

Phenotypes of IgE-mediated food allergy in Turkish children

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ABSTRACT

Data on food allergy-related comorbid diseases and the knowledge on factors associating specific food types with specific allergic outcomes are limited. The aim of this study was to determine the clinical spectrum of IgE-dependent food allergy and the specific food-related phenotypes in a group of children with IgE-mediated food allergy. Children diagnosed with IgE-mediated food allergy were included in a cross-sectional study. IgE-mediated food allergy was diagnosed in the presence of specific IgE or skin-prick test and a consistent and clear-cut history of food-related symptoms or positive open provocation test. Egg (57.8%), cow's milk (55.9%), hazelnut (21.9%), peanut (11.7%), walnut (7.6%), lentil (7.0%), wheat (5.7%), and beef (5.7%) were the most common food allergies in children with food allergy. The respiratory symptoms and pollen sensitization were more frequent in children with isolated tree nuts-peanut allergy compared with those with egg or milk allergy ($p < 0.001$); whereas atopic dermatitis was more frequent in children with isolated egg allergy compared with those with isolated cow's milk and tree nuts-peanut allergy ($p < 0.001$). Children with food allergy were 3.1 ($p = 0.003$) and 2.3 ($p = 0.003$) times more likely to have asthma in the presence of allergic rhinitis and tree nuts-peanut allergy, respectively. Interestingly, children with atopic dermatitis were 0.5 ($p = 0.005$) times less likely to have asthma. Asthma (odds ratio [OR], 2.3; $p = 0.002$) and having multiple food allergies (OR, 5.4; $p < 0.001$) were significant risk factors for anaphylaxis. The phenotypes of IgE-mediated food allergy are highly heterogeneous and some clinical phenotypes may be associated with the specific type of food and the number of food allergies.

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The reported prevalence of food allergy shows great variations among different populations.^{1,2} This heterogeneity can be explained based on ethnic, nutritional, and cultural differences among different populations as well as the differences in the study design and methodology. It is generally believed that self-reported prevalence tends to overestimate the prevalence of food allergy.^{1,3} More recent studies based on objective measures such as skin-prick tests, specific IgE to foods, and, especially, double-blind placebo-controlled food challenges (DBPCFCs) suggest that the prevalence of food allergy ranges between 1 and 10.8%.^{1,2} In Turkey food allergy shows a similar pattern, parent-reported food allergy is 5.7% in children aged between 6 and 9 years old; however the prevalence of food allergy confirmed by the DBPCFC is only 0.8%.^{4,5}

Although there are geographical, social, and nutritional differences, cow's milk and eggs in infancy and peanuts in older age groups are by far the most com-

mon foods causing allergic reactions in children.^{6,7} In recent years, prevalence of allergies to kiwi and sesame seed has increased in some countries.^{8,9}

In addition to providing epidemiologic data, these studies have focused on the clinical manifestations including anaphylaxis and on the factors that are predictive of outgrowing food allergy.^{10–13} Atopic dermatitis with food allergy is the first manifestation of the atopic march and asthma and allergic rhinitis appear later in life.¹⁴ The association of eczema and the development of food allergy in infancy is documented in several studies.^{15–17} However, the data on food allergy-related comorbid diseases other than atopic dermatitis such as asthma and allergic rhinitis are limited. Similarly, there is a gap in our knowledge on factors associating specific food types with specific allergic outcomes.

Therefore, in a cross-sectional study, we set out to determine the clinical spectrum of IgE-dependent food allergy and the specific food-related phenotypes in a group of Turkish children with IgE-mediated food allergy.

MATERIALS AND METHODS

Patients

Children with IgE-mediated food allergy who have been followed at the Pediatric Allergy and Asthma Unit, Hacettepe University School of Medicine, be-

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tween January 2002 and May 2009 are the subjects of this study. All children and their parents were interviewed and their demographic variables and physical examination findings were recorded. Special effort was given to determine a cause-and-effect relationship between the ingestion of a certain food and development of symptoms.

Children were diagnosed as having IgE-mediated food allergy when they fulfilled both of the following criteria^{18,19}:

1. Presence of specific IgE to at least one type of food as shown by elevated titers of specific IgE (>0.35 kU/L) or positive skin-prick test.
2. A consistent and clear-cut history of food-related symptoms that developed in early phase after the ingestion of a certain food or positive open food challenge.

Children without a clear-cut history of food-related symptoms had undergone an open food challenge test. In children allergic to more than one food, children had a clear history of food-related symptoms after consumption of each food along with specific IgE positivity.

All study procedures were performed in accordance with a protocol previously approved by the Ethics Committee of Hacettepe University. All parents provided written informed consent for the study procedures.

Study Measurements

Skin-prick tests were performed in all patients. In children ≤ 2 years of age, a small panel including cow's milk, egg, wheat, peanut, walnut, hazelnut, sesame, soy, and lentil was performed. In children >2 years of age, a battery of 33 food allergens including cow's milk, egg, peanut, walnut, soy, wheat, hazelnut, walnut, pistachio, beef, fish, lentil (red and green), chick pea, sesame seed, pea, corn, garlic, tomato, rice, kiwi, carrot, celery, melon, banana, apple, cumin, chicken, green beans, red capsicum, monilia, sunflower seed, and potato were tested (Alyostal ST-IR; Stallergenes SA, Antony, France) on the back of the children. Prick-to-prick testing with fresh unprocessed food was done for peaches and lettuce to the children with a history of symptoms after these foods. Reactions with wheals 3 mm greater than negative control were considered positive. For patients >2 years old, skin-prick testing was performed with an additional panel of 30 aeroallergens including tree, grass, and weed pollens; *Dermatophagoides farinae*; *Dermatophagoides pteronyssinus*; cat, dog, and horse dander; and molds on a separate day.

Total IgE levels and specific IgE to foods were measured in sera with Uni-Cap technology in accordance with the specifications of the manufacturer (Pharma-

cia, Uppsala, Sweden). Food-specific IgE concentrations of >0.35 kU/L were considered positive.

Eosinophil counts were determined from a Coulter Counter (Beckman Coulter, Fullerton, CA) leukocyte measurements.

Diagnosis of Atopic Dermatitis

Atopic dermatitis is clinically defined by the presence of pruritus and a relapsing eczematous rash typically found over flexor surfaces.²⁰ In children with atopic dermatitis, skin symptoms significantly diminished after elimination of incriminated food.

Diagnosis of Asthma

In children capable of doing spirometry, asthma was diagnosed in the presence of reversible airway obstruction as defined by at least a 12% improvement in forced expiratory volume in 1 second after bronchodilator administration²¹ or improvement in asthma symptoms after inhaled steroid or leukotriene modifier agent therapy. In younger children who could not cooperate with spirometry, asthma was diagnosed by a history of recurrent wheezing and/or cough and a favorable therapeutic response to antiasthma treatment.²²

Diagnosis of Anaphylaxis

Diagnosis of anaphylaxis was made according to the previously published reports.^{23–25} Clinically, anaphylaxis was defined as a severe, systemic syndrome involving cutaneous, respiratory, and/or cardiovascular symptoms and/or signs, such as stridor, wheezing, or hypotension after ingestion of implicated food.

Diagnosis of Allergic Rhinitis

Allergic rhinitis is clinically defined by occurrence of symptoms such as rhinorrhea, nasal obstruction, nasal itching, and sneezing in children with aeroallergen sensitivity.²⁶

Pediatric allergy specialists made diagnoses of accompanying diseases.

Statistical Analysis

Statistical analyses were performed with SPSS 15.0 for Windows (IBM SPSS Statistics, Chicago, IL). All data including age, age of onset of symptoms, eosinophil counts, total IgE showing nonnormal distribution, and the data were given as median and interquartile range, and all statistical comparisons were performed using Mann-Whitney *U* test or ANOVA on ranks as appropriate. A value of $p < 0.05$ was considered significant for all analyses.

We have performed both univariate and multivariate logistic regression analyses to establish the factors that were associated with asthma and anaphylaxis. In this model, age, age of onset of symptoms, gender, family

Table 1 Characteristics of the patients with food allergy (*n* = 315)

Age (current)	4.82 (2.1–8.2)*
Gender (male/female)	220 (69.8%)/95 (30.2%)
Age of onset of symptoms (yr)	0.5 (0.3–0.7)*
Family history of allergy, <i>n</i> (%)	127 (40.3)
Presenting symptoms, <i>n</i> (%)	
Skin	296 (94.0)
Respiratory	95 (30.2)
Gastrointestinal	61 (19.4)
Neurological	9 (2.9)
Cardiovascular	4 (1.3)
Eosinophils/mm ³	500 (296–863)*
Total IgE (kU/L)	118 (46–304)*
Patients with two or more food allergies, <i>n</i> (%)	159 (50.5)
Concomitant atopic dermatitis	191 (60.6%)
Concomitant asthma	104 (33.0%)
Concomitant allergic rhinitis	38 (12.1%)
Aeroallergen sensitivity	
House-dust mite	14 (4.4%)
Pollen	42 (13.3%)
Cat dander	10 (3.2%)

*Median (interquartile range).

history of allergy, atopic dermatitis, allergic rhinitis, specific food allergies that are present in >5% of the studied population (cow's milk, egg, tree nuts, peanut, lentil, beef, and wheat), presence of inhalant allergies, presence of multiple food allergies, eosinophil counts, and total IgE were examined in the univariate model. The factors that were significant in the univariate regression analysis or resulted in a shift in the odds ratio (OR; of >0.2) for the relationship were then included as covariates in the multiple regression analysis.

RESULTS

Three hundred fifteen children aged between 1.2 months and 19 years who fulfilled the criteria for IgE-mediated food allergy were included in the study (Table 1). All children had evidence of specific IgE either by skin-prick tests or serum-specific IgE. In 189 children (60%) there was a consistent and clear-cut history relating a specific food type with symptoms and, moreover, 82 (26%) children had a history of anaphylaxis after the incriminating food exposure whereas in the remaining 126 (40%) children, an open challenge test was necessary to confirm the diagnosis of IgE-mediated food allergy. The majority of the children presented with cutaneous symptoms (94%; eczema, urticaria, and angioedema) followed by respiratory symptoms (30.2%; wheezing, dys-

pnea, rhinitis, cyanosis, and hoarseness), gastrointestinal symptoms (19.4%; oral pruritus, nausea, vomiting, abdominal cramping, and diarrhea), neurological symptoms (2.9%; dizziness, headache, and confusion), and cardiovascular symptoms (1.3%; hypotension, tachycardia, and bradycardia).

Implicated Food

Frequency of various food allergies is given in Fig. 1, A and B. There was a striking difference in the offending food between the children whose symptoms began before (*n* = 249) and after 1 year of age (*n* = 66). Egg and cow's milk were by far the most common food allergies in children <1 year of age and hazelnut, peanut, and walnut were the most common in children >1 year of age (Fig. 1 C). Interestingly, the prevalence of lentil allergy (7%) was higher than other relatively more commonly reported causes such as wheat (5.7%) and soy (3.8). Similarly, the prevalence of allergy to sesame was equal to soy (3.8%) and higher than fish (3.2%).

Food Type and Comorbid Conditions

To see whether there is any relationship between the offending food and the clinical presentation, we analyzed isolated cases of three most common food allergies, *viz.*, cases with isolated allergies to cow's milk, egg, or tree nuts–peanut. The children with hazelnut, peanut, walnut, and pistachio were pooled together. The age of onset of symptoms and total IgE were significantly higher ($p < 0.001$ and $p = 0.001$, respectively); and respiratory symptoms were more frequent in children with isolated tree nuts–peanut allergy ($p < 0.001$; Table 2). On the other hand, atopic dermatitis was significantly more frequent in children with isolated egg allergy compared with isolated cow's milk and tree nuts–peanut allergy ($p < 0.001$; Fig. 2).

Children with food allergy were 3.1 (OR, 3.12; 95% CI, 1.49–6.53; $p = 0.003$) and 2.3 (OR, 2.34; 95% CI, 1.33–4.12; $p = 0.003$) times more likely to have asthma in the presence of allergic rhinitis and tree nuts–peanut allergy, respectively. Interestingly, children with atopic dermatitis were 0.5 (OR, 0.48; 95% CI, 0.29–0.80; $p = 0.005$) times less likely to have asthma (Table E1; supplementary material).

Aeroallergen Sensitization

Pollen sensitization was significantly more frequent in children with tree nuts–peanut (55.6%) allergy than in children with cow's milk allergy (3.1%) and egg allergy (3.6%; $p < 0.001$; Fig. 3). Interestingly, there was no house-dust mite sensitization among children with tree nuts–peanut allergy.

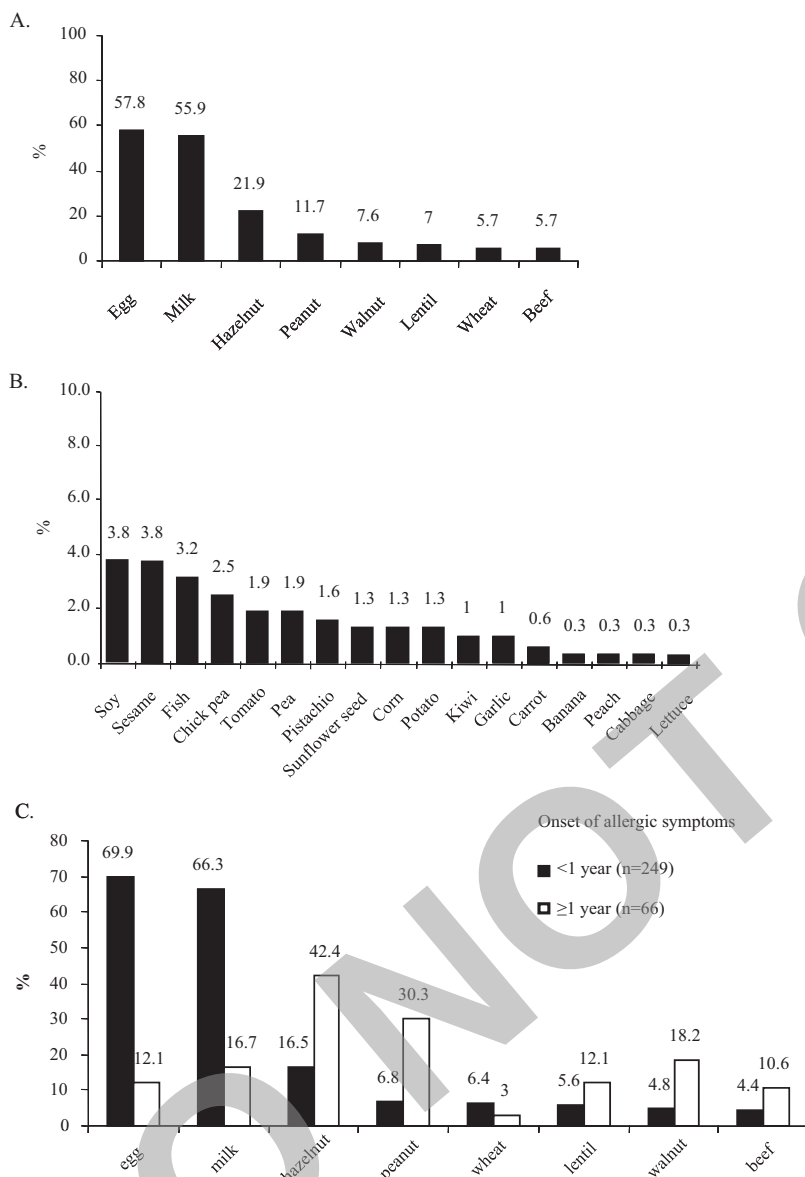


Figure 1. Frequency of food allergens in children with IgE-mediated food allergy. (A) The most frequent food allergens. (B) Uncommon food allergens responsible for symptoms induced by food intake. (C) The most frequent food allergens in children younger and older than 1 year of age.

Mono versus Multiple Food Allergies

One hundred fifty-nine children (50.5%) were multi-sensitized and 156 children (49.5%) were monosensitized. Children with multiple food allergies had a higher rate of positive family history, allergic rhinitis, and atopic dermatitis and higher eosinophil counts and plasma concentration of total IgE than monosensitized children (Table 3).

Anaphylaxis

Of the 315 children, 129 (40.9%) had acute anaphylactic reactions. Offending foods were cow's milk (62%), egg (45.7%), tree nuts-peanut (30.2%), meat (9.3%), lentil (7.6%), fish (5%), wheat (4.7%), and soy (4.7%). Multivariate logistic regression analysis showed that asthma (OR, 2.32; 95% CI, 1.35–3.97; $p = 0.002$) and having multiple food allergies (OR, 5.43;

95% CI, 2.79–10.61; $p < 0.001$) were significant risk factors for anaphylaxis (Table E2; supplementary material).

DISCUSSION

Our study shows that the type of offending food has significant influences on the targeted organs and associated allergic disease. Children with isolated egg allergy have a lower rate of respiratory allergies, whereas children with tree nuts-peanut allergy have a higher rate of pollen but not dust-mite sensitization and a higher rate of asthma. The data also suggest that multisensitized children have a more severe clinical presentation including higher risk of anaphylaxis.

The spectrum of food allergies varies greatly according to the geographical location and related dietary habits. In the United States, the most frequent food

Table 2 Comparison of the characteristics in children with isolated cow's milk, egg, and tree nuts-peanut allergies

	Isolated Cow's Milk (n = 65)	Isolated Egg (n = 55)	Isolated Tree Nuts-Peanut (n = 27)	p
Age of onset (yr)*	0.4 (0.0-5)	0.4 (0.0-5)	1.5 (1.3-3.0)	<0.001#
Gender				
Male	41 (63.1%)	34 (61.8%)	22 (81.5%)	NS§
Female	24 (36.9%)	21 (38.2%)	5 (18.5%)	
Family history of allergy	33.8%	30.9%	55.6%	NS§
Eosinophils/mm ³ *	487 (286-57)	500 (230-858)	300 (176-522)	NS#
Total IgE*	96.5 (51.7-181)	66.4 (26.5-170)	256 (83.5-558)	0.007#¶
Presentation symptoms (%)				
Skin	90.8	96.4	85.2	NS§
Respiratory	29.2	7.3	51.9	<0.001§
Gastrointestinal	21.0	7.3	14.8	NS§

*Median (interquartile range).

#Kruskal-Wallis test.

§ χ^2 -test.

¶Comparison between three groups were adjusted for age of onset of food allergy.

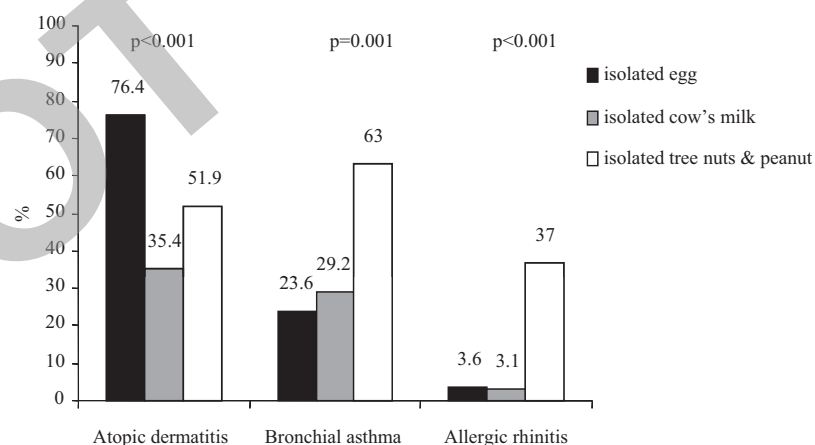


Figure 2. The frequency of atopic dermatitis, asthma, and allergic rhinitis in children with isolated egg allergy, isolated cow's milk allergy, and isolated tree nuts and peanut allergy.

allergens in young children are cow's milk, egg, peanut, wheat, soy, tree nuts, fish, and shellfish,¹⁸ whereas in the Mediterranean area some legumes and sesame seed are among the more frequent food allergies.²⁷⁻²⁹ Compared with other regions, sesame seed allergy is more frequent in Israel and lentil allergy is more common in Spain.^{9,28} Our study shows that lentil allergy also emerges as a common cause in Turkey. According to 2007 Food and Agriculture Organization reports,³⁰ India (36%), Canada (17%), and Turkey (15%) are major producers of lentil in the world. Traditionally, and probably because of its high production, lentil is introduced into the diet early in life, which may be responsible for the relatively higher frequency of lentil allergy in the Turkish population (7%). Similarly, sesame has a frequency equal to that of soy and higher than fish. This may also account for high levels of sesame in the Turkish diet.

Our study shows that hazelnut, but not peanut, is one of the major food allergens in Turkish children. Turkey is the major producer of hazelnut and provides 77% of the world's production.³¹ Hazelnut consumption is therefore very high in Turkey and replaces peanuts in the United States in this regard.

Roughly, 50% of the children in our study had multiple food allergies. This observation supports previous reports that have shown that a significant portion of food-allergic children have multiple food allergies.^{10,11,27,32-34}

In our cohort, children with multiple food allergies had a more severe atopic phenotype as evidenced by higher total IgE response; higher eosinophil counts; and higher rates of atopic dermatitis, allergic rhinitis, and anaphylaxis but not asthma. Although the mechanism of this association is not clear, it definitely indicates that children with multiple food allergies need to

Table E1 Logistic regression analysis for asthma in children with food allergy

	Univariate Analysis		Multivariate Analysis	
	OR	<i>p</i>	OR	<i>p</i>
Age of onset (yr)	1.10 (0.98–1.23)	NS		
Gender	0.64 (0.37–1.08)	NS		
Allergic rhinitis	4.22 (2.08–8.57)	<0.001	3.12 (1.49–6.53)	0.003
Atopic dermatitis	0.52 (0.32–0.84)	0.007	0.48 (0.29–0.80)	0.005
Cow's milk allergy	0.70 (0.44–1.12)	NS		
Egg allergy	0.52 (0.32–0.84)	0.007		
Wheat allergy	1.31 (0.49–3.49)	NS		
Beef allergy	2.69 (1.02–7.02)	0.044		
Lentil allergy	2.15 (0.90–5.14)	NS		
Tree nuts–peanut allergy	2.41 (1.43–4.07)	0.001	2.34 (1.33–4.12)	0.003
Pollen sensitization	2.87 (1.48–5.56)	0.002		
House-dust mite sensitization	2.10 (0.72–6.16)	NS		
Family history	1.54 (0.97–2.45)	NS		
IgE	1.00 (1.00–1.01)	0.047		
Eosinophil count	0.99 (0.99–1.00)	0.022		
More than one food allergy	1.15 (0.72–1.85)	NS		

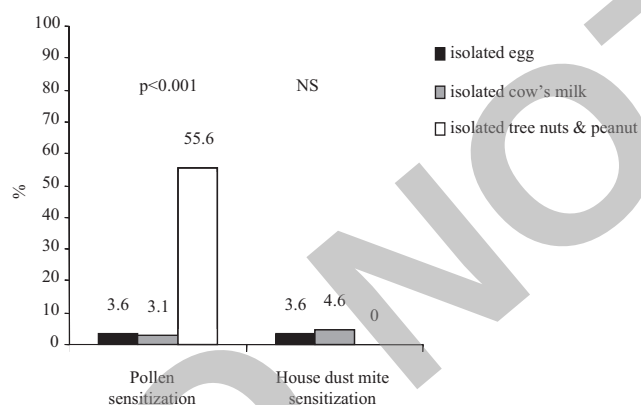


Figure 3. The frequency of pollen and house-dust mite sensitization in children with isolated egg allergy, isolated cow's milk allergy, and isolated tree nuts and peanut allergy.

be closely followed regarding the comorbid conditions with these more severe phenotypes, especially anaphylaxis.

The results of the logistic regression analysis supported the comparison between children with mono- and multisensitizations and showed that the presence of multiple food allergies is strongly and independently associated with anaphylaxis (OR, 5.43; 95% CI, 2.79–10.61; $p < 0.001$). In this regard, the association was much stronger than it is with asthma (OR, 1.16; 95% CI, 0.72–1.85; $p > 0.05$), although multiple allergies are well known to be associated with asthma.^{35–37}

Another interesting finding in the multivariate logistic regression analysis was that atopic dermatitis and egg allergy were independently associated with a decreased risk of anaphylaxis. Atopic dermatitis, in ad-

dition to being associated with a lower risk of anaphylaxis, was also associated with a lower rate of asthma, whereas allergic rhinitis and tree nuts and peanut allergy were associated with a higher rate. The associations that we observed between atopic dermatitis, asthma, and anaphylaxis are rather unexpected. Many reports have shown that atopic dermatitis is associated with increased rate of asthma.^{14,38,39} However, it should be noted that our observation is only valid for this specific group of children with IgE-mediated food allergy and therefore can not be extended to a general population. This observation needs to be confirmed in other populations and further investigated. Our study was not designed to offer a mechanistic explanation for this observation.

The presence of 156 monosensitized children allowed us to determine if there are any distinguishing clinical characteristics specific for the offending food. In parallel with the findings of Wood *et al.*,¹⁰ the children with isolated egg allergy showed a high incidence of atopic dermatitis and remarkably less involvement of the respiratory and gastrointestinal system compared with children with isolated milk or isolated tree nuts–peanut allergy in our study. Although age may obviously be a factor underlying the difference between the higher frequencies of respiratory involvement in children with tree nuts and/or peanut allergy, it can not account for the differences observed between the children with milk and egg allergy. Although the age of onset is similar in children with egg and milk allergy, respiratory and gastrointestinal involvements are much less common in children with egg allergy. These data suggest that the type of offending food may

Table 3 Comparison of the characteristics in children with one food allergy and more than one food allergy

	Allergy to One Food Antigen	Allergies to More Than One Food Antigen	<i>p</i>
<i>n</i> (%)	156 (49.5)	159 (50.5)	
Age of onset* (yr)	0.5 (0.3–0.9)	0.5 (0.3–0.6)	NS#
Family history of allergic disease (%)	32.1	48.4	0.003§
Presentation symptoms (%)			
Skin	91.0	96.9	0.030§
Respiratory	23.7	36.5	0.014§
Gastrointestinal	15.4	23.3	NS§
Asthma (%)	31.4	34.6	NS§
Allergic rhinitis (%)	8.3	15.7	0.044§
Atopic dermatitis (%)	47.4	73.6	<0.001§
Total IgE* (kU/L)	94 (43.6–192.8)	153.0 (56.5–462.5)	0.001#
Eosinophils/mm ³ *	452 (265–700)	596 (304–982)	0.011#

*Median (interquartile ranges).

#Kruskal-Wallis test.

§ χ^2 -test.

Table E2 Logistic regression analysis for anaphylaxis in children with food allergy

	Univariate Analysis		Multivariate Analysis	
	OR	<i>p</i>	OR	<i>p</i>
Age of onset (yr)	1.08 (0.97–1.22)	NS		
Gender	0.95 (0.58–1.54)	NS		
Asthma	3.59 (2.20–5.87)	<0.001	2.32 (1.35–3.97)	0.002
Allergic rhinitis	2.47 (1.33–4.95)	0.011		
Atopic dermatitis	0.31 (0.19–0.49)	<0.001	0.36 (0.20–0.65)	0.001
Cow's milk allergy	1.53 (0.97–2.41)	NS		
Egg allergy	0.43 (0.27–0.68)	<0.001	0.36 (0.18–0.69)	0.002
Wheat allergy	0.70 (0.26–1.93)	NS		
Beef allergy	3.06 (1.12–8.38)	0.03		
Lentil allergy	0.99 (0.40–2.45)	NS		
Tree nuts–peanut allergy	1.49 (0.89–2.47)	NS		
Family history	1.54 (0.97–2.45)	NS		
IgE	1.00 (1.00–1.01)	NS		
Eosinophil count	0.99 (0.99–1.00)	0.004		
More than one food allergy	1.88 (1.19–2.96)	0.007	5.44 (2.79–10.61)	<0.001

be a determinant of the targeted organ. However, the underlying pathological mechanisms remain to be discovered.

In contrast to egg, the target organ for children with tree nuts–peanut allergies was more commonly the respiratory system. Several studies have shown that allergies to tree nuts and peanuts are associated with asthma and sensitization to inhalant allergens.^{32,35,40,41} In our cohort, children with tree nuts or peanut allergy had a high rate of grass pollen sensitivity. As shown by many studies, house-dust mite sensitivity is at least as common as pollen sensitivity in this age group.⁴²

Therefore, this association between tree nuts or peanut allergy and pollen sensitization is unlikely to be caused by an epiphenomenon related to the higher frequencies of tree nuts, peanut allergy, and pollen sensitization in older children. A more likely explanation would be the cross-reactivity between peanut and grass pollen allergens, as has been shown by some studies.^{43,44}

Our study has several limitations. First, the population of this study is an extremely selected one, comprised of children with IgE-mediated food allergy that presented to or were referred to a tertiary care university clinic and therefore does not reflect on the general

population. Second, the children have had a pretty short duration of follow-up with a median of only 1.9 years (0.8–3.6 years) in our clinic. A longer follow-up would probably increase the percentage of asthma and allergic rhinitis in this population and thus may change the associations. In addition, this relatively shorter duration does not allow us to determine the factors that are associated with outgrowing food allergy. Third, and most importantly, the diagnosis of food allergy was not based on DBPCFCs, which is the golden standard for the diagnosis of food allergy. However, we believe that the presence of a clear-cut history or positive open challenge, together with demonstration of the specific IgE either by skin testing or serological testing, leaves little doubt on the diagnosis of IgE-mediated food allergy in the majority of cases in a clinical setting.

In summary, this cross-sectional study shows that phenotypes of IgE-mediated food allergy is highly heterogeneous and the characteristics of food allergies including type of food allergen and the number of food allergies may be potential confounding factors for certain clinical phenotypes.

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