



Are infants with food allergy candidates for respiratory allergy?

Besin alerjisi olan infantlar solunum yolu alerjilerine aday mı?

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The known about this topic

It is known that patients with food allergies are also prone to other allergic diseases at later ages.

Contribution of the study

It has been determined that children with food allergy become sensitive to respiratory allergens at a very early age and present with asthma and allergic rhinitis.

Abstract

Aim: Allergic sensitization in infancy generally develops against food allergens. We aimed to investigate the frequency of aero-allergens sensitization at older ages in infants with food allergy.

Material and Methods: This retrospective cross-sectional study was conducted in Dr. Behçet Uz Children's Allergy Clinic. Infants with confirmed IgE-mediated food allergy between January 1st, 2004, and December 31st, 2016, were evaluated for aero-allergen sensitivities through skin prick tests (SPT) after at least two years after diagnosis, and the data were compared with a healthy control group.

Results: A total of 187 cases, 87 of which were patients, were included in the study. The cause of food allergies was cow's milk only in 24 (27.6%) cases, egg only in 26 (29.9%) cases, both cow's milk and egg in 33 (37.9%) cases, fish only in two cases (2.3%), and both fish and egg in two (2.3%) cases. The mean age at which the aero-allergen SPT was performed was 65 (46–180) months in the patient group and 72 (48–132) months in the healthy control group. In the patient group, 39 (44.8%) had aero-allergen sensitization, whereas, in the healthy control group, five (5%) had aero-allergen sensitization. Aero-allergen sensitization was more frequent in the patient group ($p<0.05$). There was no statistically significant difference in the type and number of food allergies and the development of aero-allergen sensitization ($p>0.05$).

Conclusion: In infants with food allergies, sensitization may develop with aero-allergens at an early age. Clinical follow-up of these patients may be important in terms of allergic respiratory diseases.

Keywords: Aero-allergen, allergy, food, infant, sensitization

Öz

Amaç: İnfant dönemde alerjik duyarlanma genellikle besin alerjenlerine karşı gelişir. Amacımız besin alerjisi olan infantlarda ileri yaşlarda aero-allergenlere duyarlılık gelişimini araştırmaktır.

Gereç ve Yöntemler: Geriye dönük kesitsel bu çalışmada Dr. Behçet Uz Çocuk Hastanesi Çocuk Alerji Kliniği'nde 01.01.2004 ile 31.12.2016 tarihleri arasında başvuran IgE aracılı besin alerjisi tanısı doğrulanan infantlar en az 2 yıl sonra deri prick testi ile aero-alerjen duyarlanmaları değerlendirildi. Aero-alerjen duyarlılıkları sağlıklı kontrol grubu ile karşılaştırıldı.

Bulgular: Çalışmaya 87'si hasta olmak üzere toplam 187 olgu alındı. Olguların 24'ü (%27,6) sadece süt, 26'sı (%29,9) sadece yumurta, 33'ü (%37,9) süt ve yumurta, 2'si (%2,3) balık, 2'si (%2,3) balık ve yumurta alerjisi saptanmıştı. Aero-alerjen deri prick testin yapıldığı ortalama yaş hasta grubunda 65 (46–180) ay, kontrol grubunda 72 (48–132) ay saptandı. Hasta grubunda 39 (%44,8) olguda aero-alerjen duyarlılığı saptanırken kontrol grubunda 5 (%5) olguda aero-alerjen duyarlılığı saptandı. Aero-alerjen duyarlılık hasta grubunda daha sık saptandı ($p<0,05$). Besin alerjisinin tipi ve sayısı ile aero-alerjen duyarlılığı gelişimi açısından istatistiksel olarak anlamlı fark saptanmadı ($p>0,05$).

Çıkarımlar: Besin alerjisi olan infantlarda erken yaşlarda aero-alerjenlerle duyarlanma gelişebilmektedir. Gelişebilecek alerjik solunum yolu hastalıkları açısından bu hastaların klinik izlemi önemlidir.

Anahtar sözcükler: Aero-alerjen, alerji, besin, duyarlanma, süt çocuğu

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Introduction

In recent years, particularly in developed countries, there has been a marked increase in the prevalence of allergic diseases, including food allergies and allergic respiratory diseases (1). These diseases constitute an important burden on the affected individuals, their families, and health expenditures (2). Given the apparent overlap between allergic diseases, associations between them have been a topic of interest for researchers (3). The onset of an allergic disease presenting as eczema in early life followed by progression to the onset of asthma and allergic rhinitis is called ‘atopic march’ (4). In atopic march, food allergies are common in infants with eczema, and infants with food allergy are at increased risk of developing respiratory allergy (5). Although several studies have reported that respiratory tract disease and food allergy coexist, other studies have demonstrated that food allergy develops in the first year of life, before the onset of respiratory allergy. Although several epidemiologic studies have shown that early-onset aero-allergen sensitization is associated with a risk of developing respiratory allergic disease, the role of food sensitization is less prominent (3).

In this study, by hypothesizing that there was a high risk of aero-allergenic sensitization in children with food allergy, we aimed to determine the frequency of aero-allergenic sensitization at older ages in our patients who had been previously diagnosed as having food allergy in infancy and to investigate the effect of type and number of food allergies on the development of aero-allergen sensitization.

Material and Methods

Study design

In this retrospective cross-sectional study, files and test records of children who were given a diagnosis of immunoglobulin (Ig)E-mediated food allergies during the infancy period at Behçet Uz Children’s Hospital Children’s Allergy Clinic between January 1st, 2004, and December 31st, 2016, were examined, and all confirmed cases of IgE-mediated food allergy were included in the study. The aero-allergen sensitivities of the patients who continued with follow-up visits for 2 years (between 01.01.2004 and 31.12.2016) were evaluated by using the follow-up visits; however, those who did not attend appointments were invited to our clinic, interviewed with their parents *vis-à-vis*, and evaluated through skin prick tests (SPT). In addition, 100 randomly selected patients who were admitted to the general pediatrics outpatient clinic of our hospital, who had no food allergy during the infant period, were of a similar age, and had no contraindication for SPT, were

included as the healthy control group. Patient and healthy control groups were compared in terms of age, sex, family history of atopy, and aero-allergen sensitivities. This study was conducted in accordance with the guidelines of the Ethics Committee of the Hospital (decision dated Aug 22, 2016, protocol number 2016/104, decision approval 2016/13–07). The study was performed according to the principles of the Helsinki Declaration.

Diagnosis of food allergy

Among the cases, those which met one of the following criteria in the file records were determined as confirmed food allergy:

1. Patients describing recent IgE-mediated reaction due to food intake in their history and detected sensitization with SPT or serum-specific IgE with the accused food.
2. Patients with a history in which suspected food intake was followed by an IgE-mediated food allergy, and detected sensitization in terms of induration diameter in the SPT with the suspected food or serum-specific IgE level above the cut-off value (the serum sIgE cut-off point, which determines clinical reactivity with a 95% positive predictive value, was assumed to be 5 kU/L for cow’s milk and 2 kU/L for egg white for infants. The cut-off point for the SPT was taken as 6 mm for cow’s milk and 5 mm for egg white for infants) (6, 7).
3. Cases with food allergy confirmed by the oral food challenge test.

Sensitization assessment

Commercial extracts of the suspected foods were used for the diagnosis of food allergy; the following standard allergen panel was used for the aero-allergen susceptibility: house dust mite (HDM; *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), cat and dog epithelia, *Alternaria alternata*, cockroach, and pollen [grass, weed, grain, and tree (olive, pine)] (ALK-Abelló, Madrid, Spain). A drop of each allergen extract was introduced via lancets into the skin on the volar side of the forearm. Histamine (10 mg/mL) and glycerinated saline were used as positive and negative controls, respectively. After 15 min, the mean of the largest diameter of the wheal and its perpendicular diameter were recorded as the response. A response of at least 3 mm larger than the saline control was considered as positive.

Serum-specific IgE levels were measured for cow’s milk and egg whites. Serum samples were analyzed for sIgE using a UniCAP 100 system fluorescence enzyme immunoassay (Phadia, Uppsala, Sweden). The lowest limit of detection of the assay was 0.35 kU/L. Serum-specific IgE levels could not be measured for fish.

Oral food challenges

Open oral food challenge tests were conducted according to the European Academy of Allergy and Clinical Immunology (EAACI) guidelines (8). Oral food challenge tests were performed under medical supervision with immediate emergency support. Patients were examined prior to administration of each dose. Clinical observation was performed for at least 2 hours after the last food administration. The cow's milk challenge was conducted using cow's milk (or formula milk for infants under 12 months). Oral challenge tests of egg and fish were performed using boiled eggs and fish, respectively. Finally, oral food challenge tests were stopped and considered positive when objective signs and symptoms or repeated severe subjective symptoms were noted.

Current asthma

Patients who experienced any of the following situations were given a diagnosis of current asthma: (1) one or more asthma exacerbations; (2) use of any asthma medication for at least 1 year; (3) confirmed asthma by a medical practitioner. Patients were diagnosed as having asthma according to the Global Initiative for Asthma guidelines (9).

Current allergic rhinitis

Current allergic rhinitis was defined as positive if there was previously confirmed allergic rhinitis or perennial allergic rhinitis diagnosed by a medical practitioner. Patients were diagnosed as having allergic rhinitis according to the Allergic Rhinitis and its Impact on Asthma guidelines (10).

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) 21 and MedCalc 9 (Acaciaaan 22, B-8400 Ostend, Belgium) software were used to analyze the data. The normality of data was assessed using the Kolmogorov–Smirnov test. The Mann-Whitney U test was used for the comparison of continuous variables. Categorical data were compared using Pearson's Chi-square and linear-by-linear association tests. Pearson's correlation test was used for correlation analysis. Categorical data are expressed using *n* (number) and percentages (%). A *p*-value <0.05 was considered significant.

Results

A total of 187 participants were included in the study, 87 of whom were patients. There were 60 (69%) males in the patient group and 59 (59%) in the healthy control group. In the patient group, SPT was performed with aero-allergen after at least 2 years of age; the median age was 65 (range, 46–180) months, and the median age of the healthy control group was 72 (range, 48–132) months. A family history of

atopy was observed in 42 (48.3%) individuals in the patient group and 27 (27%) in the healthy control group. In terms of food allergy, the median age at diagnosis was 8 (range, 3–24) months; cow's milk allergy alone was found in 24 (27.6%) cases, egg allergy alone was detected in 26 (29.9%), cow's milk and egg allergy was detected in 33 (37.9%), fish allergy was found in two (2.3%), and fish and egg allergy was detected in two (2.3%). In the prick tests performed during the infant period, three (2.3%) patients had HDM sensitization. Aero-allergen sensitization was detected in 39 (44.8%) individuals in the patient group and five (5%) in the healthy control group. In the patient group, 18 (20.7%) individuals were sensitive only to indoor allergens (HDM, cat and dog epithelia, cockroach), 15 (17.2%) were sensitive to outdoor allergens (pollen and *Alternaria alternata*), and six (6.8%) were sensitive to both. In the healthy control group, three (3%) individuals were susceptible to indoor allergens, one (1%) to outdoor allergens, and one (1%) to both. Among cases of allergic sensitization, in the patient group, 18 (20.6%) had asthma, six (6.8%) had allergic rhinitis, and 15 (17.2%) had only allergic sensitization. In the asthma group, eight patients were susceptible to indoor allergens, five to outdoor allergens, and five to both. In the allergic rhinitis group, five patients were susceptible to outdoor allergens and one to indoor allergens. In the asthma group, the median age was 77 (range, 56–132) months, and the median age of the allergic rhinitis group was 98 (range, 64–180) months. The serum total IgE level was 183.9 ± 238.8 kU/L and the serum eosinophil ratio was $5.1 \pm 4.4\%$ when the diagnosis of food allergy was made. At the time of diagnosis in infants with cow's milk allergy, the mean cow's milk serum specific IgE levels were found as 8.1 ± 12.7 kU/L, and the mean cow's milk SPT wheal level was 5.2 ± 2.8 mm. In infants with egg allergy, on the other hand, the mean egg white specific IgE level was found as 10.2 ± 22.8 kU/L, and the mean egg white SPT wheal level was found as 4.9 ± 3.0 mm. The mean fish SPT wheal was 8 (range, 6–10) mm (Table 1).

There were no statistically significant differences between the patient and healthy control groups in terms of age at SPT and sex when compared on the basis of age at SPT with aero-allergen, sex, family history of atopy, and aero-allergen sensitization. However, a family history of atopy and new sensitization development were found to be significantly higher in the patient group (Table 2). The patient and healthy control groups were stratified according to preschool age. Aero-allergen sensitization was also found in 25 of 45 (55.5%) in the patient group and 5 of 77 (6.4%) the healthy control group. There was no statistically significant difference between the patient and healthy control groups in terms of age at SPT and sex. However, new sensitization development was found to be signifi-

Table 1. General characteristics of 87 patients

	n	%
Male sex	60	69
Atopic family history	42	48.3
Age at diagnosis of food allergy, (month)**	8	3–24
Age of aero-allergen SPT, (month)**	65	46–180
Total serum IgE level, kU/L*	183.9±238.8	
Blood eosinophils count, (%)*	5.1±4.4	
Cow's milk specific IgE level, kU/L*	8.1±12.7	
Egg white specific IgE level, kU/L*	10.2±22.8	
Cow's milk SPT wheal level, (mm)*	5.2±2.8	
Egg white SPT wheal level, (mm)	4.9±3.0	
Fish SPT wheal level, (mm)**	8	6–10
Food allergens		
Cow's milk	24	27.69
Egg white	26	29.9
Cow's milk and egg white	33	37.9
Fish	2	2.3
Fish and egg white	2	2.3
Aero-allergen sensitivity	39	44.8
Indoor allergens	18	20.7
Outdoor allergens	15	17.2
Indoor and outdoor allergens	6	6.8
Respiratory allergy	24	27.5
Allergic rhinitis	6	6.8
Asthma	18	20.7

SPT: Skin prick test; *: Mean±SD; **: Median (min-max). Food specific IgE and SPT wheal diameter were taken as a reference during food allergy diagnosis. The aero-allergen sensitivities of the patients were evaluated at least two years after the diagnosis of food allergy; In SPT, patients with a positive reaction to aero-allergens were considered susceptible.

cantly higher in the patient group ($p<0.001$). Also, there was no statistically significant difference between the asthma and allergic rhinitis groups in terms of age and type of sensitization ($p>0.05$).

In terms of sensitization of patients to aero-allergens in cases of food sensitivities, among the individuals who had egg allergy, 13 had sensitization and nine had respiratory allergy; in individuals who had cow's milk allergy, 11 had sensitization and six had respiratory allergy; in individuals who had cow's milk and egg allergy, 11 had sensitization and six had respiratory allergy; in those who had fish allergy together with egg or fish allergy alone,

four had sensitization and three had respiratory allergy. There was no a significant difference between the groups in terms of those who developed aero-allergenic sensitization when the cases were clustered according to the type of food to that showed sensitization (cow's milk, egg, and cow's milk + egg) (Table 3). Also, no correlations were observed between eosinophil ratio, serum total IgE level, food-specific IgE level, or induration diameter determined in SPT during food allergy diagnosis and aero-allergen sensitization.

Discussion

In our patients who had been diagnosed with food allergies, aero-allergen sensitization and the frequency towards respiratory allergic diseases were increased even in the early preschool period. In infants, cow's milk and eggs are the most common food allergies (11). In our study, most of the cases of food allergy, in accordance with the literature, were cow's milk and/or egg allergy.

Thus far, few studies have investigated the role of food sensitization in early life on the development of respiratory allergic disease at older ages (12). Aero-allergen sensitivities of infants with food allergy were assessed at the age of 12 years in the Melbourne Atopic Cohort Study (MACS) (13), and in the study by Rhodes et al., (14) the aero-allergen sensitivities of infants with food allergies were assessed at 5 and 7 years of age. In the study by Brockow et al., (15) similar to that of Rhodes et al., the aero-allergen sensitivities of patients were evaluated at 6 years of age. Similarly, in our study, the median age of assessment of the aero-allergenic sensitivities of the patients was 5.5 years. According to our results, the development of aero-allergen sensitization in food allergic infants seems to be earlier than known.

Nickel et al. (16) reported that aero-allergen sensitization was higher in children with a family history of atopy than in those without. In their study of clinical characteristics of infants with food allergies in the first year of life, Doğruel et al. (17) reported that a family history of atopy in infants with food allergy was higher than in those without food allergies. In our study, a family history of atopy in patients with food allergy was higher than in those without food allergy, in accordance with the literature.

Previous studies have shown that food allergy appeared in the first years of life and respiratory allergic diseases developed in following years (3). In the Melbourne Atopic Cohort Study (MACS) in which 620 infants with a family history of atopy were assessed at 6 months of age, 15% of infants showed only food, 4% showed only aero-allergen, and 6% showed both food and aero-allergen sensitivities

Table 2. Comparison of patient and control groups

	Patients groups n=87		Control groups n=100		p
	n	%	n	%	
Male sex	60	69	59	59	0.65
Atopic family history	42	48.3	27	27	0.03
Mean age of aero-allergen SPT, (month)*	65	46–180	72	48–132	0.36
Aero-allergen sensitization	39	44.8	5	5	<0.001

*: Mean (min-max)

Table 3. Comparison of patient groups

	Cow's milk allergy		Egg white allergy		Egg white and cow's milk allergy		p
	n	%	n	%	n	%	
Aero-allergen sensitization							
Yes	11	45.8	13	50.0	11	33.3	0.441
No	13	54.2	13	50.0	22	66.7	
Total	24	100	26	100	33	100	

Pearson Chi-square Test (Monte Carlo)

in the SPT. By contrast, when the SPT was performed at the age of 24 months, 7% of the infants had only food, 17% had only aero-allergen, and 13% had both food and aero-allergen sensitization. In the same subjects, aero-allergen sensitization was detected in 61% when the SPT test was repeated at 12 years of age (13). In a similar study by Rhodes et al. (14) performed with 100 infants who were assumed to have a high risk of developing atopic disease (i.e. parents being atopic), it was reported that egg and cow's milk allergy in the first year of life disappeared by 5 years of age; however, aero-allergen sensitization was reported to increase during childhood. In the LISApus cohort with 1180 patients in which SPTs were performed at 2 years of age, 8% of patients were found to have only food, 2% were found to have only aero-allergen, and 2% were found to have both food and aero-allergen sensitization. In these patients, aero-allergen sensitization was reported to be 15% when SPT was repeated at 10 years of age (18). In their study, Hill et al. (19) reported that respiratory allergic disease developed at older ages in 35% of children who were given a diagnosis of food allergy, and the risk of respiratory allergic disease was doubled in those compared with the general public without food allergy. In our study, in line with the literature, aero-allergen sensitization developed more frequently (44.8%) in patients with food allergy in the infant period when compared with participants without food allergy. Furthermore, respiratory allergic disease developed in 27.5% of the patients with food allergy. In addition, most of these patients were preschool age.

Studies on the relationship between specific food allergens and respiratory diseases are scarce (20). Gaffin et al. (21) reported that egg sensitization, one of the most common food allergies in childhood, is a risk factor for respiratory allergic diseases in later stages of life. In a case-control study involving 69 children with egg and/or fish allergies during infancy, Priftis et al. (22) reported that such infants with food allergy had a higher risk of asthma and bronchial hyperreactivity at school age. Bekkers et al. (12) evaluated children for respiratory allergic diseases at age 11 years who had only egg allergy when they were aged one year and concluded that egg allergy was associated with an increased cumulative risk of asthma. In a similar study, Tariq et al. (23) reported that the presence of egg allergy in the infancy period showed a correlation with the risk of developing aero-allergen sensitization up to age 4 years. In parallel with these findings, Gaffin et al. (21) reported an increase in the risk of developing asthma in children who were particularly susceptible to egg and tree nuts. In our study, among 26 cases of egg allergy, 13 patients had aero-allergen sensitization and nine developed respiratory allergic disease. Furthermore, aero-allergen sensitization was observed in all patients with fish allergy or cases of both fish and egg allergy.

In the study by Malmberg et al. (24) in which 118 children with cow's milk allergy were prospectively evaluated, IgE-mediated cow's milk allergy emerged when the children were aged 7 months, and allergic respiratory diseases, bronchial inflammation, and histamine hyperreactivity

were detected at age 8 years in the same patients. Based on their similar studies, Tariq et al. (23) and Bekkers et al. (12) reported that the presence of cow's milk allergy during infancy did not increase the risk of asthma. In our study, in concert with the literature, we observed that 11 of the 24 patients with cow's milk allergy developed aero-allergen susceptibility, and respiratory tract allergic disease developed in six.

Our study was conducted in the Aegean region of Turkey. In a previous study by Tezcan et al. (25) performed in the Aegean region, the aero-allergen sensitivities of patients were evaluated retrospectively, and it was reported that, of the patients with aero-allergenic sensitization, 42% were sensitive to HDM, 54% to weed pollen, 14% to tree pollen, 9% to mold, and 16% to animal dander. In this study, in agreement with the literature, 46.1% of subjects with aero-allergen sensitization were found to be only responsive to indoor allergens, 38.4% to outdoor allergens, and 15.3% to both. Thus, we concluded that aero-allergen type in patients with food allergy was not different from the aero-allergen type in the general population.

In their follow-up study of respiratory tract diseases in infants given a diagnosis of food allergy, Bekkers et al. (12) observed that 10.3% of patients developed asthma in later life. In terms of aero-allergenic disease, Brockow et al. (15) investigated children at 6 years of age with a family history of atopy who had developed food allergy during infancy, and they found that 14.9% of these children had allergic rhinitis and 10.7% developed asthma. Per the literature, allergic rhinitis was observed in 6.8% of patients and asthma in 20.6% in our study.

In patients with food allergy, the risk of developing respiratory disease is two-times higher as compared with the general public (26). Hill et al. (19) reported that the risk of aero-allergen sensitization increased significantly, particularly in children with cow's milk, egg, and peanut allergies, and concluded that the risk for children with multiple allergies was higher than the risk for children with a single allergy. In our study, no significant difference was found in terms of the risk of allergenic sensitization between cases with only cow's milk, only egg, or both cow's milk and egg allergy.

The major limitation of the study is the retrospective design. Our aim was to investigate aero-allergen sensitization in diagnosed patients using objective parameters (SPT and oral food challenge tests) for the diagnosis of food allergy. However, the retrospective design posed limitations for the diagnosis of asthma and allergic rhinitis. Another limitation of the study is studying open food

challenges test in the diagnosis of food allergy. Furthermore, this study included a small number of subjects; however, we are convinced that this limitation does not affect our results.

The risk for aero-allergen sensitization during the early period of life is increased in infants with food allergy. The aero-allergen type in patients with food allergy was not different from the aero-allergen type in the general population. Most infants with food allergy develop a tolerance to foods in the first few years of life; however, clinical monitoring is crucial in terms of allergic respiratory diseases that may develop despite this improved tolerance.

Ethics Committee Approval: The study was approved by the Research Ethics Board of Dr. Behçet Uz Children's Hospital (2016/13-07).

Informed Consent: Written informed consent was obtained from the parents.

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