

Immunoglobulin E-Mediated Food Allergies Differ in East Mediterranean Children Aged 0–2 Years

Melike Kahveci^a Gizem Koken^b Ümit Murat Şahiner^a Özge Soyer^a
Bülent Enis Şekerel^a

^aDepartment of Pediatric Allergy, Hacettepe University Faculty of Medicine, Ankara, Turkey;

^bDepartment of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey

Keywords

Atopic dermatitis · Breast feeding · Food allergy · Infant · Skin prick test panel

Abstract

Objective: Precise diagnosis of allergy requires knowledge of the population's food allergy (FA) spectrum and predictors. **Methods:** Medical charts of Turkish children aged 0–2 years with FA and/or atopic dermatitis (AD) were reviewed. **Results:** A total of 1,389 patients, 912 with FA and 1,140 with AD, were included. In the FA group, the most frequently diagnosed FAs were egg white (75.9%), cow's milk (55.7%), tree nuts (31.5%) and sesame (20.6%). The detection of FA in 99% of children with any kind of FA necessitate testing with egg white, cow's milk, hazelnut, sesame, walnut, cashew, and pistachio. In the FA group, 72.7 and 56.8% had AD and multiple FA respectively. Multiple FA (56.8 vs. 49.8%) and hen's egg allergy (85.5 vs. 50.2%, $p < 0.005$) were more common and cow's milk allergy (51.4 vs. 67.1%, $p < 0.005$) less common in the AD subgroup of the FA group than in the non-AD subgroup. Multiple FA likelihood increases parallel to the severity of AD ($p < 0.05$). In the AD group, 58.2% had an immunoglobulin E-mediated FA. The risk of concomitant

FA increased as the age at symptom onset of AD decreased (OR 0.800 [95% CI 0.731–0.875]; $p < 0.001$) and the severity of AD increased (OR 2.350 [95% CI 1.898–2.911]; $p < 0.001$). **Conclusion:** Although severe and early-onset AD is a predictor of the presence and magnitude of FA in infancy, the spectrum of FA is a reflection of cultural characteristics. The clinical presentations of both AD and FA may in fact be an expression of the extent of the immune dysregulation underlying atopy and allergy.

© 2020 S. Karger AG, Basel

Introduction

Food allergy (FA) is a growing public health problem with variations between different populations [1, 2]. Any food can potentially cause an allergic reaction; however, >170 foods have been determined as potentially allergenic only a minority of which lead to major reactions. The classical “8 food groups” causing the most allergic reactions around the world are cow's milk, egg, peanut, tree

Edited by: H.-U. Simon, Bern.

nuts, wheat, soy, fish, and shellfish [3]. However, the spectrum, frequency and distribution of etiology of FAs potentially vary between populations based on cultural, nutritional, and ethnical differences.

FA develops more frequently during the first year of life, where nutrition is critical. Precise evaluation for FA during infancy requires the recognition of alarming signals of FA, data regarding the most common etiologies of FAs in the population, and dynamic interpretation of the patient for the development/disappearance of allergies with appropriate methodology. During infancy, the presence of atopic dermatitis (AD) is the most important hint for concomitant FA and it is shown that >50% of infants with AD have an FA, particularly in those with severe, persistent and early-onset eczema [4–6]. In exclusively breastfed infants with uncontrolled AD, FA workup should be performed to determine which food needs to be eliminated from the mothers' diet.

The primary objective of this study was to document the extent of the food allergen panel in children aged 0–2 years living in the Eastern Mediterranean region by assessing frequencies of immunoglobulin E (IgE)-mediated FAs in the first 2 years of life. The secondary objectives were to determine the risk factors for multiple FAs and predictors for FA in patients with AD, and to obtain data on the timing and extent of FA testing in infants with AD who are exclusively breastfed.

Methods

Study Population

This retrospective study was conducted in the Pediatric Allergy Division of Hacettepe University İhsan Doğramacı Children's Hospital, which is a referral center for the entire country. Infants younger than 24 months with IgE-mediated FA and/or AD at their first visit between January 1, 2015 and March 31, 2019 were included in the study. The diagnosis of IgE-mediated FA was defined as a positive skin prick test (SPT; 3 mm or more above the negative control) and/or positive specific IgE (≥ 0.35 kU/L). It also had to meet one of the following 2 criteria: a consistent and clear-cut history of an immediate-type reaction that is strictly associated with food consumption, and benefits from an elimination diet, or a positive food challenge. AD was diagnosed according to the Hanifin-Rajka diagnostic criteria [7]. The severity of AD was scored using the Objective Severity Scoring of AD (o-SCORAD) index at the initial visit with a total o-SCORAD score <15 was classified as mild, 15–40 as moderate, and above 40 as severe AD [8].

Other data collected were age, gender, nutrition at time of admission (breast milk or formula or both), initial symptom, age at AD onset, initial reaction upon exposure, ages at SPT applications and family history of atopy. Complete blood cell count, eosinophil percentage, absolute eosinophils count, total serum IgE and serum basal tryptase level, if available, were recorded.



Fig. 1. Scheme of the study. FA, food allergy; AD, atopic dermatitis. * Exclusively breastfed infants who had allergy tests both at 0–3 and 4–6 months.

Allergy Testing Procedures

According to the routine practice of the clinic, children referred with symptoms suggesting IgE-mediated FA with or without AD were subjected to SPT with a panel of 23 food allergen extracts: cow's milk, egg white, wheat, corn, soy, lentil, chick pea, pea, haricot bean, peanut, hazelnut, walnut, pistachio, cashew, almond, sesame, sunflower seed, pumpkin seed, fish, beef, chicken meat, kiwi and potato. However, in the case of regular consumption of any food from the SPT panel, those were eliminated from the panel to decrease the discomfort due to the testing procedure. SPT were performed on patients' upper back and evaluated after 15 min. Histamine (histamine phosphate, 10 mg/mL) and sterile saline solutions were utilized as positive and negative controls respectively.

According to the routine practice of the clinic, SPT was performed if the patient did not use any drug such as antihistamine that could interfere with the SPT within the last 5 days. Furthermore, serum specific IgE levels (Phadia, Uppsala, Sweden) were measured in patients with dermatographism, borderline positive results, or current antihistamine use.

Statistical Analysis

FA prevalence of each allergen was first determined using frequencies and percentages. A step-by-step conditional approach was utilized to classify allergens from those causing the highest increase in the prevalence of allergy to those causing the lowest increase. Starting with the most frequent allergen and continuing in decreasing order of frequency, the allergen source causing the highest prevalence of allergy was investigated in the subgroup of subjects not sensitized to the previous allergen. The procedure was repeated until 99% coverage for the presence of SPT sensitization was achieved. SPSS 22.0 software (Chicago, IL, USA) was used for the statistical analysis. Statistical analyses also included univariate and multivariate analyses. ORs with relevant 95% CIs were calculated for evaluating the potential associations between various predictors (including age at symptom onset, gender, total IgE, disease severity and eosinophil percent) and FA in AD.

Table 1. Characteristics of FA group and its subgroups

	FA group (<i>n</i> = 912)	FA without AD (<i>n</i> = 249)	FA with AD (<i>n</i> = 663)	<i>p</i> value [#]
Gender (male), <i>n</i> (%)	606 (66.4)	159 (63.9)	447 (67.4)	0.308
Age at symptom onset, months, median (IQR)	3 (2–5)	6 (5–6)	2 (1.5–3)	<0.001
Age at admission, months, median (IQR)	8.6 (6.0–14.6)	11.4 (7.1–18.5)	8 (5.6–13.2)	<0.001
Initial symptoms, <i>n</i> (%)				–
AD	663 (72.7)	–	663 (100)	
Urticaria/angioedema	184 (20.2)	184 (73.9)	–	
Anaphylaxis	42 (4.6)	42 (16.9)	–	
Nausea, vomiting	23 (2.5)	23 (9.2)	–	
Multiple FA, <i>n</i> (%)	518 (56.8)	124 (49.8)	394 (59.4)	0.009
≤6, months	<i>n</i> = 577	<i>n</i> = 80	<i>n</i> = 497	
Allergies, <i>n</i> (%)				
1	228 (39.5)	43 (53.8)	185 (37.2)	
2	248 (43)	32 (40)	216 (43.5)	
3	53 (9.2)	2 (2.5)	51 (10.3)	0.001
≥4	48 (8.3)	3 (3.8)	45 (9.1)	
7–12, months	<i>n</i> = 305	<i>n</i> = 146	<i>n</i> = 159	
Allergies, <i>n</i> (%)				
1	153 (50.2)	72 (49.3)	81 (50.9)	
2	75 (24.6)	39 (26.7)	36 (22.6)	
3	63 (20.7)	29 (19.9)	34 (21.4)	0.870
≥4	14 (4.6)	6 (4.1)	8 (5)	
13–24, months	<i>n</i> = 30	<i>n</i> = 23	<i>n</i> = 7	
Allergies, <i>n</i> (%)				
1	13 (43.3)	10 (43.5)	3 (42.9)	
2	6 (20)	4 (17.4)	2 (28.6)	
3	7 (23.3)	7 (30.4)	–	0.836
≥4	4 (13.3)	2 (8.7)	2 (28.6)	
Concomitant asthma	38 (4.2)	25 (3.8)	13 (5.2)	0.353
Family history of atopy, <i>n</i> (%)	361 (39.6)	259 (39.1)	102 (41)	0.648
Total IgE, median (IQR)	<i>n</i> = 869	<i>n</i> = 234	<i>n</i> = 635	
	49.8 (19.6–150.5)	43.7 (17.4–143)	79.5 (25.8–183.5)	<0.001
AEC, mm ³ , median (IQR)	<i>n</i> = 875	<i>n</i> = 242	<i>n</i> = 633	
	500 (250–800)	400 (200–700)	500 (300–900)	0.003
Eosinophils, %, median (IQR)	<i>n</i> = 875	<i>n</i> = 242	<i>n</i> = 633	
	4.6 (2.7–7.7)	4.1 (2.6–6.5)	4.9 (2.8–8)	0.007
Tryptase level, µg/L, median (IQR)	<i>n</i> = 85	<i>n</i> = 21	<i>n</i> = 64	
	3.7 (2.3–5.8)	3.2 (2.2–5.5)	3.9 (2.4–6.1)	0.511

[#] *p* value is given for the comparison of FA without AD and FA with AD subgroup. Italic *p* values (*p* < 0.05) are statistically significant. FA, food allergy; AD, atopic dermatitis; IQR, interquartile range; AEC, absolute eosinophil count.

Results

The medical records of 912 patients with FA and 1,140 patients with AD were evaluated in this study (Fig. 1). All the patients were younger than 24 months at their initial visits.

FA Group

Characteristics

The FA group consisted of 912 children with a median (interquartile range) age of 8.7 months (6–14.6 months) at the first visit, with a male predominance (66.4%). The median age at FA onset was 3 months (1–20 months). The first reaction after exposure was manifested as anaphylaxis in 42 (4.6%) children. Hence, 170 children (18.7%) had expe-

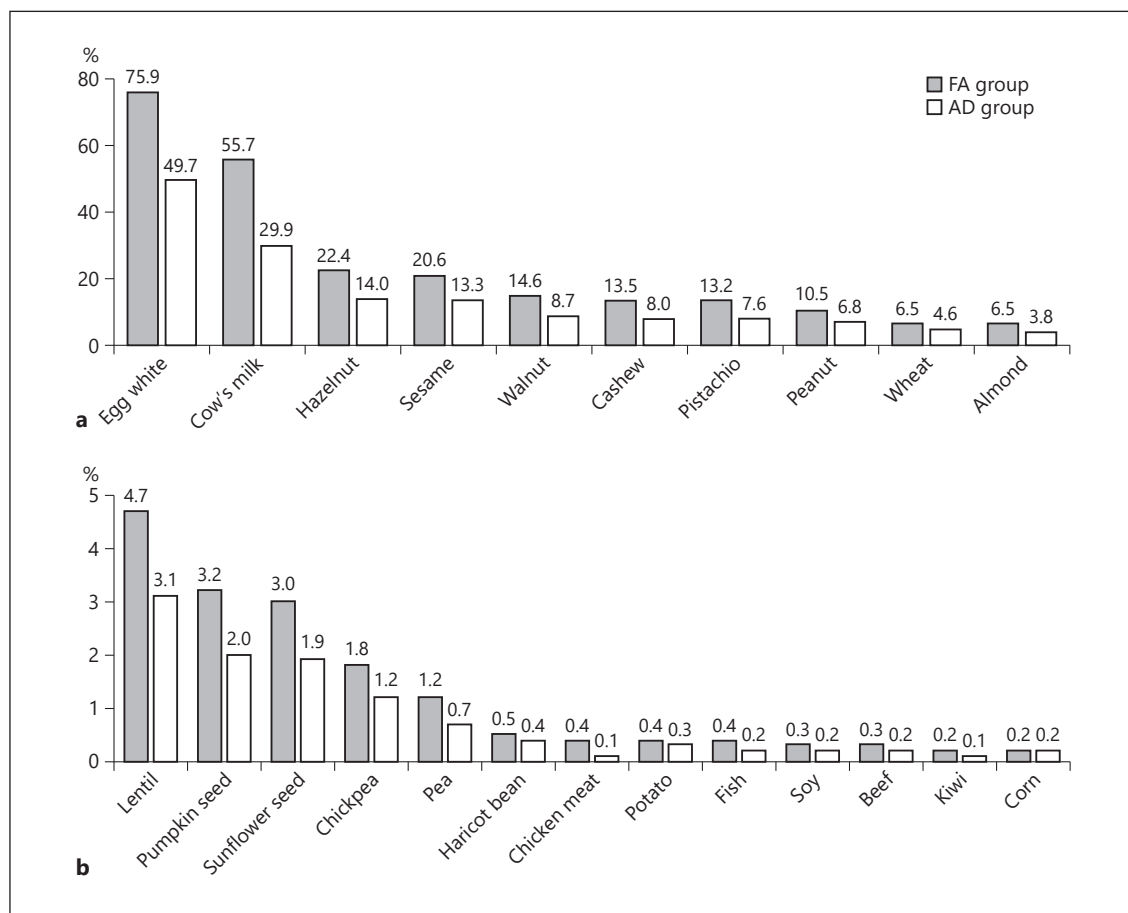


Fig. 2. Distribution of FA rates in FA and AD groups. **a** 10 most common FAs. **b** Less common FAs. FA, food allergy; AD, atopic dermatitis.

rienced anaphylaxis after incriminated food intake within the 2 years. The median age at initial FA evaluation was 6 months (5–7 months). Most of the patients (83.7%) were being fed with breast milk only, but some of them with formula (0.5%) and breast milk and formula (15.8%) during the first 6 months of life. Family history of atopy was present in 361 (39.6%) patients and 72.7% had AD. The FA group was further evaluated according to the presence of AD and significant differences were found between the groups in the age at symptom onset and admission, presence of multiple FAs, absolute eosinophil count, eosinophil percentage, and total IgE level (Table 1). However, there was no difference in gender, concomitant asthma, family history of atopy, and tryptase levels.

Causative Foods

Egg white was the most frequent food allergen source (75.9%) followed by cow's milk (55.7%), hazelnut (22.4%),

and sesame (20.6%). Soy, beef, kiwi and corn were observed as less frequent FAs (Fig. 2). The detection of FA in 99% of children with any kind of FA necessitate testing with at least 7 allergens in the test panel (Table 2). The most common allergens were egg white, cow's milk, hazelnut, sesame, walnut, cashew, and pistachio respectively. On the other hand, if all tree nuts were classified as a single group, the results were classified as follows: egg white (75.9%), cow's milk (55.7%), tree nuts (31.5%), sesame (20.6%), peanuts (10.5%), wheat (6.5%), and lentil (4.7%). Allergies to pumpkin seed, sunflower seed, chickpea, and pea had a prevalence of >1% in this age group.

When the FA group was divided into 2 subgroups, AD and non-AD, the most important difference for the allergy spectrum was the 2 most common allergies. Egg was the most common allergy followed by milk in the AD subgroup, whereas cow's milk allergy followed by egg in the non-AD subgroup (Fig. 3).

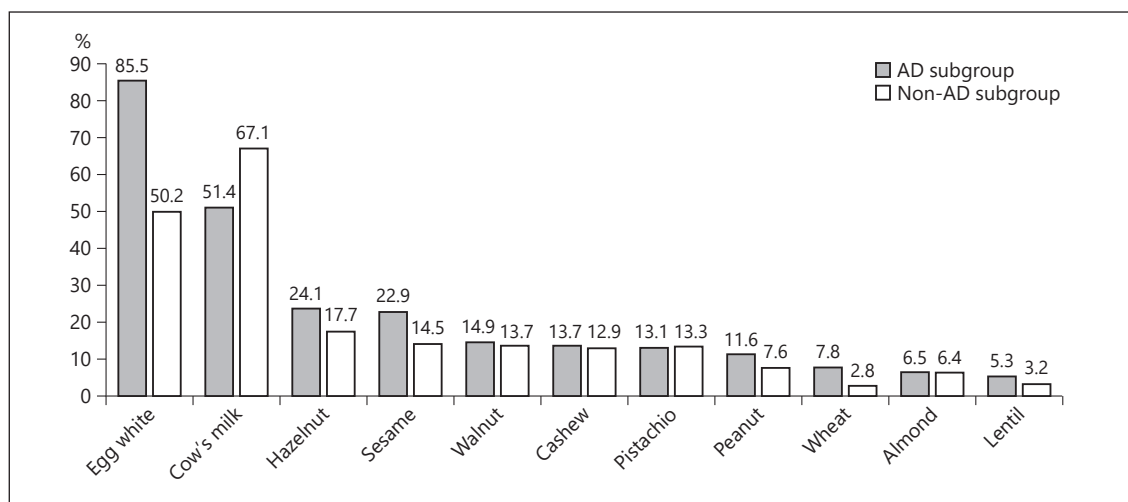


Fig. 3. Distribution of FA rates in FA subgroups. FAs, food allergy; AD, atopic dermatitis.

Table 2. Detecting 99% of children with any FA in the first 2 years of life

Allergen	n (%)	Added patients, n (%)	Total atopy, %
Egg white	692 (75.9)	–	75.9
Cow's milk	508 (55.7)	153 (16.8)	92.7
Hazelnut	204 (22.4)	36 (3.9)	96.6
Sesame	188 (20.6)	10 (1.1)	97.7
Walnut	133 (14.6)	5 (0.5)	98.2
Cashew	123 (13.5)	6 (0.7)	98.9
Pistachio	120 (13.2)	3 (0.35)	99.3
Peanut	96 (10.5)	0	
Almond	59 (6.5)	1	
Wheat	59 (6.5)	1	
Lentil	43 (4.7)	1	
Pumpkin seed	29 (3.2)	0	
Sunflower seed	27 (3.0)	0	
Chickpea	16 (1.8)	0	
Pea	11 (1.2)	0	
Others	23 (2.3)	0	

FA, food allergy.

Multiple FA (≥ 2 food category) was more common in the AD subgroup (56.8%) than in the non-AD subgroup (49.8%) of the FA group ($p = 0.009$) and subgroup analysis showed that the significance was due to very young infants (< 6 months; Table 1). Furthermore, we showed that as the severity of AD increased the number of allergies increased as well (Fig. 4).

AD Group Characteristics

The AD group consisted of 1,140 children with a median (interquartile range) age of 7.4 months (5.3–12.1 months) and male predominance (65.4%). The median age at AD onset was 2.5 months (1.5–4 months). The severity at AD was graded as mild (46.7%), moderate (31.6%) and severe (21.7%) at their initial outpatient clinic visit. Six hundred sixty-three (58.2%) of the patients had an IgE-mediated FA. Severe AD was significantly more frequent in the FA subgroup when compared to AD without FA (31.6 and 8.2% respectively; $p < 0.001$). Additionally, absolute eosinophil count, eosinophil percentage, and total IgE levels were significantly higher in AD with FA when compared to AD without FA in this subgroup ($p < 0.001$; Table 3).

Predictors of FA

The most common FA was egg white (49.7%) followed by cow's milk (29.9%), hazelnut (14%) and sesame (13.3%; Fig. 2) and 59.4% of the children had multiple FAs. The study group was evaluated according to the severity, that is, mild, moderate and severe AD, and the frequency of FA in these groups was found 36.6, 70.8, and 84.1% respectively. Risk factors of FA among infants with eczema were determined as the age at symptom onset and severity of AD. The risk of concomitant FA increased as the age at onset of AD decreased (OR 0.800 [95% CI 0.731–0.875]; $p < 0.001$) and the severity of AD increased (OR 2.350 [95% CI 1.898–2.911]; $p < 0.001$).

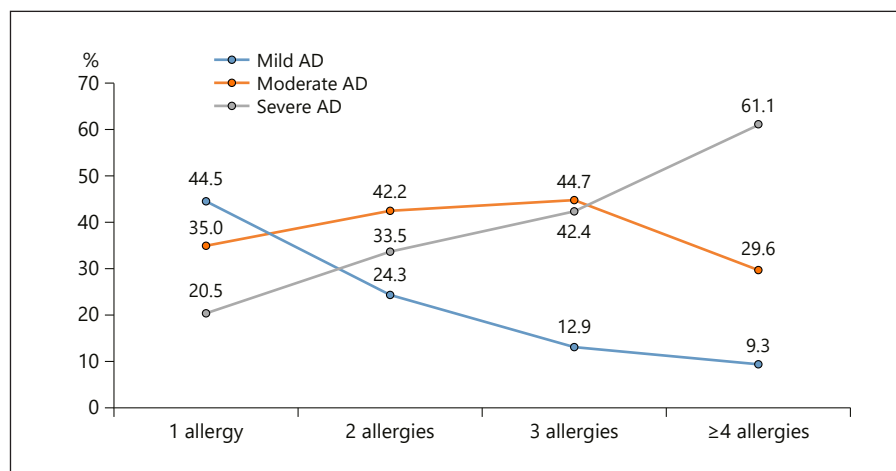


Fig. 4. Disease severity according to the number of FAs. AD, atopic dermatitis.

Table 3. Characteristics of AD group and its subgroups

	AD group (<i>n</i> = 1,140)	AD with FA (<i>n</i> = 663)	AD without FA (<i>n</i> = 477)	<i>p</i> value [#]
Gender, male, <i>n</i> (%)	746 (65.4)	447 (67.4)	299 (62.7)	0.055
Age at AD onset, months, median (IQR)	2.5 (1.5–4)	2 (1.5–3)	3 (2–5)	<0.001
Severity of AD, <i>n</i> (%)				<0.001
Mild	527 (46.7)	133 (29.6)	334 (70)	
Moderate	356 (31.6)	252 (38.7)	104 (21.8)	
Severe	245 (21.7)	206 (31.6)	39 (8.2)	
Total IgE, median (IQR)	<i>n</i> = 949 28.3 (10.4–109)	<i>n</i> = 635 43.7 (17.4–143)	<i>n</i> = 314 11.5 (4.5–28.2)	<0.001
AEC, mm ³ , median (IQR)	<i>n</i> = 1,001 400 (200–700)	<i>n</i> = 633 500 (300–900)	<i>n</i> = 368 300 (200–500)	<0.001
Eosinophils, %, median (IQR)	<i>n</i> = 1,001 4.2 (2.6–7.1)	<i>n</i> = 633 4.9 (2.8–8)	<i>n</i> = 368 3.6 (2.3–5.6)	<0.001

[#] *p* value is given for the comparison of AD with FA and AD without FA subgroups. Italic *p* values (*p* < 0.05) are statistically significant. IQR, interquartile range; AEC, absolute eosinophil count; FA, food allergy; AD, atopic dermatitis; IgE, immunoglobulin E.

Course of FA during the First (0–3 months) and Second 3 months (4–6 months) of Life in Exclusively Breastfed Infants

In order to assess FA course in exclusively breastfed infants with AD, 61 infants (68.9% boys) with at least 2 allergy testing (i.e., one within 0–3 months and second within 4–6 months of life [just before starting complementary feeding]) were analyzed for the change in FA spectrum and frequencies. The median age at onset of AD was 2 months (1–2 months) and 41% (*n* = 25) of them were diagnosed as severe AD according to o-SCORAD. The most common FAs in exclusively breastfed

infants (aged 0–3 months) were egg white (80.3%), cow's milk (62.3%), tree nuts (6.6%), sesame (6.6%) with 54% of the patients having multiple FAs. The distribution of common food allergens during 4–6 months was similar to 0–3 months; however, the frequency of multiple FAs during this period increased from 54 to 68.3%. No difference in egg white allergy rate between first and second 3 months of life was seen; however, higher rates of allergies were obtained in terms of cow's milk, hazelnut, sesame, walnut, cashew, pistachio, almond, wheat, lentil, and peanut (Table 4).

Table 4. The course of FAs during the first and second 3 months of life in breastfed children with atopic dermatitis ($n = 61$)

Allergen	0–3 months, n (%)	4–6 months, n (%)
Egg white	49 (80.3)	49 (80.3)
Cow's milk	38 (62.3)	42 (68.9)
Wheat	–	3 (4.9)
Lentil	–	2 (3.3)
Chickpea	–	1 (1.6)
Peanut	1 (1.6)	4 (6.6)
Sesame	4 (6.6)	7 (11.5)
Hazelnut	1 (1.6)	8 (13.1)
Walnut	4 (6.6)	9 (14.8)
Almond	–	1 (1.6)
Pistachio	1 (1.6)	3 (4.9)
Cashew	–	1 (1.6)

FAs, food allergies.

Discussion

FA evaluation is of great importance during the first 2 years of life in terms of both higher prevalence of FAs in this age group and for prediction of the reactions that will occur during the first introduction of complementary foods. In this study, we showed that the classical “8 food allergen panel” was not the most appropriate skin test panel for the children with prediagnosis of FA in the Eastern Mediterranean region. Sesame, lentil, pumpkin seed, and chickpea should be added to the food panel list. Furthermore, the different spectrum of tree nut allergies and lower rates of peanut allergy vary from western countries. Multiple FA was more common in the AD subgroup of the FA group, and as the severity of AD increased, the number of FAs increased as well. Similar to previous studies published in western countries, in addition to the presence of AD, the presence of early onset and severe eczema predicted the concomitant FA in our patients [4]. Our results reveal a significant change in the spectrum and frequency of FAs between the 0–3 and 4–6 months of life in exclusively breast-fed infants with AD indicating that FA evaluation should be considered before the initiation of complementary feeding.

The spectrum of FAs depends on geographical location, living style, and dietary habits. FA prevalence and patterns in children <5 years by some countries are summarized in Table 5. A previous study conducted in Turkey showed that the most frequent food allergens were egg, cow's milk, hazelnut, peanut, walnut, lentil, and wheat [9]. However, this study was criticized for

inappropriate food allergen panel [10]. Our study showed that cow's milk, egg, hazelnut, sesame, walnut, cashew, pistachio, peanut, wheat and almond allergy were the top 10 food allergens among young children in Turkey. The most common 2 allergies were found different in AD and non-AD subgroups. Egg was the most common allergy followed by milk in the AD subgroup, whereas cow's milk allergy followed by egg in the non-AD subgroup. In a study from Germany, 406 infants were included at age 4–6 months for egg sensitization and allergy and the risk ratio for being sensitized to egg was 14.0 for infants with eczema (95% CI 6.3–31.3) compared with those without eczema [11]. In another study of 2,184 patients with AD from 94 different centers in 12 countries, egg white was found the most common allergen in all countries, particularly Australia (54%), Italy (53%) and the United Kingdom (53%) [12]. The reason why egg was found to be more closely related to AD is still unknown. One hypothesis is that the interaction between the microbial proteins and the skin and presence of homologous proteins between microbes and egg allergen may be related to the development of IgE sensitization and egg allergy [13]. In a study including 51 children with AD IgE sensitization to egg white there was a significant association with IgE sensitization to staphylococcal superantigens in older children [14]. The larger studies are needed for confirmation of these findings.

In the literature, characteristics of allergy to the tree nuts species are extremely variable [15]. In the USA, the most common tree nut allergens are walnut and cashew nut [16], whereas hazelnut and walnut allergies are more common in Spain [17]. In our study, hazelnut, walnut, cashew, and pistachio were the most common tree nut allergies. Turkey is one of the leading countries in the production and consumption of tree nuts like hazelnut, pistachio and walnut and they are used in many local cuisine recipes. The high rates of tree nuts allergy are consistent with the country's consumption patterns [10]. However, in Turkey, cashew is not cultivated and cashew consumption is low. Thus, the high rate of cashew allergy observed in the present and previous studies may be due to cross-reaction with pistachios [18].

In recent years, given the increased awareness of its benefits, sesame has become more prevalent in western diet [19]. The prevalence of sesame allergy varies geographically and is common in countries where sesame is regularly consumed. In Israel, sesame is the third common food allergen after egg and cow's milk and the second leading cause of anaphylaxis after milk [20]. The

Table 5. FA prevalence and allergens by region

Country	Prevalence of clinical FA <5 years, %	Most common food allergens <5 years	Reference
China	3.8	Egg, cow's milk, peanut, fish, shrimp, and fruit	[33]
Japan	4.2	Egg, cow's milk, wheat, peanut, fish, fruits	[34]
Hong Kong	4.6–5.3	Shellfish, egg, peanut, milk, fish, fruits	[35, 36]
Australia	5.1	Egg, peanut, cow's milk, tree nuts and soy	[37]
USA	6	Cow's milk, peanut, egg, shellfish, tree nuts, fish (soy)	[38, 39]
Canada	8	Cow's milk, egg, peanut, tree nuts, fish and soy	[40]
United Kingdom	4–6	Egg, cow's milk, peanut, tree nuts, fish	[41]
France	4.19	Cow's milk, egg, kiwi, peanut, fish, tree nuts, and shrimp	[42, 43]

FA, food allergy.

population prevalence estimates of self-reported sesame allergy in the USA and Canada ranged from 0.1 to 0.2% [21, 22]. In our previous report, the ratio of sesame allergy among children with FA was 3.8% [9]. However, the current study showed that sesame allergy emerged as a common cause of FA in Turkey. Sesame seeds are commonly consumed in Turkey as the form of simit, tahini, and halva. The reason for the low prevalence in the previous study can be explained by the lack of sesame in the routine skin test panel and low awareness. Therefore, panels should include region specific allergens.

Multiple FAs are on the rise all over the world. In a recent study of 74 children aged 9 months to 7 years reported that 69% of the study population had multiple FAs [23].

In a study including 196 children and adolescents, the rate of multiple FAs was 57%, whereas in another study with 602 participants, it was found 78% [24, 25]. In the present study, we demonstrated 58% of children with FA had multiple FAs. This finding leads to the opinion that if an infant experiences an immediate allergic reaction with a food at first tastings during the course of complementary feeding, the risk of coexistence of other FAs increases by nearly 50%. In this case, each infant with immediate-type FA history needs to be tested with other possible food allergens beyond empirical elimination of the culprit food. In FA group, multiple allergy was considerably more common in children with AD (59.4%) than those without (49.8%), where the significance appears mainly due to very young infants (<6 months). This finding is in line with the previous study in which allergic children from the Netherlands were analyzed with specific IgE measurements for sensitization to the 10 most common foods and inhaled allergens [26]. In this retrospective study, polysensitization (≥ 5 allergens) was found to be significantly more common

in children with AD ($p < 0.001$, OR 4.96, 95% CI 3.35–7.35). The hypothesis is that allergy occurs through a defective skin barrier of AD during very early months of life.

Studies have described risk factors for FA in children with AD. Although two-thirds of AD patients are sensitive to food antigens, 15–40% have clinical findings [27, 28]. In a cohort of 620 infants with a family history of atopy, a strong association was also found between IgE-mediated FA and AD severity [29]. The other retrospective study have found that risk factors for FA were associated with the onset of eczema at 6 months or younger, SCORAD score of >40 (“severe eczema”) as well as younger than 2 years of age [30]. Martin et al. [4] reported that infants with AD were approximately 5 times more likely to develop IgE-mediated FA than infants without AD. Similarly, we established that the presence of AD and its early onset and severity predict concomitant FA.

It is not clear which food allergens need to be included in the SPT panel done in breastfed infants. Rennick et al. [31] evaluated 59 breastfed infants who had moderate to severe generalized AD and found that 90% of them had positive SPT for 1 or more of the 5 common food allergens (egg white, cow's milk, peanuts, wheat or soy). The most common positive SPT results were egg white, cow's milk and peanut. In another study, Flohr et al. [32] examined 619 exclusively breastfed infants at 3 months of age for AD and disease severity. They showed that children with AD were significantly more likely to be sensitized and a strong association between food sensitization and AD severity and sensitization to individual foods such as egg, cow's milk, and peanut was found. Our study showed that breastfed infants with AD were allergic to egg white and cow's milk, which is in line of previous studies. Unlike previous studies, hazelnut was the third most com-

mon cause of allergy in our subgroup of breastfed infants with AD.

Exclusively breastfed infants particularly with early onset of severe AD tend to have FA as shown in the previous and current study [4]. Therefore, these infants must be evaluated for FA. It is ideal to perform allergy tests just before starting complementary feeding. However, there is a continuing debate regarding when infants need to be tested. If it is done too early, a repetition of skin test is required immediately before onset of complementary feeding, since the allergic profile can change over time as demonstrated in this study. Moreover, evaluation of test results of young infants seems more difficult than children and adults. Another option, we suggest, is to avoid allergy testing to ensure that the mother makes empirical food elimination until the time of allergy testing. Our study provides guidance for parents that prefer empirical food elimination. Mothers of these young infants might be subjected to eliminate hen's egg, cow's milk, tree nuts, or sesame until allergen test is performed just before complementary feeding.

In conclusion, our findings showed that the classical "8 food allergen panel" was not the most appropriate food allergen panel for young children with prediagnosis of FA in the Eastern Mediterranean region possibly due to cultural differences. Western countries are dominant in the medical literature and each population should determine their priorities. Besides, due to the dynamic nature of cul-

tures, it should be kept in mind that these evaluations may need to be repeated at certain time intervals. Although medical evaluations are based on requirements and hints, knowing the characteristics and predictors of certain populations can pave the way for cost-effective allergy assessments through empirical practices as suggested in exclusively breastfed infants with AD.

Statement of Ethics

The study was approved by the local Ethics Committee (GO-19/913) of the Hacettepe University Faculty of Medicine.

Disclosure Statement

The authors declare that there is no conflict of interest and no funding.

Funding Sources

There is no funding.

Author Contributions

M.K. wrote the article. G.K., U.M.S., and O.U.S. examined the patients and made the follow-ups. M.K. and U.M.S. made the statistical analysis. B.E.S. had primary responsibility for protocol development, outcome assessment and data analysis, and prepared the article with M.K.

References

- 1 Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, et al. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol*. 2007 Sep;120(3):638–46.
- 2 Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored expert panel report. *Nutr Res*. 2011 Jan;31(1):61–75.
- 3 Allen KJ, Koplin JJ. The epidemiology of IgE-mediated food allergy and anaphylaxis. *Immunol Allergy Clin North Am*. 2012 Feb;32(1):35–50.
- 4 Martin PE, Eckert JK, Koplin JJ, Lowe AJ, Gurrin LC, Dharmage SC, et al. Which infants with eczema are at risk of food allergy? Results from a population-based cohort. *Clin Exp Allergy*. 2015 Jan;45(1):255–64.
- 5 du Toit G, Tsakok T, Lack S, Lack G. Prevention of food allergy. *J Allergy Clin Immunol*. 2016 Apr;137(4):998–1010.
- 6 Genuiteit J, Seibold AM, Apfelbacher CJ, Konstantinou GN, Koplin JJ, La Grutta S, et al.; Task Force 'Overview of Systematic Reviews in Allergy Epidemiology (OSRAE)' of the EAACI Interest Group on Epidemiology. Overview of systematic reviews in allergy epidemiology. *Allergy*. 2017 Jun;72(6):849–56.
- 7 Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol*. 1980; 92 Suppl:44–7.
- 8 Oranje AP, Glazenburg EJ, Wolkerstorfer A, de Waard-van der Spek FB. Practical issues on interpretation of scoring atopic dermatitis: the SCORAD index, objective SCORAD and the three-item severity score. *Br J Dermatol*. 2007 Oct;157(4):645–8.
- 9 Yavuz ST, Sahiner UM, Buyuktiryaki B, Soyer OU, Tuncer A, Sekerel BE, et al. Phenotypes of IgE-mediated food allergy in Turkish children. *Allergy Asthma Proc*. 2011 Nov-Dec;32(6):47–55.
- 10 Cetinkaya PG, Buyuktiryaki B, Soyer O, Sahiner UM, Sackesen C, Sekerel BE. Phenotypical characterization of tree nuts and peanut allergies in east Mediterranean children. *Allergol Immunopathol (Madr)*. 2019, Epub ahead of print.
- 11 Bellach J, Schwarz V, Ahrens B, Trendelenburg V, Aksünger Ö, Kalb B, et al. Randomized placebo-controlled trial of hen's egg consumption for primary prevention in infants. *J Allergy Clin Immunol*. 2017 May;139(5):1591–1599.e2.
- 12 de Benedictis FM, Franceschini F, Hill D, Naspitz C, Simons FE, Wahn U, et al.; EP-AAC Study Group. The allergic sensitization in infants with atopic eczema from different countries. *Allergy*. 2009 Feb;64(2):295–303.
- 13 Ong PY. The PATHOGENESIS of Food Allergy. *Front Pediatr*. 2019 Nov;7:484.
- 14 Ong PY. Association between egg and staphylococcal superantigen IgE sensitizations in atopic dermatitis. *Allergy Asthma Proc*. 2014 Jul-Aug;35(4):346–8.
- 15 McWilliam V, Peters R, Tang ML, Dharmage S, Ponsonby AL, Gurrin L, et al.; HealthNuts investigators. Patterns of tree nut sensitization and allergy in the first 6 years of life in a population-based cohort. *J Allergy Clin Immunol*. 2019 Feb;143(2):644–50.e5.

- 16 McWilliam V, Koplin J, Lodge C, Tang M, Dharmage S, Allen K. The Prevalence of Tree Nut Allergy: A Systematic Review. *Curr Allergy Asthma Rep*. 2015 Sep;15(9):54.
- 17 Haroun-Díaz E, Azofra J, González-Mancebo E, de Las Heras M, Pastor-Vargas C, Esteban V, et al. Nut Allergy in Two Different Areas of Spain: Differences in Clinical and Molecular Pattern. *Nutrients*. 2017 Aug;9(8):E909.
- 18 Cetinkaya PG, Karaguzel D, Esenboğa S, Sahiner UM, Soyer O, Buyuktiryaki B, et al. Pistachio and cashew nut allergy in childhood: predictive factors towards development of a decision tree. *Asian Pac J Allergy Immunol*. 2019, Epub ahead of print.
- 19 Gangur V, Kelly C, Navuluri L. Sesame allergy: a growing food allergy of global proportions? *Ann Allergy Asthma Immunol*. 2005 Jul;95(1):4–11; quiz 11–3, 44.
- 20 Dalal I, Binson I, Reifen R, Amitai Z, Shohat T, Rahmani S, et al. Food allergy is a matter of geography after all: sesame as a major cause of severe IgE-mediated food allergic reactions among infants and young children in Israel. *Allergy*. 2002 Apr;57(4):362–5.
- 21 Ben-Shoshan M, Harrington DW, Soller L, Fragapane J, Joseph L, St Pierre Y, et al. A population-based study on peanut, tree nut, fish, shellfish, and sesame allergy prevalence in Canada. *J Allergy Clin Immunol*. 2010 Jun;125(6):1327–35.
- 22 Sicherer SH, Muñoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. *J Allergy Clin Immunol*. 2010 Jun;125(6):1322–6.
- 23 Herbert LJ, Mehta P, Sharma H. Mealtime behavior among parents and their young children with food allergy. *Ann Allergy Asthma Immunol*. 2017 Mar;118(3):345–50.
- 24 Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol*. 1997 Oct;100(4):444–51.
- 25 Park J, Ahn S, Sicherer S. Prevalence of allergy to multiple versus single foods in a pediatric food allergy referral practice. *J Allergy Clin Immunol*. 2010;125(2):AB216.
- 26 Broeks SA, Brand PL. Atopic dermatitis is associated with a fivefold increased risk of polysensitisation in children. *Acta Paediatr*. 2017 Mar;106(3):485–8.
- 27 Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BA, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics*. 1998 Mar;101(3):E8.
- 28 Spergel JM, Boguniewicz M, Schneider L, Hanifin JM, Paller AS, Eichenfield LF. Food Allergy in Infants With Atopic Dermatitis: Limitations of Food-Specific IgE Measurements. *Pediatrics*. 2015 Dec;136(6):e1530–8.
- 29 Hill DJ, Hosking CS. Food allergy and atopic dermatitis in infancy: an epidemiologic study. *Pediatr Allergy Immunol*. 2004 Oct;15(5):421–7.
- 30 Gray CL, Levin ME, Zar HJ, Potter PC, Khumalo NP, Volkwyn L, et al. Food allergy in South African children with atopic dermatitis. *Pediatr Allergy Immunol*. 2014 Oct;25(6):572–9.
- 31 Rennick GJ, Moore E, Orchard DC. Skin prick testing to food allergens in breast-fed young infants with moderate to severe atopic dermatitis. *Australas J Dermatol*. 2006 Feb;47(1):41–5.
- 32 Flohr C, Perkin M, Logan K, Marrs T, Radulovic S, Campbell LE, et al. Atopic dermatitis and disease severity are the main risk factors for food sensitization in exclusively breastfed infants. *J Invest Dermatol*. 2014 Feb;134(2):345–50.
- 33 Sandin A, Annus T, Björkstén B, Nilsson L, Riikjäär MA, van Hage-Hamsten M, et al. Prevalence of self-reported food allergy and IgE antibodies to food allergens in Swedish and Estonian schoolchildren. *Eur J Clin Nutr*. 2005 Mar;59(3):399–403.
- 34 Kusunoki T, Morimoto T, Nishikomori R, Heike T, Fujii T, Nakahata T. Allergic status of schoolchildren with food allergy to eggs, milk or wheat in infancy. *Pediatr Allergy Immunol*. 2009 Nov;20(7):642–7.
- 35 Leung TF, Yung E, Wong YS, Lam CW, Wong GW. Parent-reported adverse food reactions in Hong Kong Chinese pre-schoolers: epidemiology, clinical spectrum and risk factors. *Pediatr Allergy Immunol*. 2009 Jun;20(4):339–46.
- 36 Ho MH, Lee SL, Wong WH, Ip P, Lau YL. Prevalence of self-reported food allergy in Hong Kong children and teens—a population survey. *Asian Pac J Allergy Immunol*. 2012 Dec;30(4):275–84.
- 37 Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and pre-determined challenge criteria in infants. *J Allergy Clin Immunol*. 2011 Mar;127(3):668–76.e1–2.
- 38 Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongracic J, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics*. 2011 Jul;128(1):e9–17.
- 39 Taylor-Black S, Wang J. The prevalence and characteristics of food allergy in urban minority children. *Ann Allergy Asthma Immunol*. 2012 Dec;109(6):431–7.
- 40 Soller L, Ben-Shoshan M, Harrington DW, Fragapane J, Joseph L, St Pierre Y, et al. Overall prevalence of self-reported food allergy in Canada. *J Allergy Clin Immunol*. 2012 Oct;130(4):986–8.
- 41 Venter C, Pereira B, Voigt K, Grundy J, Clayton CB, Higgins B, et al. Prevalence and cumulative incidence of food hypersensitivity in the first 3 years of life. *Allergy*. 2008 Mar;63(3):354–9.
- 42 Kanny G, Moneret-Vautrin DA, Flabbee J, Beaudouin E, Morisset M, Thevenin F. Population study of food allergy in France. *J Allergy Clin Immunol*. 2001 Jul;108(1):133–40.
- 43 Rancé F, Grandmottet X, Grandjean H. Prevalence and main characteristics of schoolchildren diagnosed with food allergies in France. *Clin Exp Allergy*. 2005 Feb;35(2):167–72.