ and Symptom n = 680 %	(4) SPT+ Infants With at Least One SPT+ n = 193 %
Pollen	Meadow fescue	37.3	52.1	1.3	4.7
	Timothy	38.4	53.8	2.9	10.4
	White oak	21.6	30.3	1.8	6.2
	Maple mix	23.4	32.4	2.5	8.8
	American elm	16.5	23.0	1.0	3.6
	Red cedar	12.3	15.2	1.9	6.7
	Short ragweed	43.1	60.4	1.2	4.1
Mold	*Alternaria*	18.0	26.4	2.5	8.8
	Aspergillus fumigatus	7.8	11.0	2.1	7.3
	Penicillium	5.6	6.9	1.5	5.2
	Cladosporium	18.2	23.0	2.6	9.3
Dust	Dust mite	30.9	42.0	3.1	10.9
	German cockroach	9.4	11.4	1.8	6.2
Animal	Cat	21.0	29.7	2.5	8.8
	Dog	9.0	12.5	1.3	4.7
Food	Milk	—	—	4.7	16.6
	Egg	—	—	12.2	43.0
	Allergens by Category				
	Pollen	62.3	86.4	9.7	34.2
	Pollen only	14.7	20.5	4.4	15.5
	Mold	37.0	49.8	7.5	26.4
	Mold only	1.5	1.5	2.6	9.3
	Dust	35.7	47.7	4.3	15.0
	Dust only	3.1	4.1	1.3	4.7
	Animal	25.0	35.1	3.5	12.4
	Animal only	1.6	2.3	0.7	2.6
	Food (regardless of aero)	—	—	14.7	51.8
	Food only	—	—	10.4	36.8
	Aeroallergen (regardless of food)	—	—	18.0	63.2
	Aeroallergen only	—	—	13.7	48.2
	Both Aero and Food	—	—	4.3	15.0
	Positive to Any	73.2	100.0	28.4	100.0

[1] All prevalence values are per total number tested

[2] There were 16 sets of twins resulting in 664 parents tested and 680 infants tested