

Skin sensitization in asthmatic children less than 36 months of age

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Background: Atopy is reported to play an insignificant role in wheezing during infancy in contrast to later childhood. For this reason skin testing may not be included in a workup of wheezing infants.

Objective/Method: In order to evaluate the degree and evolution of skin sensitization to allergens in infants with asthma, we have retrospectively analyzed the skin test results from 40 referred asthmatic children less than 36 months of age, who had had more than three wheezing episodes and whose symptoms improved on treatment with beta-agonist and anti-inflammatory agents.

Results: Skin sensitization (epicutaneous) to common indoor and outdoor aeroallergens and foods were demonstrated in 23 (58%) of these patients. Asthmatic children with the onset before 12 months of age and duration of less than 12 months were sensitive predominantly to foods. Those with later onset asthmas and longer duration developed sensitivity first to indoor and then to outdoor allergens. The most common food, indoor, and outdoor allergens were egg, dust mite, and pollens, respectively. Six of these patients had repeat skin tests later. Two demonstrated a decrease in skin sensitivities to foods, one gained a new sensitivity to grass, while three remained unsensitized.

Conclusion: Skin sensitization to allergens was common in selected asthmatic infants and evolves in the order of exposures: foods, indoor allergens, and outdoor allergens. Repeat skin tests showed changing skin test patterns in some patients.

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INTRODUCTION

More than two-thirds of older children with asthma demonstrate skin sensitization to various allergens.^{1,2} In comparison, only a minority of wheezing infants show evidence of allergic sensitization,^{3,4} unless simultaneously affected by atopic dermatitis.⁵ Some data^{6,7} also indicate that atopy during the first 2 years of life as demonstrated by either positive skin tests or RAST has little predictive value for the development of asthma.

Since the above articles described wheezing infants seen in emergency rooms or asymptomatic infants followed up for the prospective study, we

decided to study a group of infants referred to our allergy clinic with persistent wheezing. Our objective was to investigate to what extent these "asthmatic" infants develop positive skin tests to common allergens and to analyze the patterns and evolution of skin sensitivity according to the age of onset, and the duration, of asthma.

METHODS

Selection of Patients

The study population comprised children with histories of wheezing who were referred to an allergy and immunology clinic of CIGNA Healthcare of California. Forty patients were selected on the basis of the following criteria:

- children less than 36 months of age,
- a history of wheezing more than three times,
- a history of response to beta-agonist therapy, and

- currently symptomatic requiring beta-agonist rescue treatment in addition to the anti-inflammatory medicine; either a corticosteroid or cromolyn.

These children were defined as having asthma. Allergy evaluation included detailed nutritional and family history, and a history of exposures to maternal smoking and other environmental factors. Family history included presence of current or past asthma and/or rhinitis in parents and siblings. Patients were evaluated for skin reactivity to indoor, outdoor, and food allergens.

Skin Tests

Epicutaneous tests were administered with 1:20 (wt/vol) commercial extracts (Allermed, San Diego, CA) in 50% glycerin using Multi-test (Center Laboratories, Port Washington, NY) on the back. Histamine (1.8 mg/mL) and normal saline were used as a positive and negative control, respectively. The skin test scores were assigned as 0 to 4+, depending on the wheal size: 0 = a wheal size equal to or smaller than saline control, 3+ = a wheal size equal to histamine control, and 4+ = a wheal size larger than histamine control, 2+ = a wheal size greater than 0 by more than 50% of the difference in wheal size between 0 and 3, and +1 = a wheal size greater than 0 by less than 50% of the difference in wheal size between 0 and 3.

Skin tests were defined as positive only when the scores were 2+ and above to avoid over-reading. For example, a wheal size measuring 7 mm, with histamine control of 14 mm and saline control of 2 mm, would be scored +1, since the wheal size was greater than 0 by 5 mm (7 mm - 2 mm), which was smaller than 50% (6 mm) of the difference in wheal size between 3 and 0 (14 mm - 2 mm = 12

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mm). The allergens were used for skin tests were dust mite (*D. pteronyssinus* and *D. farinae*), cat, dog, indoor mold mixture, outdoor mold mixture, tree mixture, grass mixture, weed mixture, egg, milk, peanut, wheat, and soy.

Indoor mold mixture contained *Aspergillus* and *Penicillium*. Outdoor mold mixture contained *Alternaria* and *Cladosporium*. Weed mixture contained false ragweed, careless weed, pigweed, lenscale, shadscale, wing-scale, lamb's quarters, Russian thistle, burning bush, English plantain, and sagebrush. Tree mixture contained elm, oak, olive, mulberry, and ash. Grass mixture contained Kentucky bluegrass, Bermuda grass, smooth brome grass, Johnson grass, perennial rye, and wild oat.

RESULTS

The age range for 40 asthmatic children was from 8 months to 35 months with the mean of 22 months. There were more boys than girls (24:16). Twenty-three (58%) demonstrated skin sensitization to at least one allergen, 15 (38%) to food allergens, 13 (32%) to indoor allergens, and 10 (25%) to outdoor allergens.

To determine whether the manifestation of skin sensitivity was related to exposure to potential allergens in a temporal fashion, patients were divided into four groups depending on the age of onset and the duration of asthma at the time of skin testing (Table 1). We reasoned that exposure to indoor and outdoor aeroallergens would increase as children began to ambulate. Hence, 12 months of age was used to divide these children into the separate groups. We also postulated that the longer the duration of asthma, the likelier the chance of exposure to different kinds of allergens. The duration of 12 months was chosen as an arbitrary dividing line.

Skin test results from four groups of asthmatic children are summarized in Table 1. The details of the sensitization status of each group follow.

Among 12 asthmatic infants whose asthma started before 12 months of age and lasted less than 12 months, seven

Table 1. Skin Test Results of Asthmatic Children Depending on the Age of Onset and the Duration of Asthma

Onset of Asthma	Duration of Asthma	
	<12 months	≥12 months
<12 months		
Number of patients	12	13
Mean age (mo)	12	23
Age range (mo)	8–16	19–32
Sex ratio (M/F)	6/6	8/5
Skin test +	7 (58%)	6 (46%)
Indoor	0	3 (23%)
Outdoor	1 (8%)	3 (23%)
Food	7 (58%)	4 (31%)
≥12 months		
Number of patients	6	9
Mean age (mo)	26	29
Age range (mo)	20–32	20–35
Sex ratio (M/F)	5/4	5/4
Skin test +	3 (50%)	7 (78%)
Indoor	2 (33%)	4 (44%)
Outdoor	2 (33%)	4 (44%)
Food	2 (33%)	2 (22%)

patients (58%) had positive skin test results. All of these patients were sensitive to foods; four to egg, two to milk, and one to peanut. One patient showed sensitivity to grass in addition to egg.

In 13 patients whose asthma started before 12 months of age and lasted for 12 months or longer, six (46%) demonstrated positive skin test reactions. Three of these were sensitive to indoor allergens (mite: 3 and mold: 1), three to various outdoor allergens (grass: 1, tree: 2, weed: 3, and mold: 1), and four to food allergens (milk: 2, egg: 1, peanut: 1, soy: 1, and wheat: 1).

Among six patients whose asthma started 12 months of age or after and lasted less than 12 months, three (50%) had positive skin test reactions. Two were sensitive to indoor allergens (mite: 2, cat: 1, and mold: 1), two were sensitive to various outdoor allergens (grass: 1 and tree: 1), and two were sensitive to food allergens (milk: 1 and egg: 1).

In nine patients whose asthma started at 12 months of age and after and lasted for 12 months or longer, seven (78%) had positive skin test results. Four of these were sensitive to indoor allergens (mite: 4, cat: 1, dog:

1, and mold: 1), four to various outdoor allergens (grass: 1, tree: 2, and mold: 1) and two to food allergens (egg: 1, peanut: 1, soy: 1, and wheat: 1).

Parental history strongly suggestive of atopy such as asthma and seasonal rhinitis was reported in 19 of 23 (83%) patients with positive skin tests and in 11 of 17 (64%) patients with negative skin tests. Association between parental allergic history and the status of skin sensitivity was not significant (chi square = .825, $P = .356$). Exposure to parental smoking was reported in 9 of 23 (39%) patients with positive skin tests and in 5 of 17 (30%) patients with negative skin tests. Association between smoke exposure and the status of skin sensitivity was not significant (chi square = .091, $P = .763$).

In three of five children with milk sensitivity, wheezing episodes significantly decreased with food elimination. None of the parents of these children suspected milk as a potential cause of asthma. In four of seven children with egg sensitivity, there was no history of egg ingestion. In the remaining three children, elimination of egg did not relieve the symptoms.

Among six patients whose skin tests were repeated 12 months later, three with initially negative skin tests remained unchanged. Of the other three with initially positive skin tests, two lost sensitivity to foods and one developed a new skin test reaction to grass.

DISCUSSION

In contrast to the low prevalence of sensitization to common allergens in unselected wheezing children less than 2 years of age,^{3,4} more than half of our patients demonstrated skin sensitivity to common allergens from early life, although only two were affected by atopic dermatitis. This would indicate that some selected asthmatic children, such as our referrals with recurrent and chronic asthma, had encountered sufficient allergen exposure to incur sensitization of the skin and presumably the lungs.

Parental allergic disorders such as asthma and seasonal allergic rhinitis are commonly cited as risk factors associated with asthma during infancy.^{8,9} Respiratory viruses¹⁰ and maternal smoking^{11,12} may also play a significant etiologic or precipitating role in the disease process during infancy. Our study population had likewise high incidence of parental allergic diseases (75%) and exposure to cigarette smoking in the home (35%) (Table 2). It is interesting to note that there was no statistically significant association between risk factors and the status of the skin test sensitivity; hence, they may be important contributors to

asthma symptoms regardless of skin sensitization.

During early life, contacts with allergens occur most likely in chronological order of significant exposure: foods, then indoor aeroallergens followed by outdoor aeroallergens.¹³ Skin sensitization is therefore expected to evolve along the same pattern. Our data are in keeping with such a paradigm.

The youngest infant group showed the highest (58%) incidence of skin sensitivity to foods (Table 1). Sensitizing allergens were common foods such as milk, egg, and peanut. As reported by others,¹⁴ egg, but not milk, was the most common skin sensitizing food allergen even among infants without a history of egg ingestion.¹⁵ One must assume that egg protein is more allergenic than milk protein and that skin sensitization to egg may have occurred in utero or through breast milk in patients without history of egg ingestion.

With a later onset and a longer duration of asthma, more sensitization to indoor and outdoor allergens was observed (Table 1). Changing patterns of allergen skin test responses have been reported in atopic patients.¹ As shown in three of our six infants who had repeat skin tests 12 months later, asthmatic children may gain allergen skin sensitivities or lose them. The extent of change in skin test responsiveness that occurs in young asthmatic children is not known. We hope to learn more about this by following these and other infants over a longer period of time.

The relevance of skin sensitivity to current clinical symptoms may not be obvious. Among five children with milk sensitivity, only three responded to food elimination. In seven children with egg sensitivity, elimination of egg did not relieve the symptoms. Thus, skin sensitivity may be an atopic response to some common allergens these patients had been exposed to without being currently related to asthma.

Infants with a genetic propensity for atopic disease often develop skin sensitivity before they exhibit allergic symptoms.^{6,12} It is therefore not easy to

say, unless ascertained by allergen challenge tests, which of current skin sensitizing allergens cause symptoms and which predict future symptoms. For example, one of our study subjects, a 20-month-old asthmatic boy with skin sensitivity to mite and grass, may be suffering from allergy induced more likely from mites than from grass because exposure to mite would have antedated that to grass. In other words, it is possible that his lungs are not yet affected by grass allergy, although the skin had been sensitized. As he gets older, his asthma may be aggravated by grass allergy.

Skin sensitization to some allergens may therefore be a predictor of developing asthma. Skin sensitivity to dust mites has been shown to be a risk factor for the development of childhood asthma^{16,17} and a reduction in bedroom dust mites has been associated with a decreased incidence of asthma.^{18,19} Hagy and Settignano et al²⁰ reported asymptomatic college students with positive skin tests had a higher risk of subsequently developing hay fever than students with negative skin tests.

It is important to study skin sensitivities early in the workup of asthmatic infants. The skin test results need to be correlated with clinical symptoms. By avoiding and controlling exposure to the sensitizing allergens, asthma may be treated effectively and even prevented.

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Table 2. Percentage of Asthmatic Children with History of Parental Allergic Diseases and Smoke Exposure

	Parental Allergic Diseases	Exposure to Cigarette Smoke
Skin test + patients (23)	19/23 (83%)*	9/23 (39%)†
Skin test - patients (17)	11/17 (64%)*	5/17 (30%)†

* chi-square = .85, *P* = .36.

† Chi-square = .76, *P* = .76.

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