

Clinical phenotypes of childhood food allergies based on immune mechanisms: A multicenter study

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ABSTRACT

Background: Food allergies (FA) are an important public health concern that place a major burden on the lives of children and their families. The complex pathogenesis of FAs results in multisystemic and heterogenous clinical presentations.

Objective: To evaluate, according to immune mechanisms, the characteristics and risk factors of childhood FA in Turkey.

Methods: This descriptive multicenter study included 1248 children with FA, aged < 18 years,, who were evaluated by pediatric allergists in 26 different centers.

Results: Immune mechanisms of FA were immunoglobulin E (IgE) mediated in 71.8%, non-IgE mediated in 15.5%, and mixed IgE/non-IgE mediated in 12.7% of the patients. An episode of anaphylaxis had occurred in 17.6% of IgE-mediated FA. The most common food allergens were classified into five categories (in order of decreasing frequency): cow's milk, egg, tree nuts and/or peanut, wheat, and seafood. Allergies to cow's milk and egg declined significantly with age, whereas tree nuts and/or peanut allergies increased with age. The 0–2 year age group accounted for 62.5% of the cases. The most frequent cause of FA and food anaphylaxis was cow's milk before age 13 years and tree nuts and/or peanut during adolescence (ages 13–18 years). Compared with other phenotypes, male sex (odds ratio [OR] 1.486; $p = 0.032$), sibling (s) (OR 1.581; $p = 0.021$), and maternal atopy (OR 1.531; $p = 0.045$) increased the likelihood of IgE-mediated FA, whereas high household income (OR 1.862; $p = 0.026$) increased the likelihood of non-IgE-mediated FA in multivariate regression analysis.

Conclusion: This study showed that the clinical findings of FA were highly variable, depending on age and underlying immune mechanism. Knowing the population characteristics will enable better management of FA in children.

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Food allergies (FA) place a substantial burden on the lives of children who are affected and their families, and may lead to important consequences.¹ FA is the development of an immune response in the body against a certain food, and the clinical presentation is known to vary, depending on the underlying immune mechanism. Although they vary by country, the most prevalent FAs in general are cow's milk, egg, wheat, tree nuts, peanut, fish, and other seafood. In addition to these major food groups, allergy to various other foods may also develop. Immune responses against food may be immunoglobulin E (IgE) mediated, non-IgE-mediated, or mixed IgE-mediated/non-IgE-mediated responses. Despite the

steady stream of new data, the characteristic features of the different immunologic types of FA and their associated risk factors remain unclear.^{2,3}

Although there are some well-known risk factors reported in the etiology of FA, their characteristics may vary among populations.^{4,5} As with many chronic diseases, FA is also influenced by epigenetic factors.^{6,7} Food consumption and preparation habits, and social, cultural, ethnic, and geographic characteristics lead to societal differences in FAs.^{8,9} Therefore, the characteristic features of FAs must be determined in detail for each society. Population data based on clinical evaluations performed by pediatric allergists will provide more accurate information than telephone-based surveys or reviews of electronic medical records. The ability to obtain complete and reliable data is a major concern in such studies. Our aim was to compare the defining clinical characteristics and risk factors of children diagnosed with FA by pediatric allergists according to immune mechanism in Turkey. To the best of our knowledge, there are no other studies in the literature that present national FA data when using this method.

The affiliations of the members of the writing committee and the names of all the authors are provided in the online appendix

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METHODS

Study Population

This study was designed as a descriptive and multicenter study. Because Turkey is a large area and has different geographic regions, allergy centers from all the regions were invited to participate (Mediterranean, Aegean, Marmara, Black Sea, Central Anatolia, and Eastern Anatolia). Pediatric allergy departments from 26 tertiary hospitals participated in the study. The study was conducted in children <18 years of age with FA diagnosed by pediatric allergists who worked in these centers. Case collection was performed between December 2017 and January 2019. Consecutive children with FA who presented to any of these centers after initiation of the study were included. Informed consent was obtained from the families of all the children included in the study. Patients who did not fulfill the diagnostic criteria for FA, those whose family did not provide informed consent, and those with chronic diseases other than allergic disease were excluded from the study.

All the centers used similar diagnostic modalities for FA, including a detailed medical history, physical examination, elimination diets, skin-prick test (SPT), and/or specific IgE (sIgE) tests. If the results were inconsistent with the clinical history or if the patient's food-related history was unclear, then oral food challenge (OFC) was planned. OFC was not performed in patients who had food anaphylaxis, showed a risk of severe food-related reactions, or whose family did not consent to the challenge. OFC protocols were developed based on guidelines according to FA phenotypes.^{4,10,11}

FAs Were Diagnosed in Accordance with the Underlying Immune Mechanism as Follows

IgE-Mediated FA. The diagnosis of IgE-mediated FA was defined as the presence of sIgE to a certain food demonstrated by elevated sIgE titers (>0.35 kU/L) and/or positive SPTs (≥ 3 mm above the negative control). It also had to meet one of the following three criteria:

- A consistent and clear-cut history of immediate-type reactions (wheezing, urticaria, angioedema, oral allergy syndrome, rhinitis, and gastrointestinal symptoms) that occur after food ingestion benefit from an elimination diet⁴
- Anaphylaxis with the causative food
- A positive OFC result with the suspected food

Food Anaphylaxis. A diagnosis of food anaphylaxis was made according to the guidelines and widely accepted criteria.^{4,12} Clinically, food anaphylaxis is a severe multisystem reaction characterized by rapidly

developing airway, breathing, and/or circulation symptoms, usually associated with skin and mucosal changes after ingestion of the causative food.

Non-IgE-Mediated FA. Allergic proctocolitis, food protein-induced enterocolitis syndrome, and food protein-induced enteropathy were included in the non-IgE-mediated group. The diagnosis was based on typical clinical features (vomiting, diarrhea, mucous stool, blood in stool), resolution with removal of the offending food, and reoccurrence of symptoms with food challenge.^{4,11}

Mixed IgE-/Non-IgE-Mediated FA. The mixed IgE-/non-IgE-mediate group included children diagnosed with both IgE- and non-IgE-mediated FA simultaneously, those with eosinophilic esophagitis (EoE), and those with certain types of atopic dermatitis (who had IgE-mediated FA and presented with both immediate and delayed reactions to foods). The diagnosis of mixed-type FA was largely based on food-related clinical features. Endoscopy and biopsy were performed to confirm the diagnosis of EoE.^{4,7,10}

Data Collection

To ensure standard data collection in all the centers, a data collection form was created, which included detailed demographic, environmental exposure, clinical, and laboratory parameters (SPT, prick-to-prick test, total eosinophil count, and total IgE and sIgE levels). Data were entered into these forms by the participating pediatric allergists in face-to-face interviews with the patients and their families. Clinical histories were taken from the children's parents or legal guardians. Each site attended to the study with at least 40 cases. There were no differences between the case numbers of the sites. All data were compiled and analyzed in the Department of Public Health in Akdeniz University Faculty of Medicine. Of the 1270 cases evaluated, 1248 with sufficient data (~90% of the data collection form) were included in the analysis. Approval for this study was granted by the ethics board of Cukurova University School of Medicine, Adana (2017/63-50).

Statistical Methods

Statistical analyses were performed by using SPSS 20.0 Software (Chicago, IL, USA). Normality of variable distributions was analyzed by using graphic and analytical methods. Student's *t*-test and χ^2 goodness-of-fit test were used as appropriate, and one-way analysis of variance was used for variables, with homogeneity of variances shown by using the Levene test. If a significant difference was detected among the groups, then pairwise *post hoc* comparisons were

Table 1 Demographic characteristics of the children with food allergies

Characteristic	n (%)	Group			p
		IgE Mediated (n = 896 [71.8%])	Non-IgE Mediated (n = 193 [15.5%])	Mixed IgE/non-IgE Mediated (n = 159 [12.7%])	
Sex, n (%)					0.006*
Boys	774 (62.0)	580 (64.7)	104 (53.9)	90 (56.6)	
Girls	474 (38.0)	316 (35.3)	89 (46.1)	69 (43.4)	
Age at onset, median (IQR), mo	4.0 (2.0–6.0)	5.0 (2.5–6.0)	2.0 (1.0–5.0)	3.5 (2.0–6.0)	<0.001*#§
Age at diagnosis, median (IQR), mo	6.0 (4.0–11.75)	7.0 (5.0–12.0)	4.5 (2.4–7.0)	6.0 (4.0–12.0)	<0.001*§
Age groups, n (%)					
0–2 y	780 (62.5)	526 (58.7)	155 (80.3)	99 (62.3)	
3–5 y	321 (25.7)	243 (27.1)	38 (19.7)	40 (25.2)	
6–12 y	119 (9.6)	103 (11.5)	—	16 (10.0)	
13–18 y	28 (2.2)	24 (2.7)	—	4 (2.5)	
Absolute eosinophil count, median (IQR), mm ³	369.0 (209.6–590.4)	393.3 (221.8–633.8)	246.9 (153.7–431.0)	405.0 (207.5–570.8)	<0.001*§
IgE level, median (IQR), IU/L	57.5 (17.6–210.8)	86.0 (25.0–253.0)	12.0 (5.0–26.8)	53.4 (15.0–183.0)	<0.001*#§

IgE = Immunoglobulin E; IQR = interquartile range.

Bonferroni adjustment ($p = 0.017$) was applied for the group responsible for significance. Categorical variables were compared using chi-square test and continuous variables were compared using Mann–Whitney U test. Columns: 1, IgE-mediated; 2, Non-IgE-mediated; 3, Mixed IgE/non-IgE mediated.

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performed by using the Tukey test. Variables with non-normal distribution were expressed in median values. Non-normally distributed parameters and ordinal variables were compared by using the Mann–Whitney U test, Wilcoxon test, and Kruskal–Wallis test. If a significant difference was detected among the groups, then pairwise comparisons were made by using the Mann–Whitney U test with Bonferroni correction. A p value of <0.05 was considered statistically significant.

Logistic regression analysis was used to determine the risk factors for immune mechanisms of FA, which were defined as the dependent variables. The significance of parameters (independent variables) that affected each dependent variable was evaluated by using univariate analysis. Parameters found to be significant were included in the multivariate logistic regression model. Models with a Hosmer and Lemeshow test statistic of >0.05 were regarded as showing a good fit. The odds ratios (OR) of the parameters included in the model are given in the tables and figures.

RESULTS

A total of 1248 children with FA, 774 boys (62%) and 474 girls (38%), were evaluated. Immune mechanisms of FA were identified as IgE mediated in 71.8% ($n = 896$), non-IgE mediated in 15.5% ($n = 193$), and mixed IgE/non-IgE mediated in 12.7% ($n = 159$) of all the patients. The majority of the patients (62.5%) were in the age group of 0–2 years. Another 25.7% of the patients were 3–5, 9.6% were 6–12, and 2.2% were 13–18 years of age. The most common immune mechanism in all the age groups was IgE mediated (Tables 1 and 2). The IgE-mediated group had a significantly higher male ratio, mean age at onset and diagnosis, absolute eosinophil count, and total IgE levels compared with the other groups. Of the non-IgE-mediated FAs, 73.6% ($n = 142$) were allergic proctocolitis, 20.2% ($n = 39$) were food protein-induced enterocolitis syndrome, and 6.2% ($n = 12$) were food protein-induced enteropathy.

Of the patients with mixed-type FAs, 54.7% ($n = 87$) have the diagnosis of both IgE- and non-IgE-mediated FAs, 13.2% ($n = 21$) had EoE, and 32.1% ($n = 51$) had

Table 2 Clinical characteristics of children with FAs

Clinical characteristics	n (%)	Groups, n (%)			p
		IgE Mediated, 896 (71.8)	Non-IgE Mediated, 193 (15.5)	Mixed IgE/non-IgE Mediated, 159 (12.7)	
Major FAs					
Cow's milk					<0.001*#§
No	384 (30.8)	339 (37.8)	14 (7.3)	31 (19.5)	
Yes	864 (69.2)	557 (62.2)	179 (92.7)	128 (80.5)	
Egg					<0.001*§
No	521 (41.7)	318 (35.5)	146 (75.6)	57 (35.8)	
Yes	727 (58.3)	578 (64.5)	47 (24.4)	102 (64.2)	
Tree nuts and/or peanut					<0.001*§
No	1052 (84.3)	730 (81.5)	192 (99.5)	130 (81.8)	
Yes	196 (15.7)	166 (18.5)	1 (0.5)	29 (18.2)	
Wheat					<0.001*#§
No	1140 (91.3)	819 (91.4)	190 (98.4)	131 (82.4)	
Yes	108 (8.7)	77 (8.6)	3 (1.6)	28 (17.6)	
Seafood					0.002 #§
No	1201 (96.2)	864 (96.4)	191 (99)	146 (91.8)	
Yes	47 (3.8)	32 (3.6)	2 (1.0)	13 (8.2)	
Multiple FA					<0.001*#§
Single food	657 (52.6)	444 (49.6)	156 (80.8)	57 (35.8)	
Multiple foods	591 (47.4)	452 (50.4)	37 (19.2)	102 (64.2)	
Food-related symptoms					
Anaphylaxis					<0.001*#§
No	1081 (86.6)	738 (82.4)	193 (100)	150 (94.3)	
Yes	167 (13.4)	158 (17.6)	—	9 (5.7)	
Wheezing					<0.001*§
No	1148 (92.0)	808 (90.2)	193 (100)	147 (92.5)	
Yes	100 (8.0)	88 (9.8)	—	12 (7.5)	
Urticaria					<0.001*#§
No	668 (53.5)	379 (42.3)	193 (100)	96 (60.4)	
Yes	580 (46.5)	517 (57.7)	—	63 (39.6)	
Angioedema					<0.001*#§
No	1090 (87.3)	750 (83.7)	193 (100)	147 (92.5)	
Yes	158 (12.7)	146 (16.3)	—	12 (7.5)	
Oral allergy syndrome					0.001*§
No	1177 (94.3)	838 (93.5)	193 (100)	146 (91.8)	
Yes	71 (5.7)	58 (6.5)	—	13 (8.2)	
Rhinitis					0.001*§
No	1174 (94.1)	831 (92.7)	193 (100)	150 (94.3)	
Yes	74 (5.9)	65 (7.3)	—	9 (5.7)	
Eczema exacerbation					<0.001*§
No	859 (68.8)	560 (62.5)	193 (100)	106 (66.7)	
Yes	389 (31.2)	336 (37.5)	—	53 (33.3)	
Vomiting					<0.001*#§
No	1091 (87.4)	782 (87.3)	183 (94.8)	126 (79.2)	
Yes	157 (12.6)	114 (12.7)	10 (5.2)	33 (20.8)	

Table 2 Continued

Clinical characteristics	n (%)	Groups, n (%)			p
		IgE Mediated, 896 (71.8)	Non-IgE Mediated, 193 (15.5)	Mixed IgE/non-IgE Mediated, 159 (12.7)	
Diarrhea					<0.001 [#]
No	1172 (93.9)	853 (95.2)	181 (93.8)	138 (86.8)	
Yes	76 (6.1)	43 (4.8)	12 (6.2)	21 (13.2)	
Mucous stool					0.001 ^{*#}
No	1093 (87.6)	846 (94.4)	141 (73.1)	106 (66.7)	
Yes	155 (12.4)	50 (5.6)	52 (26.9)	53 (33.3)	
Bloody stool					<0.001 ^{*#}
No	1127 (90.3)	874 (97.5)	145 (75.1)	108 (67.9)	
Yes	121 (9.7)	22 (2.5)	48 (24.9)	51 (32.1)	
Other atopic diseases					
Asthma					<0.001 ^{*\$}
No	1117 (89.5)	780 (87.1)	193 (100)	144 (90.6)	
Yes	131 (10.5)	116 (12.9)	—	15 (9.4)	
Allergic rhinitis					<0.001 ^{*\$}
No	1109 (88.9)	774 (86.4)	193 (100)	142 (89.3)	
Yes	139 (11.1)	122 (13.6)	—	17 (10.7)	
Allergic conjunctivitis					0.005 ^{*\$}
No	1199 (96.1)	852 (95.1)	193 (100)	154 (96.9)	
Yes	49 (3.9)	44 (4.9)	—	5 (3.1)	
Atopic dermatitis					<0.001 ^{*#\$}
No	690 (55.3)	389 (43.4)	193 (100)	108 (67.9)	
Yes	558 (44.7)	507 (56.6)	—	51 (32.1)	

FA = Food allergy; IgE = Immunoglobulin E.

Bonferroni adjustment ($p = 0.017$) was applied for the group responsible for significance. Categorical variables were compared using chi-square test and continuous variables were compared using Mann–Whitney U test. Columns: 1, IgE-mediated; 2, Non-IgE-mediated; 3, Mixed IgE/non-IgE mediated.

*1–2.

#1–3

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atopic dermatitis (Online Supplemental Table 1). Diagnostic OFC was performed in 56.5% ($n = 506$) of the children with IgE-mediated FA in our study. The most challenged food was cow's milk (76.9% [$n = 389$]) followed by egg (58.3% [$n = 295$]), wheat (12.8% [$n = 65$]), tree nuts and/or peanut (10.5% [$n = 53$]), seafood (3.2% [$n = 16$]), and other foods (5.3% [$n = 27$]). The rate of anaphylaxis was 14.2% ($n = 72$) in diagnostic OFCs ($n = 506$). Cow's milk was the most common trigger food for both non-IgE-mediated and mixed-type FAs.

Food Allergens

The most common FAs were classified into five categories: cow's milk, egg (white and yolk), tree nuts and/

or peanut, wheat, and seafood (fish and other seafood). Other less-common FAs were not included in further statistical analyses due to the small patient numbers (Online Supplemental Table 2). Among all the children with FA who were analyzed, irrespective of immune mechanism, the most common causative food was cow's milk, followed by egg, tree nuts and/or peanut, wheat, and seafood (Table 2). When evaluated in terms of immune mechanism, the most common causes of IgE-mediated and non-IgE-mediated FAs were egg and cow's milk, respectively (Fig. 1).

Evaluation of FAs by age group (Table 3) showed that the most common culprit food was cow's milk before adolescence and tree nuts and/or peanut in adolescence (13–18 years of age). The relative distribution of common FAs by age group irrespective of

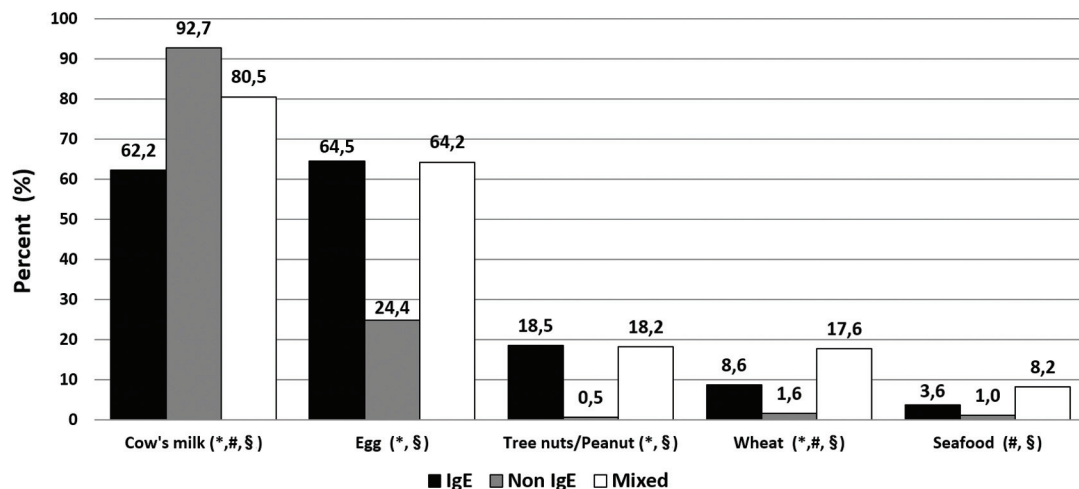


Figure 1. Comparison of the proportions of common food allergens within the immunologic types. Bonferroni adjustment ($p = 0.017$) was applied for the group responsible for significance. Categorical variables were compared using chi-square test. IgE = Immunglobulin E. Bars: 1, IgE-mediated; 2, Non-IgE-mediated; 3, Mixed IgE/non-IgE mediated. *1–2, #1–3, §2–3.

Table 3 Characteristics of major food allergies by age group

Characteristic	No. Subjects	Age Group, n (%)			
		0–2 y	3–5 y	6–12 y	13–18 y
Total children per group		780 (62.5)	321 (25.7)	119 (9.6)	28 (2.2)
Food allergens					
Cow's milk	864	551 (70.6)	236 (73.5)	70 (57.4)	7 (25)
Egg	727	492 (63.1)	178 (55.5)	50 (41)	7 (25)
Tree nuts and/or peanut	196	85 (11.0)	63 (9.6)	36 (29.5)	12 (42.8)
Wheat	108	63 (8.0)	27 (8.4)	13 (10.7)	5 (17.9)
Seafood	47	22 (2.8)	13 (4.0)	9 (7.4)	3 (10.7)
Food anaphylaxis					
Cow's milk	91	28 (3.6)	38 (11.8)	23 (19.3)	2 (7.1)
Egg	43	21 (2.7)	16 (5.0)	5 (4.2)	1 (3.6)
Tree nuts and/or peanut	34	2 (0.3)	16 (5.0)	11 (9.2)	5 (17.9)
Wheat	3	1 (0.1)	1 (0.3)	1 (0.8)	—
Seafood	3	—	2 (0.6)	1 (0.8)	—

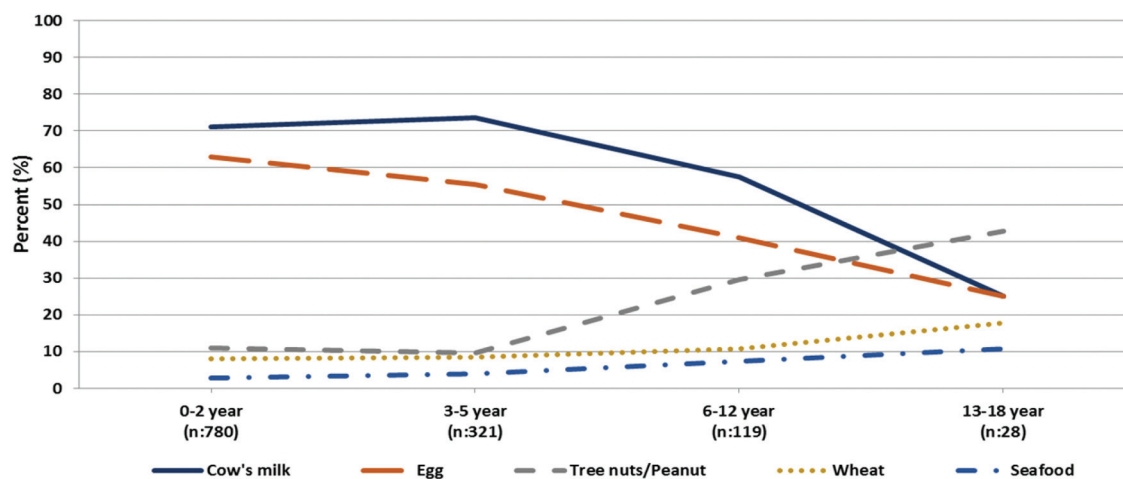
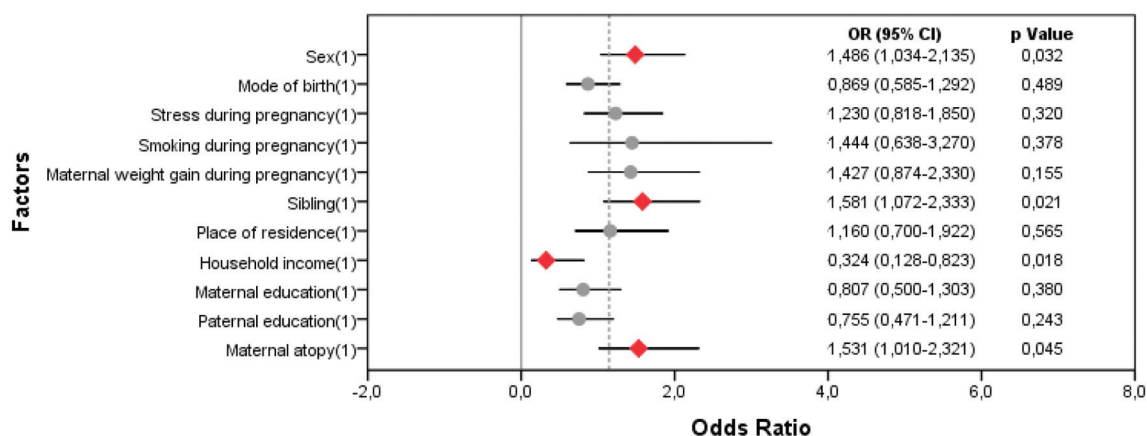
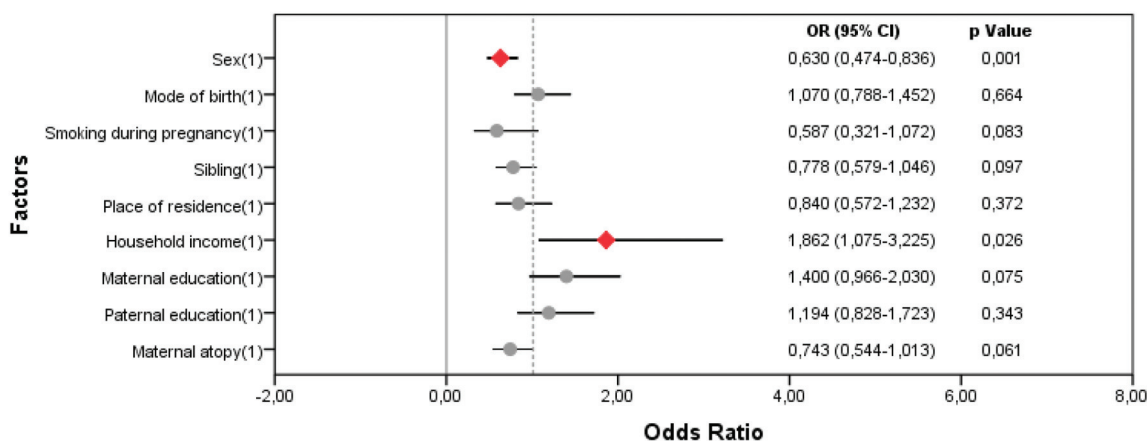


Figure 2. Distribution of common food allergies by age group ($N = 1248$).

A. IgE-mediated food allergies



B. Non-IgE-mediated food allergies



C. Mixed IgE and non-IgE-mediated food allergies

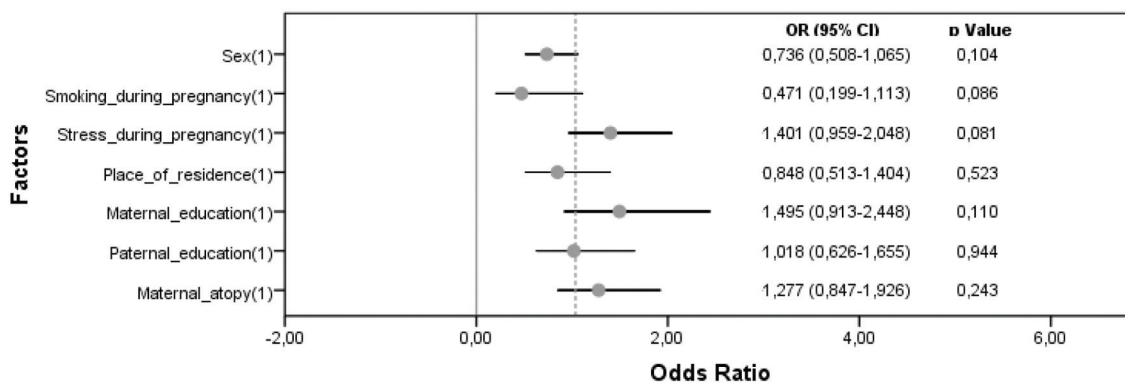


Figure 3. Risk factors for immunologic types of FA determined in logistic regression analysis. (A) IgE-mediated FAs. (B) Non-IgE-mediated FA. (C) Mixed IgE- and non-IgE-mediated FAs. FA = Food allergy; IgE = immunoglobulin E.

immune mechanism is shown in Fig. 2. Allergies to cow's milk and egg declined significantly with older age, tree nuts and/or peanut allergies were uncommon initially but increased with age, whereas allergies to wheat and seafood were uncommon in children of all ages.

Food Anaphylaxis

A history of anaphylaxis was reported in 17.6% ($n = 158$) of IgE-mediated and 5.7% ($n = 9$) of mixed-type FAs. Cow's milk was the most common cause of anaphylaxis (54.5% [$n = 91$]), followed by egg (25.7% [$n = 43$]), tree nuts and/or peanut (20.4% [$n = 34$]), wheat (1.8% [$n = 3$]), seafood (1.8% [$n = 3$]), and other foods (10.8% [$n = 18$]). When analyzed by age, the most common causes of anaphylaxis were cow's milk before adolescence and tree nuts and/or peanut during adolescence (Tables 2 and 3, and Online Supplemental Table 2).

Characteristics and Risk Factors of FA by Immune Mechanism

Comparison of the study groups in terms of clinical characteristics is shown in Table 2. Evaluation of immune types based on the number of causative foods revealed that a significantly higher proportion of non-IgE-mediated FAs (80.8%) were triggered by a single food compared with the other immune types. This proportion was 49.6% in the IgE-mediated group and 35.8% in the mixed group (Table 2). Symptoms associated with immediate hypersensitivity and atopic comorbidities were significantly more prevalent in the IgE group than in the other groups. Diarrhea was significantly more frequent in the mixed-type group than in the IgE group. The prevalence of bloody and mucous stool was significantly higher in the non-IgE-mediated and the mixed-type groups than in the IgE group.

Evaluation of the family characteristics of the children with FA showed that more than half were the only child ($n = 664$ [53.2%]) and a large proportion were born by cesarean delivery ($n = 806$ [64.6%]). We observed no significant differences among the immune types in terms of mode and timing of delivery, maternal characteristics during pregnancy (stress, weight gain), place of residence, parental smoking, and family and/or sibling history of FA (data not shown).

Risk factors associated with each immune type compared with other immune types were evaluated by using regression analysis (Fig. 3, A–C and Online Supplemental Table 3). Children with an IgE-mediated FA showed significantly higher rates of male sex (OR 1.486 [95% confidence interval {CI}, 1.034–2.135; $p = 0.032$), have siblings (OR 1.581 [95% CI, 1.072–2.333]; $p = 0.021$), and maternal atopy (OR 1.531 [95% CI, 1.010–2.321]; $p = 0.045$), whereas significantly fewer

children came from families with high household income level (OR 0.324 [95% CI, 0.128–0.823]; $p = 0.018$). However, it was observed that, in the non-IgE-mediated group, male sex was significantly less frequent (OR 0.630 [95% CI, 0.474–0.836]; $p = 0.001$) and significantly more families had high household income level (OR 1.862 [95% CI, 1.075–3.225]; $p = 0.026$). No significant risk factor was found for mixed-type FA in the multivariate regression analysis.

DISCUSSION

To our knowledge, this study was the first to evaluate national and multicenter data with regard to FAs of different immunologic mechanisms that were diagnosed in the clinical setting by pediatric allergists. As with other allergic diseases, FA is a heterogeneous clinical picture that develops as a result of multifactorial influences. As found in our study, reports in the literature indicate that FA is most common in infancy. The majority of children with FA (62.5%) in our patient population were in the 0–2 years age group, whereas only 2.2% were in the adolescent group (13–18 years of age).

According to our results, cow's milk was the most common FA and cause of food anaphylaxis among all the children with FA in our study. This was followed by egg, tree nuts and/or peanut, wheat, and seafood. Previous studies conducted in Turkey and abroad reported that cow's milk and egg were the most common causes of FA in children and that these allergies diminish with age.^{13–19} Our study also indicated that the rate of cow's milk allergy in the children with FA was 70.6% in the 0–2 years age group and decreased to 25% in the 13–18 years age group. Similarly, the rate of egg allergy in the children with FA also showed a marked reduction. In the literature, it was shown that 80% of children with cow's milk allergy and egg allergy developed tolerance for these foods at ~16 years of age.^{20,21} Although our study was not longitudinal, our findings of reductions in the prevalence of cow's milk and egg allergy can be explained by tolerance. In contrast, we found that the prevalence of tree nuts and/or peanut allergy increased with age and was the most common cause of FA (42.8%) and food anaphylaxis in the 13–18 years age group, compatible with the results of previous studies.^{1,22,23} Because tree nuts and peanut can cause co-sensitization and co-allergy, and are generally consumed together in Turkish culture, these foods were evaluated as a single group in the present study.²⁴

Of the five major FA groups, the prevalence of wheat and seafood allergies was lower in our sample and showed no pronounced differences in relation to age. In epidemiologic studies performed by Hill *et al.*,²⁵ the most common FA was peanut, followed by milk, egg,

shellfish, and soy. However, numerous epidemiologic studies on FA reported that the most common causes of FA were cow's milk, egg, peanut, fish, and tree nuts.²⁶ Soy allergy was uncommon in our study (Online Supplemental Table 2). Similarly, Nwaru *et al.*¹⁸ determined in their meta-analysis that the prevalence of soy allergy is low in Europe. In addition to FAs that are common worldwide, there are also less common FAs that vary by country. Of these, the top three in the present study were lentil, soy, and sesame. Lentils and sesame are commonly consumed in the Mediterranean area and the Middle East. In Israel, sesame is the third most common food allergen after egg and cow's milk, and is the second leading cause of anaphylaxis after milk.^{17,27} In Turkey, the rate of sesame allergy among children with FA is very common and on the rise (3.8–20.6%).^{13–16} These rare food sensitivities are affected by geographic factors.

Evaluation of the children with FA according to immune mechanism of FA revealed different characteristics and risk factors. Cow's milk allergy was more frequent in the non-IgE-mediated group, whereas egg allergy was more frequent in the IgE-mediated group than in the other groups, consistent with the results obtained in previous studies.^{13–15} IgE-mediated FA showed more laboratory findings and symptoms specific to early hypersensitivity reactions and was more associated with atopic multimorbidity and multiple FA. In addition, among the IgE-mediated FAs, 17.6% resulted in anaphylaxis. Consistent with the literature,²⁸ male sex was predominant in our IgE-mediated FA group (1.486). In addition, having sibling(s) (OR 1.581) and maternal atopy (OR 1.531) increased the likelihood of IgE-mediated FA. Whereas most IgE-mediated cases were in the 0–2 years age group, there also were some cases in the 3–5 years age group in our study. In the literature, it was reported that non-IgE-mediated FA may persist after 3 years of age.²⁹ In contrast, when compared with other immune types, we determined that non-IgE-mediated FAs were more associated with a single FA and that high household income increased the likelihood of non-IgE-mediated FA (OR 1.862).

As in other allergic diseases, both genetic predisposition and epigenetic risk factors have been implicated in the development of FA. Risk factors for FA early in life, such as atopic dermatitis, are believed to start in the pre- and perinatal periods. We observed significant relationships between IgE-mediated FA and male sex, familial atopy, and comorbidities, risk factors that were also shown to be associated with FA in previous studies.^{28,30,31} However, among the factors related to familial atopy, our results indicated that maternal atopy in particular constituted a risk for FA. In the literature, the presence of siblings was proposed to be a protective factor against FA.⁷ When our entire patient

group was evaluated together, we determined that more than half were the only child. In addition, although the majority of the children in study had a high household income, this proportion was significantly higher in the non-IgE-mediated FA group.

The strength of our study was that it homogeneously represented national data and included a large number of cases. To our knowledge, it is the first large-scale study conducted by pediatric allergists not based on a telephone or electronic survey that investigates associations between the immunopathogenesis and clinical features of FA. Our study had some limitations. Prospective data were not included; therefore, exact data on prognosis and tolerance rates could not be obtained. In addition, this was not a prevalence or a controlled study, so a comparison could not be made with children without FA.

Previous large-scale epidemiologic studies on FA reported the general characteristics of FA because it is methodologically difficult to differentiate IgE- and non-IgE-mediated reactions. In fact, there are no distinct boundaries between categories of FA based on immunopathology. Laboratory tests used in the diagnosis of FA do not provide yes or no results; they do support the clinical diagnosis.^{32,33} The pediatric allergist's knowledge and experience are important both in diagnosing FA and in determining its immune mechanisms. Because there are no similar studies that compared FAs based on their immunopathogenesis, we could not compare our striking results with those of other researchers.

CONCLUSION

The clinical presentations of childhood FA are highly variable, depending on age and underlying immune mechanism. It has been shown that the most common immune mechanism in all age groups was IgE mediated. Although the most frequent cause of FA and food anaphylaxis was cow's milk before age 13 years and tree nuts and/or peanut during adolescence (13–18 years of age), cow's milk was the most common FA and cause of food anaphylaxis among all the children with FA in our study. Understanding of the population's characteristics and underlying pathogenesis of FA will provide the physicians better management of the children with FA.

REFERENCES

1. Uguz A, Lack G, Pumphrey R, et al. Allergic reactions in the community: a questionnaire survey of members of the anaphylaxis campaign. *Clin Exp Allergy*. 2005; 35:746–750.
2. Burks AW, Tang M, Sicherer S, et al. ICON: food allergy. *J Allergy Clin Immunol*. 2012;129:906–920.
3. Eigenmann PA. Mechanisms of food allergy. *Pediatr Allergy Immunol*. 2009; 20:5–11.

4. Muraro A, Werfel T, Hoffmann-Sommergruber K, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy*. 2014; 69:1008–1025.
5. Peters RL, Allen KJ, Dharmage SC, et al. Differential factors associated with challenge-proven food allergy phenotypes in a population cohort of infants: a latent class analysis. *Clin Exp Allergy*. 2015; 45:953–963.
6. Sicherer SH, Allen K, Lack G, et al. Critical issues in food allergy: a National Academies Consensus Report. *Pediatrics*. 2017; 140:e20170194.
7. Sicherer SH, Sampson HA. Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. *J Allergy Clin Immunol*. 2018; 141:41–58.
8. Orhan F, Karakas T, Cakir M, et al. Prevalence of immunoglobulin E-mediated food allergy in 6–9-year-old urban schoolchildren in the eastern Black Sea region of Turkey. *Clin Exp Allergy*. 2009; 39:1027–1035.
9. Doğruel D, Bingöl G, Altıntaş DU, et al. Clinical features of food allergy during the 1st year of life: the ADAPAR Birth Cohort Study. *Int Arch Allergy Immunol*. 2016; 169:171–180.
10. Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the Diagnosis and Management of Food Allergy in the United States: summary of the NIAID-Sponsored Expert Panel Report. *J Allergy Clin Immunol*. 2010; 126:1105–1118.
11. Nowak-Węgrzyn A, Chehade M, Groetch ME, et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: executive summary-Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol*. 2017; 139:1111–1126.e4.
12. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report–Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *Ann Emerg Med*. 2006; 47:373–380.
13. Yavuz ST, Sahiner UM, Buyuktiryaki B, et al. Phenotypes of IgE-mediated food allergy in Turkish children. *Allergy Asthma Proc*. 2011; 32:47–55.
14. Kahveci M, Koken G, Şahiner ÜM, et al. Immunoglobulin E-mediated food allergies differ in East Mediterranean children aged 0–2 years. *Int Arch Allergy Immunol*. 2020; 181:365–374.
15. Cetinkaya PG, Kahveci M, Karaatmaca B, et al. Predictors for late tolerance development in food protein-induced allergic proctocolitis. *Allergy Asthma Proc*. 2020; 41:e11–e18.
16. Doğruel D, Bingöl G, Yılmaz M, et al. The ADAPAR Birth Cohort Study: food allergy results at five years and new insights. *Int Arch Allergy Immunol*. 2016; 169:57–61.
17. Dalal I, Binson I, Reifen R, 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; 57:362–365.
18. Nwaru BI, Hickstein L, Panesar SS, et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy*. 2014; 69:992–1007.
19. Sanchez-Lopez J, Gazquez V, Rubira N, et al. Food allergy in Catalonia: clinical manifestations and its association with airborne allergens. *Allergol Immunopathol (Madr)*. 2017; 45:48–54.
20. Skripak JM, Matsui EC, Mudd K, et al. The natural history of IgE-mediated cow's milk allergy. *J Allergy Clin Immunol*. 2007; 120:1172–1177.
21. Savage JH, Matsui EC, Skripak JM, et al. The natural history of egg allergy. *J Allergy Clin Immunol*. 2007; 120:1413–1417.
22. Kaya A, Erkoçoğlu M, Civelek E, et al. Prevalence of confirmed IgE-mediated food allergy among adolescents in Turkey. *Pediatr Allergy Immunol*. 2013; 24:456–462.
23. Mustafayev R, Civelek E, Orhan F, et al. Similar prevalence, different spectrum: IgE-mediated food allergy among Turkish adolescents. *Allergol Immunopathol (Madr)*. 2013; 41:387–396.
24. Cetinkaya PG, Buyuktiryaki B, Soyer O, et al. Phenotypical characterization of tree nuts and peanut allergies in east Mediterranean children. *Allergol Immunopathol (Madr)* 2020; 48:316–322.
25. Hill DA, Grundmeier RW, Ram G, et al. The epidemiologic characteristics of healthcare provider-diagnosed eczema, asthma, allergic rhinitis, and food allergy in children: a retrospective cohort study. *BMC Pediatr*. 2016; 16:133.
26. Radlovic N, Lekovic Z, Radlovic V, et al. Food allergy in children. *Srp Arh Celok Lek*. 2016; 144:99–103.
27. Pereira MJ, Belver MT, Pascual CY, et al. The allergenic significance of legumes. *Allergol Immunopathol (Madr)*. 2002; 30:346–353.
28. Willits EK, Park MA, Hartz MF, et al. Food allergy: a comprehensive population-based cohort study. *Mayo Clin Proc*. 2018; 93:1423–1430.
29. Leonard SA, Pecora V, Fiocchi AG, et al. Food protein-induced enterocolitis syndrome: a review of the new guidelines. *World Allergy Organ J*. 2018; 11:4.
30. Mastroiilli C, Caffarelli C, Hoffmann-Sommergruber K. Food allergy and atopic dermatitis: prediction, progression, and prevention. *Pediatr Allergy Immunol*. 2017; 28:831–840.
31. Sardecka I, Łoś-Rycharska E, Ludwig H, et al. Early risk factors for cow's milk allergy in children in the first year of life. *Allergy Asthma Proc*. 2018; 39:e44–e54.
32. Soares-Weiser K, Takwoingi Y, Panesar SS, et al. The diagnosis of food allergy: a systematic review and meta-analysis. *Allergy*. 2014; 69:76–86.
33. Bartuzi Z, Kaczmarek M, Czerwionka-Szaflarska M, et al. The diagnosis and management of food allergies. Position paper of the Food Allergy Section the Polish Society of Allergology. *Postepy Dermatol Alergol*. 2017; 34:391–404. □

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