

Sensitization to food allergens in Iranian children with mild to moderate persistent asthma

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Background: Asthma is the most common chronic respiratory disease in childhood. The clinical presentation of asthma may worsen after food allergen ingestion in sensitized patients. To avoid nonspecific dietary restrictions in children with asthma, laboratory-based advice about foods is potentially helpful. The purpose of this study was to determine food sensitization in children with asthma.

Methods: Seventy-nine children with mild to moderate persistent asthma were included in this study. Commercial food allergens including cow's milk, egg white, almond, potato, and soybean were used in skin prick tests. Specific IgE to 20 common food allergens was also measured in serum.

Results: Twelve (15.2%) of the patients had a positive skin prick test to at least one of the five food extracts. Sensitization was detected by skin prick tests to cow's milk and egg white (each 6.3%), almond (3.8%), potato (2.5%) and soybean (1.3%). Specific IgE levels ≥ 0.35 kAU/L were detected in the serum of 47% of the children with asthma. The most common food allergens were cow's milk (26.6%), hazelnuts (25.3%), wheat flour (15.2%) and egg white (12.6%). Patients with a history of at least one hospital admission due to asthma attack had a higher rate of sensitization to egg.

Conclusions: In our study, food sensitization was frequent in Iranian children with asthma. Although clinical food allergy could not be evaluated because food challenge tests were not used in our study, skin prick

tests and serum-specific IgE to common food allergens might be helpful in identifying children with food sensitization.

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Key words: childhood asthma; food sensitization; serum-specific IgE; skin prick test

Introduction

Asthma is an inflammatory condition resulting in increased bronchial responsiveness and airway narrowing in response to an inhaled or ingested allergen. The World Health Organization estimated that 300 million people in the world suffer from asthma.^[1] The production of IgE after exposure to relevant allergens is one of the major routes of inflammation.^[2] Skin prick tests to detect sensitization (IgE titers) are informative, and are safe and easy to perform. In addition, the determination of specific IgE in serum has become popular in recent years. This assay is safe and unlike skin prick tests, the results are not influenced by skin disease or medications. Several authors have established decision points for serum-specific IgE that predict clinically relevant food allergy.^[3]

Food allergy is an adverse immune reaction to food proteins which can cause immediate serious reactions or chronic disorders. Currently, there is some evidence suggesting that food antigens can provoke bronchial hyperreactivity.^[4] Food is estimated to be a trigger allergen for respiratory symptoms in 4%-8% of all children with asthma.^[5] Children who have food sensitization are at higher risk for hospitalization. Notably, however, the only established therapy for food allergy is recognition of the offending food and strict elimination.

This study was designed to document the relationship between food sensitization and clinical tests in children with asthma. The correlation between hospitalization and food sensitization and the relationship between family history of asthma, atopic eczema and prolonged breast-feeding were determined.

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Methods

This cross-sectional study involved children with asthma referred to an allergy clinic at a university hospital. Following approval of the study protocol by our university's ethics committee, a total of 79 children were enrolled in this study after informed consent was obtained from their parents. All the patients were diagnosed with mild to moderate persistent asthma according to the Expert Panel Report 3 criteria.^[6] The patients ranged in age from 7 months to 5 years (mean 36.6±18.02 months). Asthma was diagnosed on the basis of maternal report of pediatrician diagnosis of asthma or having symptoms such as recurrent (>2) episodes of wheezing, cough, shortness of breath, or a combination of all the three during the survey. Clinical presentations of food allergy including skin, respiratory, cardiovascular and gastrointestinal symptoms within 4 to 8 hours following food ingestion were asked from mothers. Food allergy was determined by gathering explained clinical data and detectable specific IgE for the reported food allergen. Concurrent atopic eczema was determined with the International Study of Asthma and Allergies in Childhood questionnaire.^[7] Family history of asthma, prolonged breast-feeding during infancy and history of hospital admission due to asthma attack were recorded for each patient.

Skin prick tests were done for five food allergens (cow's milk, egg white, almond, potato and soybean) with commercial extracts (Steallergen, Antony, France). Histamine (10 mg/mL) and saline were used as positive and negative controls, respectively. The results were measured 15 minutes after application. Topical corticosteroids (one day) and antihistamines (seven days) were stopped before the skin prick tests. The results of these tests were considered positive when the wheal was 3 mm or greater in diameter than the negative control.

Serum samples were evaluated for specific IgE (R-Biopharm AG, Darmstadt, Germany) to hazelnut, peanut, almond, walnut, milk, egg yolk, egg white, casein, celery, carrot, tomato, potato, cod fish, crab, orange, apple, wheat flour, rye flour, sesame and soybean. All assays were done according to the manufacture's instructions.

On the basis of specific IgE levels to each allergen, the children were divided into 4 groups. Group 1 had food-specific IgE levels ranging from 0.35 to 0.69 kAU/L (low threshold); group 2 had food-specific IgE levels from 0.70 to 3.49 kAU/L (slightly increased); group 3 had IgE levels from 3.5 to 17.49 kAU/L (significantly increased); and group 4 had specific IgE levels from 17.5 to 49.9 kAU/L (high).

Statistical analysis

Statistical analysis was done with the chi-square test in version 6 of Epi Info. *P* values <0.05 were considered statistically significant.

Results

We analyzed IgE results for food allergens in 79 children (39 girls and 40 boys) with mild to moderate persistent asthma. Around 15.2% of the children showed sensitization by skin prick tests for at least one of the food extracts. In a decreasing order of frequency, sensitization was seen to cow's milk and egg white (6.3% each), almond (3.8%), potato (2.5%) and soybean (1.3%). Three children had positive reactions to milk and egg white and one showed positive reactions to almond and milk. The comparison of positive skin prick test results in patients according to their age is shown in Table 1.

Sensitization to at least one of the food allergens (specific IgE ≥0.35 kAU/L) was seen in 47% of the children. Ranges of food-specific IgE levels in children with asthma to different food allergens are shown in Table 2. The comparison of the number of patients with serum-specific IgE to tested food allergens according to their age (children ≤1 year and >1 year) is shown in the Fig.

Table 1. Positive skin prick tests in children with mild to moderate persistent asthma according to age

Allergens	≤1 year (n=11)	>1 year (n=68)	Total (n=79)
Cow's milk	3 (27.3%)	2 (2.9%)	5 (6.3%)
Egg white	2 (18.2%)	3 (4.4%)	5 (6.3%)
Almond	0	3 (4.4%)	3 (3.8%)
Potato	0	2 (2.9%)	2 (2.5%)
Soybean	0	1 (1.5%)	1 (1.3%)

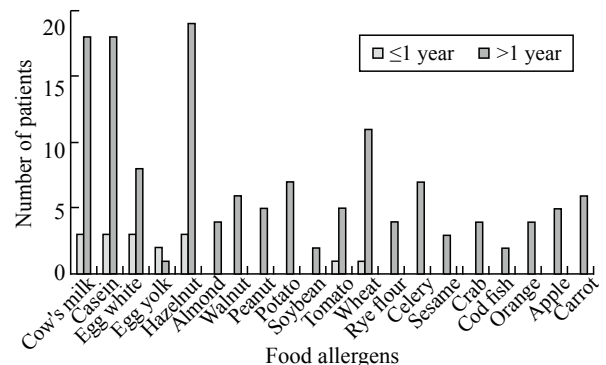


Fig. Comparison of the number of asthmatic children with serum-specific IgE to different food allergens according to age (children ≤1 year and >1 year).

Table 2. Ranges of food-specific IgE levels in children with asthma and sensitization to different foods

Allergens	Group 1	Group 2	Group 3	Group 4
Cow's milk	9	11	1	0
Casein	9	11	1	0
Egg white	3	6	1	0
Egg yolk	2	1	0	0
Hazelnut	13	6	1	0
Almond	1	3	0	0
Walnut	1	4	1	0
Peanut	2	3	0	0
Potato	2	4	1	0
Soybean	1	1	0	0
Tomato	3	1	2	0
Wheat	7	3	2	0
Rye flour	2	0	2	0
Celery	2	3	1	1
Sesame	1	2	0	0
Crab	2	2	0	0
Cod fish	2	0	0	0
Orange	1	2	1	0
Apple	1	2	2	0
Carrot	1	4	1	0

Group 1: low threshold, 0.35-0.69 kAU/L; group 2: slightly increased, 0.70-3.49 kAU/L; group 3: significantly increased, 3.5-17.49 kAU/L; group 4: high, ≥ 17.50 kAU/L.

Skin prick tests and serum-specific IgE were negative in 31 children (39.2%). Thirteen (16.5%) children had food allergy according to their maternal reports, while only 7 (8.8%) of them had specific IgE in their serum (3 serum samples had specific IgE to cow's milk, 3 samples to hen's egg and 1 sample to both celery and cow's milk). Children with specific IgE levels 0.35-3.49 kAU/L (groups 1 and 2) had no maternal report of food allergy.

None of the children with mild to moderate asthma who were sensitized to milk showed sensitization to soybean. Only three children showed sensitization to both egg yolk and egg white.

Fifty (63.3%) out of 79 children had a history of at least one hospital admission for asthma attack. None of the children had a history of admission in pediatric intensive care unit. We found a significant correlation between hospitalization and egg white sensitization (specific IgE ≥ 0.35 kAU/L, $P=0.007$). Almost half of the patients (48%) had a parent with asthma, 26% had a history of atopic eczema and 95% had a history of prolonged breast feeding, but there was no relationship between their asthma and food sensitization. Of the 7 children (8.8%) with food allergy, 6 (86%) had a maternal history of atopic eczema.

Discussion

Food allergy is manifested as an adverse immune reaction to food allergens, and can occur through IgE-mediated, cell-mediated or a combination of IgE and non-IgE mechanisms. The stimulation of IgE-sensitized cells leads to the release of potent mediators which can trigger immediate hypersensitivity.^[2] However, although *in vivo* skin prick tests and *in vitro* serum-specific IgE tests are recognized as the standard tests for measuring specific IgE in immediate-type hypersensitivity, they are not reliable enough to diagnose food allergy, for which food challenge is more reliable. In this study, 15.2% of the children had positive skin prick tests for at least one of the food allergens, and 47% had serum-specific IgE ≥ 0.35 kAU/L. Among 908 children with asthma in China, 37.1% had positive results in skin prick tests for food allergens. This proportion is higher than that in the present study, which might be explained by the use of only five food extracts versus shrimp, tuna and mussel extracts in the Chinese study.^[8]

Although double-blind placebo-controlled food challenge remains the gold standard for diagnosing food allergy, increasing levels of food-specific IgE may be correlated with increasing probabilities of clinical manifestations. In this study, one of the patients showed a very high level of specific IgE to celery. According to the 95% positive predictive value of a food-specific IgE positivity of 53 kAU/L or higher, this patient was considered as one with clinical food allergy.^[2] The history of this patient was also in favor of allergic reaction to celery.

Our data showed that according to serum-specific IgE measurements, the most common sensitizations were to cow's milk (26.6%) followed by hazelnut (25.3%), wheat (15.2%), and egg white (12.6%). In our study, sensitization to hazelnut was much more frequent than to peanut, although peanuts are rarely eaten as part of the Iranian diet. This finding may reflect the cross-reactivity between hazelnuts and other foods or inhalant allergens which remain to be identified.^[9]

Wheat sensitization was found in 26% of the children in this study. In Iran and some neighboring countries, wheat flour is one of the first foods added to an infant's diet. In some parts of the country, infants as young as 6 months may be given foods that contain wheat flour and this early exposure may help them sensitize to this food.

Food allergy was found to be one of the main risk factors for life-threatening asthma in children.^[10] Both peanut and cow's milk were related with increased hospitalization and steroid use in patients with asthma in other countries,^[10] whereas reactions to egg white were the reason of hospitalization in children with mild to moderate persistent asthma in our study.

According to our results, 15.2% of the children were sensitized to food allergens while only 8.9% of them were symptomatic and belonged to groups 3 and 4. This shows that the sensitivity of food-specific IgE in serum is high, but the specificity is poor. However oral food challenge is the only reliable method for the diagnosis of food allergy, but it was unethical and impractical in our study.

In this study, 3 of the children who were sensitized to egg yolk were also sensitized to egg white. The cross-reactivity between egg white and egg yolk proteins has previously been explained by the presence of certain epitopes.^[11] None of the children in the present study had concurrent sensitization to cow's milk and soybean. Therefore, soymilk might be considered as an alternative feeding supplement for infants with cow's milk allergy in Iran.

Although all children included in the present study had mild to moderate persistent asthma, no relationship was found among food sensitization, family history of asthma, atopic eczema, and prolonged breast-feeding among our patients.

The results of the present study showed that 6 (86%) of 7 asthmatic children who also suffered from food allergy had also a history of atopic eczema. Skin barrier dysfunction and abnormal immunoregulation in atopic eczema might lead to increasing food allergy in asthmatic children. Accordingly, Lack et al^[12] showed that sensitization to peanut protein may occur in children by using peanut oil on the inflamed skin.

In conclusion, determining sensitizations to common food allergens is an important step in the appropriate management of children with asthma. Morbidity and mortality from asthma may increase after food sensitization, and these risks underline the importance of identifying children who have become sensitized to common foods.

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