

The spectrum of aeroallergen sensitization in children diagnosed with asthma during first 2 years of life

Umit Murat Sahiner, M.D., Ayse Betul Buyuktiryaki, M.D., Suleyman Tolga Yavuz, M.D., Ebru Arik Yilmaz, M.D., Ozlem Cavkaytar, M.D., Ayfer Tuncer, M.D., and Bulent Enis Sekerel, M.D.

ABSTRACT

*Aeroallergens may trigger symptoms in sensitized children with asthma. Documentation of sensitization is crucial to enable effective implementation of measures to prevent asthma exacerbations. To document the sensitization patterns of very young children (≤ 2 years) with asthma, we retrospectively analyzed the skin-prick test (SPT) results of the largest referral center in the country. During a 4-year period, 432 children (median age, 1.21 years; male/female, 2.35) were referred. All patients had recurrent wheezing attacks and good response to inhaled bronchodilators and were diagnosed with asthma by their referring physician. SPT with eight aeroallergens (grass mix, weed mix, tree mix, mold mix, house-dust mite, cockroach, cat, and dog) was performed in 209 patients (full panel group) and the remaining 223 were tested only with a mixture of two house-dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*; house-dust mite group). The sensitization rates in house-dust mite and full panel groups were 3.2% (7/223) and 3.3% (7/209), respectively. Univariate and multivariate modeling was unable to identify a predictor for the presence of aeroallergen sensitization. During first 2 years of life, low rates of aeroallergen sensitization and lack of predictors of sensitization in children with asthma suggest that skin testing for aeroallergens may not be a routine procedure. When there is a high index of suspicion, testing only for indoor aeroallergens including house-dust mites, molds, and pets may identify the majority of sensitized children.*

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IgE-mediated sensitization may be determined by an allergen-specific IgE in the serum and/or skin-prick tests (SPTs) using the suspected allergens.^{1,2} The SPT is the standard for the diagnosis of IgE-mediated allergic diseases.² Those allergens to which we become frequently sensitized play an active role in driving sensitization. Properties of allergens clearly have a direct role in influencing allergic diseases as do the airway epithelial cells.³ Exposure to aeroallergens triggers symptoms in sensitized patients with asthma and documentation of sensitization is crucial to enable effective implementation of measures to prevent asthma exacerbations.^{4–7} The SPT is done either to identify the allergen responsible for an IgE-mediated allergic disease in clinical practice or to determine the sensitization patterns of different populations in epidemiological studies. The incidence of aeroallergen sensitization in very young children in different risk groups reported by previous studies has a wide range.^{8–15} Previous studies performed with very young children were mostly related to the prevalence and natural course of the sensitization patterns of aeroallergens on

an epidemiological basis in healthy children or in those at high risk for allergic diseases. Some studies also tried to determine the predictive value of aeroallergen sensitization for the subsequent development of allergic diseases.^{9,10,12–16} The issue was not approached from a clinical management point of view.

The aim of the present study was to show the sensitization patterns of aeroallergens among very young children diagnosed with asthma and to determine factors that predicted sensitization, if it existed.

METHODS

Patients

This retrospective study used the SPT database of the Pediatric Allergy and Asthma Unit of Hacettepe University İhsan Doğramacı Children's Hospital, Ankara, Turkey. Although the clinic serves as a referral center for the entire country, patients may be seen without a referral. Thus, it functions as both a primary and a tertiary health care service. The SPT results from very young children with the diagnosis of asthma (≤ 2 years) who were referred for testing for aeroallergen sensitization were analyzed within the last 4 years (January 2007–December 2010). This study period was chosen because reliable records were available within this span of time. All children had a history of at least three wheezing attacks with good response to bronchodilators and had been diagnosed with asthma by their referring physicians. Of the entire study group, 209

From the Department of Pediatrics, Pediatric Allergy and Asthma Unit, Hacettepe University School of Medicine, Ankara, Turkey

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Address correspondence to Bulent Enis Sekerel, M.D., Pediatric Allergy and Asthma Unit, Hacettepe University Faculty of Medicine, 06600 Ankara, Turkey

E-mail address: b_sekerel@yahoo.com

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were skin-prick tested with a standard panel consisting of eight aeroallergens (full panel group) and 223 children were tested only with a mixture of house-dust mite allergens (house-dust mite group), based on the decision of the physician evaluating them at the time. All patients were free of medications which interfere with the SPT results for at least 1 week before the testing. The study protocol was approved by the Ethical Committee of Hacettepe University (approval number of the study protocol was B.30.2.HAC.0.20.05.04/1039,11.08.2011). Informed consent could not be provided because it is a retrospective study.

SPT Procedures

Patients were subjected to SPT on their upper back. The house-dust mite group was tested with a mixture of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, and the full panel group was tested with a house-dust mite mixture (*D. pteronyssinus* and *D. farinae*), *Blattella germanica*, cat, dog, mold mixture (*Alternaria alternata* and *Cladosporium herbarum*), weed mixture (*Parietaria judaica*, *Chenopodium alba*, *Artemisia vulgaris*, *Plantago*, and *Salsola kali*), tree pollen mixture (*Corylus avellana*, *Betula alba*, *Populus alba*, *Platanus vulgaris*, *Olea europaea*, *Ulmus campestris*, *Quercus robur*, and *Salix caprea*), and grass mixture (*Poa pratensis*, *Festuca pratensis*, *Phleum pratense*, *Avena sativa*, *Dactylis glomerata*, and *Lolium perenne*). The positive control for both groups was histamine (10 mg/mL of histamine phosphate) and the negative control was 0.9% sterile saline. Standardized SPT extracts (Stallergenes, Antony, France) were used and SPTs were evaluated 15–20 minutes after application and were considered positive if the mean wheal diameter was ≥ 3 mm greater than the negative control. The SPT was performed using the Stallerpoint prick device (Stallergenes) with gentle vertical pressure and 90° clockwise rotation. All skin tests were performed by two experienced nurses and evaluated by clinic physicians. Each nurse had previously been shown to have a coefficient of variation for the SPT of $<15\%$. Sensitization was considered to have occurred when there was a positive SPT to at least one of the allergens.

Statistical Analysis

The prevalence of sensitization to each aeroallergen was first determined using frequencies and percentages. Statistical analyses included univariate and multivariate analyses and odds ratios with relevant 95% confidence intervals. These analyses were performed to evaluate the potential associations between various predictors (and various combinations of predictors) and aeroallergen sensitization. A value of $p < 0.05$ was considered statistically significant. The SPSS 16.0 soft-

ware program (SPSS, Inc., Chicago, IL) was used for statistical analysis.

RESULTS

A total of 432 children with a median (interquartile) age of 1.21 (0.85–1.64 years) years and a male/female ratio of 2.35 were analyzed in this study. The familial atopy rates in the entire group, full panel group, and house-dust mite group were 19.2, 23.4, and 15.2%, respectively. The rates of having current atopic dermatitis were 8.8, 10.0, and 7.6%, respectively. The characteristics of the study group are summarized in the Table 1.

Of the entire study group, 223 children were skin-prick tested for house-dust mites and a sensitization rate of 3.2% (7/223) was found. In the full panel group ($n = 209$), eight aeroallergens were tested and an overall sensitization rate of 3.3% (7/209) was found. The sensitized aeroallergens were house-dust mites in three children and one child was found to be sensitized in each of the following groups: tree mix, grass mix, mold mix, and dog allergens. The overall sensitization to indoor aeroallergens in the full panel group was 2.4%. Although there was a trend toward increased sensitization rates with increasing patient age within the full panel group (0–6 months, 6–12 months, 12–18 months, and 18–24 months), this trend did not reach statistical significance (Fig. 1).

In the univariate and multivariate analysis, none of the factors, both individually and in combination, including gender, age, prematurity, prenatal and postnatal cigarette smoke exposure, familial atopy, breastfeeding, number of family members, number of children, total IgE levels, eosinophilia, and animal exposure were found to be related to the presence of aeroallergen sensitization.

DISCUSSION

In the present study, we identified the sensitization patterns of very young children, diagnosed with asthma, to aeroallergens and defined the number and spectrum of SPT allergens required to identify a child as sensitized. We found that only a minority of these children (3–4%) was sensitized and that the majority of these were sensitized to indoor allergens. Furthermore, we were unable to identify any patient characteristic, either alone or in combination that could predict the presence of aeroallergen sensitization.

Previously, a number of studies focused on aeroallergen sensitizations in very young children. However, the methodology, inclusion criteria, disease definitions, diagnosis, age groups, markers of atopy, testing procedures, and allergen selection vary considerably between studies,^{8–15} making it difficult to compare the results of different studies (Table 2). The most similar

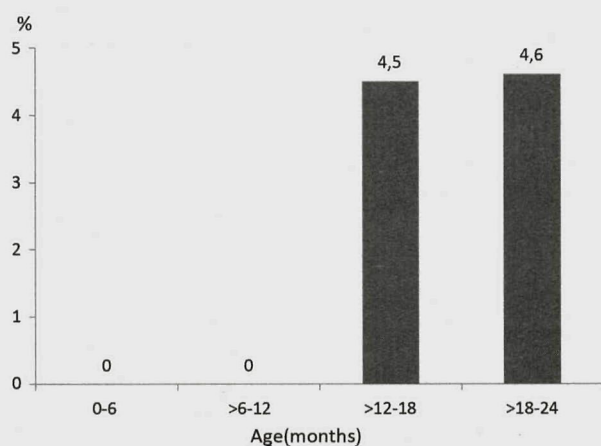
Table 1 Characteristics of the study group

	House-Dust Mite Group <i>n</i> = 223	Full Panel Group <i>n</i> = 209	Whole Group <i>n</i> = 432
Age (yr)*	1.06 (0.79–1.50)	1.35 (0.98–1.73)	1.21 (0.85–1.64)
Gender <i>n</i> , M/F (M %)	152/71 (68.2%)	151/58 (72.2%)	303/129 (70.1%)
Total IgEkU/L*	17.0 (6.7–50.7)	23.0 (6.0–78.3)	19.6 (6.5–66.5)
Eosinophil %*	2.8 (1.8–4.4)	2.6 (1.7–4.2)	2.7 (1.7–4.3)
Prematurity (%)	15.7%	10.5%	13.2%
Prenatal cigarette exposure history (%)	9.0%	8.1%	8.5%
Breastfeeding* (mo)	12.0 (8.5–18.0)	9.0 (7.0–16.0)	11.5 (7.2–18.0)
Familial history of atopy (%)	15.2%	23.4%	19.2%
Food sensitization in SPT (%)	6.3%	3.3%	4.8%
Atopic dermatitis (%)	7.6%	10.0%	8.8%
No. of children in the family*	0.82 ± 0.80	0.93 ± 0.92	0.88 ± 0.86
No. in the household**	3.73 ± 0.78	3.9 ± 1.0	3.83 ± 0.93
Animal exposure at home in the first 2 yr (%)	4.0%	3.3%	3.7%

*Median (interquartile).

**Mean ± SD.

SPT = skin-prick test.

Figure 1. Rates of aeroallergen sensitization in different age groups (full panel group, *n* = 209).

study to ours was one that was performed in Boston, by Sheehan *et al.*⁹ In that study, children who had been referred for SPT to the pediatric allergy program for any reason were evaluated retrospectively.⁹ Among the 204 children included in the study, aged 0–2 years of age, a sensitization rate of 26.5% was found. The most common allergens were cats and dogs followed by house-dust mites.⁹ In our study, we found much lower sensitization rates and 75% of all sensitizations were actually caused by house-dust mites (3.3% in the house-dust mite group and 2.3% in the whole study group). Only one child was sensitized to dog and there was no cat sensitization. Although it is becoming an increasing trend, keeping pets (cats and dogs) in the home is uncommon in our country because of religious and traditional factors.^{17,18} In our recent study, we

documented a pet sensitization (cat and dog) rate of 6.8% in children aged 2–18 years,¹⁹ which was similar to a previous population-based study from the same region.²⁰ However, in western countries, the practice of keeping pets in the home has an incidence of up to 35% for cats and dogs,²¹ leading to sensitization rates between 18.4% (Belgium) and 42.1% (Switzerland).²² Although the study by Sheehan *et al.*⁹ did not give the prevalence of pets in the home, the high prevalence of cat and dog sensitization suggests that many of the patients had pets at home and this may explain the difference in prevalence rates between their study and the present study.

The study by LeMasters *et al.* found an aeroallergen sensitization rate of 18.0 and 36.3% at the ages of 1 and 2 years, respectively, in high-risk children with parental atopy,¹⁰ with pollens, molds, and house-dust mites being the most common aeroallergens. We believe that the prerequisite characteristic of parental atopy of the study group may partly explain the high frequency of sensitization compared with our study. They also showed that there was no concordance between parent and child sensitizations.¹⁰ In the Prevention of Early Asthma in Kids study, Guilbert *et al.* evaluated children with recurrent wheezing at high risk for the development of childhood asthma with a mean age of 3 years. Within this high-risk cohort, a 54% aeroallergen sensitization rate was found.²³ However, having sensitization to an aeroallergen was one of the inclusion criteria, and this may explain the differing results between their study and ours. A study from England by Dean *et al.* reported aeroallergen sensitization rates of 1.3, 6.4, and 10.7% at the ages of 1, 2, and 3 years,

Table 2 Aeroallergen sensitizations in children at young ages in different populations

Author/country (yr)	Study group	Age, Number	Aeroallergen Sensitization	Aeroallergens Found
Halmerbauer ⁸ /Europe, 2003	Infants at increased atopy risk	1 yr, <i>n</i> = 696	5.0%	House-dust mite (only tested aeroallergen)
Sheehan ⁹ /United States, 2010	Children with allergy referred to allergy clinic	0–2 yr, <i>n</i> = 204	26.5%	Dog, cat, house-dust mites, tree, mice, roaches, grass, and weed
LeMasters ¹⁰ /United States, 2006	High-risk infants	1 yr, <i>n</i> = 680	18.0%	Pollens, molds, house-dust mite, cockroach, dog, and cat
Vasar ¹¹ /Estonia, 2000	Population-based birth cohort	6 mo, <i>n</i> = 170 12 mo, <i>n</i> = 220 24 mo, <i>n</i> = 222	6 months, 0% 12 mo 3.5% 24 mo 7.0%	Cat, dog, house-dust mite, and birch
Arshad ¹² /United Kingdom, 2001	Population-based birth cohort	4 yr, <i>n</i> = 981	19.2%	House-dust mite, grass pollen, cat, <i>Alternaria</i> , dog, and <i>Cladosporium</i>
Julge ¹³ /Estonia, 2001	Population-based birth cohort	0–5 yr, <i>n</i> = 213	7% at 0.5, 1, and 2 yr of age and 3% at 5 yr of age (including cows milk, and egg white allergy)	Cat, dog, house-dust mite, and birch, and at age 5 yr, timothy
Dean ¹⁴ /United Kingdom, 2007	Population-based birth cohort	0–3 yr, <i>n</i> = 543	1.3, 6.4, and 10.7% at ages 1, 2, and 3 yr	House-dust mite, cat, and grass pollens
Kjaer ¹⁵ /Denmark, 2009	Population-based birth cohort	0–6 yr, <i>n</i> = 562	2.4, 4.5, and 13% at ages 1, 3, and 6 yr	House-dust mite, cat, dog, grass, birch, and horse
Present study/Turkey, 2012	Children with asthma referred to allergy clinic	0–2 yr of age, <i>n</i> = 432	3.3%	House-dust mite, dog, grass mix, mold mix, and tree mix

respectively, in a population-based cohort.¹⁴ Frequency of sensitization to each aeroallergen was below 1% in the 1st year of life. However, when the children were 3 years old, their house-dust mite sensitization reached 7% and their cat sensitization reached 3.7%.¹⁴ Kjaer *et al.* evaluated the natural course of sensitization in an unselected, population-based cohort and found overall aeroallergen sensitization rates of 2.4 and 4.5% at 1 and 3 years old, respectively. Interestingly, they observed that children with early sensitization to aeroallergens had no increased risk of allergic disease at age 6 years.¹⁵ Overall, the aforementioned studies were mainly conducted in western populations and the sensitization rates of aeroallergens vary significantly within western countries and were mostly higher

than our results even in unselected, population-based studies. In addition, these studies showed aeroallergen sensitization changes and increases with age throughout childhood. Similar to this finding, we previously showed that aeroallergen sensitization rates increased in conjunction with an increase in age as follows: 16.1% for 2- to 6-year-old patients (preschool children), 43.1% for 6- to 12-year-old patients (school children), and 55.1% for 12- to 18-year-old patients (adolescents).¹⁹

There are a limited number of studies from developing countries concerning the sensitization rates in young patients. Voor *et al.* compared the sensitization patterns and atopic dermatitis rates of Estonian and Swedish children and found much lower rates of both

atopic sensitization and atopic dermatitis in Estonia.²⁴ They evaluated 109 Estonian children and did not find any aeroallergen sensitization at 1 year of age. However, four children were sensitized to cats, one child to cockroaches, and one child to house-dust mites at the age of 2 years.²⁴ In another study, Julge *et al.* determined the sensitization in a birth cohort of Estonian children and found a 2.8% sensitization rate to aeroallergens at 1 year of age (most commonly house-dust mite followed by cat).²⁵ These findings were similar to our results in that young children have low rates of sensitization, as measured by SPTs, and mainly indoor allergens were the cause of sensitization when it occurred.

We found lower aeroallergen sensitization rates in very young children with asthma symptoms compared with studies performed in western countries. There may be several reasons for this finding. First, in very young children, mainly the indoor allergens are the major causes of sensitization. In cultures where the practice of keeping pets in the home is low, having low cat and dog sensitization rates as in our study is an expectation. Second, house-dust mite and cockroach sensitization rates were also found to be low in addition to the low sensitizations of pollens. This may be explained by the unfavorable climate properties of our region for house-dust mites because it belongs to the Csb (warm temperature, dry and hot summer) climate regions in contrast to most western countries that belong to the Cfb (warm temperature, fully humid, warm summer) and Dfb (snow, fully humid, warm summer) climate regions according to the Köppen-Geiger climate map.²⁶ Another possible explanation may be the young ages of the children. Especially in geographical regions similar to ours 2 years of life may not be enough for the aeroallergen sensitizations to develop. Genetic factors may also explain the difference, although the methodology of the studies differs considerably.

In our previous study, we found that the proportion of aeroallergen sensitization in children with a history suggestive of respiratory allergy increases as children age. The present article is complementary to this article and extends its finding by showing that almost 3% of very young children (0–2 years) are sensitized if tested using the same methodology and inclusion criteria.

Guidelines for SPT and/or specific IgE measurement promote routine testing for patients with a history suggestive of an allergic disease.²⁷ However, these recommendations are solely based on patient history. As it was shown in our study, the age of the patient and the type of disease need to be taken into account. For instance, in the case of a very young child with asthma, the low probability of having a positive test result, test-related discomfort (pain), low tolerance of test-related stress, and optimum use of limited health re-

sources are our major reasons for not performing routine SPTs.²⁸ It may be better to perform SPTs with only indoor allergens or to postpone the testing until the child is older or to give the test to a younger child with the intention to repeat the test when the child is older. Our results conflict with the very recent European Academy of Allergology and Clinical Immunology position statement, which reflects the consensus reached by the authors of the statement.²⁹ It is a well-known fact that children are not born with aeroallergen sensitization, but rather that they acquire them after several exposures in a time-dependent manner. Moreover, during the early years of life, children spend relatively more time doing indoor activities compared with older children. Thus, it is a logical conclusion that there is less of a possibility of an outdoor aeroallergen sensitization in the early years of life when compared with later ages, and this hypothesis is supported by our study.¹⁹

We could not determine any predictive factors or combination of factors that could predict the presence of aeroallergen sensitization in our young-aged study group. Because the study population was very young, it is likely that none of the potential risk factors have had enough time to effect the development of sensitization to aeroallergens.

As with most studies, there are some limitations to the current study. First, this is a study designed to focus on children with complaints of respiratory symptoms, so this is a patient-based survey and the results may differ from epidemiological studies. Second, we documented sensitizations but we did not investigate whether they were able to trigger symptoms. Third, the precise diagnosis of asthma in this age group is always problematic and some may suggest that the study group includes wheezing phenotypes that are actually not associated with atopy. However, these children were referred with a diagnosis of asthma and have a clear history of recurrent episodes and a good response to short-acting β_2 -agonists. In fact, the study population reflects clinical practice and the main aim of the study is to document what physicians faced in their daily clinical practice. Finally, it should be kept in mind that when trying to determine a predictive factor, the patients' demographic characteristics were included but we were unable to use the history of exposure trigger, because it was a retrospective study. However, it is interesting to note that all of our patients were referred by their physicians to our allergy clinic because of histories that were highly suggestive of allergic sensitization.

In conclusion, the low rates of aeroallergen sensitization in young children (0–2 years) with asthma symptoms suggest that aeroallergen testing may not be a routine procedure, at least in similar geographic and cultural areas. None of the demographic characteristics

predicted the presence of sensitization and in patients where there is a high index of suspicion, testing only for indoor allergens may document the majority of sensitized children.

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