

ORIGINAL ARTICLE

Prevalence of immunoglobulin E-mediated food allergy in 6–9-year-old urban schoolchildren in the eastern Black Sea region of Turkey

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Summary

Background The prevalence of adverse reactions to food in childhood in Turkey is not known. **Objective** We aimed to investigate the prevalence and characteristics of IgE-mediated food allergies (FAs) in 6–9-year-old urban schoolchildren.

Methods This cross-sectional study recruited 3500 of the randomly selected 6–9-year-old urban schoolchildren from the eastern Black Sea region of Turkey during 2006. Following a self-administered questionnaire completed by the parents and the child, consenting children were invited for skin prick tests (SPTs) and oral food challenges. Children with suspected IgE-mediated FA were skin prick tested with a predefined panel of food allergens (milk, hen's egg, soy, wheat, peanut, fish, and hazelnut), aeroallergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat, dog, *Alternaria*, grass pollen mix, weed pollen mix, and tree pollen mix), and food allergens reported in the questionnaire. All children with a positive SPT to any food were invited for a double-blind, placebo-controlled food challenge (DBPCFC). The prevalence of IgE-mediated FA was established using DBPCFCs.

Results The response rate to the questionnaire was 78.2% (2739/3500). The estimated prevalence of parental-reported IgE-mediated FA was 5.7% (156/2739) [95% confidence interval (CI), 4.83–6.57%]. The rate of sensitization to the food allergens was 33.1% (48/145) in the parental-reported group. The confirmed prevalence of IgE-mediated FA by means of DBPCFC in 6–9-year-old urban schoolchildren living in the eastern Black Sea region of Turkey was 0.80% (22/2739) (95% CI, 0.47–1.13%). The most common allergenic foods were beef (31.8%), cow's milk (18.1%), cocoa (18.1%), hen's egg (13.6%), and kiwi (13.6%).

Conclusions The rate of reported IgE-mediated FA was significantly higher than clinically confirmed FA by means of DBPCFC (odds ratio, 7.46; 95% CI, 4.67–12.01; $P < 0.0001$). The order of allergenic foods was different and somewhat unique to the eastern Black Sea region of Turkey when compared with western countries.

Keywords children, IgE-mediated food allergy, prevalence

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Introduction

Food allergy (FA) can affect multiple organs, causing cutaneous, oral/gastrointestinal, respiratory, and generalized reactions, including fatal anaphylaxis [1]. It is considered that adverse reactions to food have become a major health concern in most countries, especially in the past two decades, [1] and at present are among the most frequent health complaints. The European Academy of Allergology and Clinical Immunology proposed a nomenclature that advised that any adverse reaction to a food should be called food hypersensitivity. When immunolo-

gic mechanisms have been demonstrated, the appropriate term is FA, and, if the role of IgE is highlighted, the term is IgE-mediated FA. All other reactions, previously sometimes referred to as 'food intolerance', should be referred to as non-allergic food hypersensitivity [2].

The true prevalence of adverse reactions to food in the general population is not well known. The majority of studies that have investigated the prevalence of FAs have been based on perceived (self- or parent-reported) symptoms, sensitization to food allergens using skin prick tests (SPT), specific serum IgE, or any combination of these methods [3–13]. On the other hand, population-based

studies that have included a double-blind, placebo-controlled food challenge (DBPCFC), the gold standard of diagnosis, in assessing the prevalence of FA are scarce [14–25]. The applied diagnostic criteria essentially affect the prevalence of FA: it increases up to 35% according to parental-reported symptoms in children from birth to the age of 2 years [7] and decreases to <1% in some populations using oral food provocation tests [15].

The order of allergic foods varies in different countries, showing a possible interaction of cultural, geographical, and social differences in dietary habits as well as genetic factors. While peanut is a very common allergenic food in western countries [8, 26, 27], fish allergy is common in the Mediterranean [28], sesame in Israel [13], and bird's nest in Singapore [29].

In the present study, we aimed to report the results of an epidemiologic survey to determine the prevalence and characteristics of IgE-mediated FAs in 6–9-year-old urban schoolchildren living in the eastern Black Sea region of Turkey.

Methods

Study population

This is a cross-sectional study that was performed in 2006 in the eastern Black Sea region of Turkey, which is comprised of six cities. The total population of 6–9-year-old urban schoolchildren in these six cities is 33 552. Random sampling of 10% of children from the public primary schools in these six cities was performed in each age group and there were comparable numbers of boys and girls in all age groups.

This study was carried out in three phases. In phase 1, questionnaires were dispensed to the children and collected after approximately 1 week. In phase 2, children who consented to participate were skin prick tested. In phase 3, oral challenges were carried out: SPT-positive children were invited for an oral DBPCFC, while SPT-negative children were invited for an open challenge that was followed by a DBPCFC in case of a positive reaction. Verbal and written informed consents were obtained for SPTs and oral challenges from both parents and children.

The study was approved by the Karadeniz Technical University Ethics Committee.

Questionnaire

Each child took home a standard questionnaire to be completed by the parents/caregiver and child. The questionnaire began with questions on the child's demographics (age and sex). We then asked respondents the following question: 'Has your child ever had an adverse reaction to any food within two hours following consumption?' If the answer was 'yes', respondents were then

asked to indicate which symptoms occurred following food(s) intake from a list including cutaneous (eruption, itching, rash, swelling), nasal (sneezing, itching, secretion, blockage), ocular (redness, itching, secretion), bronchial (cough, wheezing, shortness of breath), gastrointestinal (stomachache, nausea, vomiting, diarrhoea), laryngeal (difficulty in swallowing, difficulty in speaking), cardiovascular (palpitations/tachycardia, hypotension), and other (sweating, pallor, fainting, loss of consciousness) symptoms. We also asked respondents to specify the food(s) that caused the reaction. Respondents were also asked whether the child consumed the same food on another occasion following the adverse reaction and, if so, did the same/similar reaction occur. The last question requested consent for the child's participation in further analyses including SPTs and oral challenges.

In preparing the questionnaire, we took great care to ask, to the extent possible, simple and brief questions in order to increase participation, ensure comprehensibility, and enable parents to provide accurate answers. The questionnaires were then validated on a sample of 25 subjects through 25 in-depth interviews.

Information on familial atopy (a history of asthma, allergic rhinitis, and/or atopic dermatitis in the father, mother or any of the siblings) and atopic diseases such as asthma, rhinitis, and atopic dermatitis of the children who were invited for SPTs was obtained at the clinic via interview with the parents and by searching health care records of the children.

Skin prick tests

Among the children who reported an adverse reaction to any food, the following were invited for SPTs: (1) those who experienced any reaction following consumption of the same food that previously caused a reaction, (2) those who avoided the suspicious food after the reaction, and (3) those who consented to participate in further evaluation. All the children with suspected IgE-mediated FA who consented to participate were invited for SPTs to a predefined panel of food allergens (milk, hen's egg, soy, wheat, peanut, fish, and hazelnut), aeroallergens [*Dermaphagoides pteronyssinus* (Dp), *Dermatophagoides farinae* (Df)], cat, dog, *Alternaria*, grass pollen mix, weed pollen mix, and tree pollen mix), and food allergens reported in the questionnaire. All children who reported a reaction with chocolate were skin prick tested not only with cocoa and milk but also with hazelnut, almond, and peanut, since these are widely used additives in marketed chocolate in Turkey. Sensitization to fresh fruits or vegetables or beef was tested using prick-to-prick testing [30].

SPTs were carried out with commercially available extracts of standard food allergens (Allergopharma, Reinbek, Germany) and aeroallergens (ALK, Horsholm, Denmark). The mean weal diameter was calculated by measuring the

largest weal diameter and the diameter orthogonal to it after transferring to paper from skin with a translucent tape. Results were expressed as positive if the mean diameter was 3 mm or more in the presence of a negative control and a positive histamine reaction after 15 min.

Oral food challenges

All SPT-positive children were invited for DBPCFC following a 7-day elimination diet. A diet list including possible hidden sources of suspicious food items was prepared previously for each food that was positive in SPTs. DBPCFCs were performed with cocoa, cow's milk, hen's egg, hazelnut, peanut, walnut, chickpea, corn, kiwi fruit, banana, tomato, beef, fish, and black pepper.

All food for challenges was freshly prepared for each child. Challenge protocols were developed on the basis of the currently available literature [31–36].

The titrated doses used for hazelnut, peanut, walnut, chickpea, and corn were of the same magnitude: 0.1, 0.3, 0.6, 1.5, 2.5, 5, and 15 g, in total 25 g of the respective food. The dose steps for cow's milk were 5, 10, 40, 75, and 150 mL, in total 280 mL; 0.1, 0.3, 0.6, 1.5, 2.5, 5, 15, and 25 g for hen's egg, kiwi fruit, banana, and tomato, in total 50 g; 1, 2, 5, 7, and 10 g for cocoa, in total 25 g; 1, 2, 7, 15, 25, and 50 g for beef and fish, in total 100 g; and 0.1, 0.3, 0.6, 1.5, 2.5, and 5 g for black pepper, in total 10 g.

Hazelnut, peanut, walnut, chickpea, and corn were masked in chocolate pudding and oat grains (placebo). Kiwi fruit, banana, and tomato were masked in pear pulp (placebo) and a vegetable juice produced by crushing fresh mint, parsley, and dill together in a bowl. Green, yellow, and red liquid colouring were used for kiwi fruit, banana, and tomato placebo drinks, respectively. All ingredients were mixed in a blender. Before administration, kiwi fruit and tomato were filtered to remove the seeds. Cocoa was administered in a form diluted with warm water. For placebo cocoa, we used fine-ground corn flour, brown liquid colouring, and cocoa essence. Beef was masked in a mixture of spice (cumin, black pepper, thyme, rosemary, mustard, and paprika), onion, garlic, and turkey meat (placebo) and administered as grilled meat patties. Fish was masked in a mixture of spice (cumin, black pepper, thyme, rosemary, mustard, and paprika), onion, garlic, and ground turkey (placebo) and administered as grilled patties. Black pepper was masked in a spice mixture (cumin, thyme, rosemary, mustard, and paprika) and mashed potatoes. Milk was masked in banana and a well-cooked hen's egg in mashed potato (placebo) with ingredients of mint, paprika, and black pepper. Hen's egg for food challenges was used in well-cooked form since it is generally consumed in this form in the eastern Black Sea region of Turkey. All active and placebo foods were as similar as possible in colour, flavour-taste, consistency, and texture so as not to be differentiated by the patients.

All SPT-negative children were invited for an open food challenge that would be followed by a DBPCFC in case of a positive reaction.

DBPCFC were considered positive if a single or a combination of the clinical reactions, including cutaneous (eruption, itching, rash, swelling), nasal (sneezing, itching, secretion, blockage), ocular (redness, itching, secretion), bronchial (cough, wheezing, shortness of breath), gastrointestinal (vomiting, diarrhoea), laryngeal (difficulty in swallowing, difficulty in speaking), cardiovascular (tachycardia, hypotension), and other (sweating, pallor, fainting, loss of consciousness) symptoms were noted.

Food challenge was not performed when a patient failed to provide informed consent or when a patient had a convincing history within the last year of severe anaphylaxis to the food, which was defined as objective findings (marked laryngeal oedema, significant wheezing, or hypotension) that developed immediately after the isolated ingestion of the suspected food and required emergency management.

Negative DBPCFCs were followed by open challenges. The duration between a negative DBPCFC and the open challenge was 2 h. Patients were instructed not to eat the suspect food between the negative DBPCFC and open challenges. In the open challenge, patients received a larger quantity of food (a meal-size portion for age). Challenges were stopped at the discretion of the evaluating physician when objective signs and symptoms indicated a positive response, and medications were administered as needed. A previously described scoring system was used to determine the severity of the challenge reactions [37], which were scored as minimal, mild, moderate, or severe.

The dose interval was 15 min. Children were observed at least 2 h following the last dose of the challenge.

Statistics

All analyses were performed using SPSS statistical software version 10.0 (SPSS Inc., Chicago, IL, USA). A descriptive analysis was used for the characterization of the study population. Results were expressed as the mean SEM or percentages of the responses to each question. The prevalence of responses was compared with the Pearson χ^2 test (with the Yates correction when applied) or the Fisher exact test when needed. The odds ratio (OR) and its 95% confidence interval (CI) were calculated. To compare age between two or more groups, the Wilcoxon–Mann–Whitney test and Kruskal–Wallis one-way ANOVA were used. $P < 0.05$ was considered statistically significant.

Results

Of the 3500 children, 2739 (78.2%) returned a complete questionnaire. Among them, 156 [5.7%, (95% CI,

Table 1. Prevalence of immunoglobulin E-mediated food allergy according to a questionnaire (reported), a skin prick test, and a double-blind, placebo-controlled food challenge in age groups

Age (n)	Reported n (%)	SPT		DBPCFC	
		Performed n children	Positive n (%)	Performed n children	Positive n (%)
6 (487)	24 (4.9)	22	9 (40.9)	9	4 (0.82)
7 (765)	34 (4.4)	30	12 (40.0)	10	6 (0.78)
8 (775)	55 (7.1)	51	16 (31.4)	15*	7 (0.90)*
9 (712)	43 (6.0)	42	11 (26.2)	10†	5 (0.70)
<i>P</i>	0.124		0.527		0.978
6–9 (2739)	156 (5.7)	145	48 (33.1)	44	22 (0.80)
95% CI					0.47–1.13%

*In two SPT-negative children, DBPCFC is performed and resulted positive following positive open food challenge (OFC).

†In one SPT-negative child, DBPCFC is performed and resulted negative following positive OFC.

SPT, skin prick test; DBPCFC, double-blind, placebo-controlled food challenge.

4.83–6.57%) estimated prevalence of parental-reported IgE-mediated FA] children with suspected IgE-mediated FA according to the questionnaire were recruited for the second-phase study. There were no significant differences between age groups ($P = 0.124$) (Table 1) and gender [67 (42.9%) boys, OR, 1.18; 95% CI, 0.84–1.65; $P = 0.366$].

The foods ($n = 256$) most commonly reported to cause a positive reaction are listed in Table 2, and included chocolate, hen's egg, beef, and cow's milk. Seventy-four (47.4%) children were reported as having one FA, while 59 children (37.8%) had two, 19 (12.1%) had three, three (1.9%) had four, and one (0.6%) had five FAs. Eleven children were reported to have allergic reactions to both cow's milk and beef. In 19 of 81 children who were reported to have allergic reactions to chocolate, parents also reported allergic reactions to cow's milk in 14, to hazelnut in four, to peanut in one, and to both cow's milk and hazelnut in one.

The most frequently reported clinical manifestations were cutaneous ($n = 118$, 75.6%), followed by gastrointestinal ($n = 88$, 56.4%), nasal ($n = 58$, 37.2%), bronchial ($n = 50$, 32.0%), and ocular ($n = 35$, 22.4%). In 88 (75.6%) children, the reaction was reported to involve more than one organ system. Collapse was not reported in any child.

Of the 156 children, 145 (92.9%) were skin prick tested and 48 (33.1%) were found to be positive to one or more foods. Nine children refused SPT and we could not reach the remaining two. The foods ($n = 88$) that most commonly caused a positive SPT reaction are listed in Table 2, and included hen's egg, cocoa, cow's milk, beef, kiwi, fish, and pepper. Eleven (22.9%) of the 48 children were found to have positive SPT to one food, while 28 children (58.3%) had positive SPTs to two foods and nine children (18.7%) had positive SPTs to three foods. Three children were sensitized to both beef and cow's milk. Of the 13 children sensitized to cocoa, five were also sensitized to cow's milk, two to hazelnut, and one to peanut. Analysis of the reactivity to SPT by age groups of the 145 children revealed that 40.9% of 6–; 40.0% of 7–; 31.4% of 8–; and

Table 2. List of parental-reported, skin prick test-positive and double-blind, placebo-controlled food challenge-confirmed foods

	Reported n (%)	SPT n (%)	DBPCFC n (%)
Cocoa	81 (31.6)	13 (14.7)	4 (18.1)
Hen's egg	52 (20.3)	25 (28.4)	3 (13.6)
Beef	38 (14.8)	9 (10.2)	5* (22.7)
Cow's milk	26 (10.1)	11 (12.5)	4 (18.1)
Fish	9 (3.5)	5 (5.6)	1 (4.5)
Tomato	8 (3.1)	2 (2.2)	1 (4.5)
Hazelnut	8 (3.1)	2 (2.2)	0 (0)
Kiwi	8 (3.1)	7 (7.9)	3 (13.6)
Black pepper	5 (1.9)	4 (4.5)	1 (4.5)
Chickpea	5 (1.9)	2 (2.2)	0 (0)
Peanut	3 (1.1)	2 (2.2)	0 (0)
Walnut	3 (1.1)	2 (2.2)	0 (0)
Corn	3 (1.1)	2 (2.2)	0 (0)
Banana	3 (1.1)	2 (2.2)	0 (0)
Strawberry	2 (0.7)	0 (0)	0 (0)
Potato	2 (0.7)	0 (0)	0 (0)

*Two children whose SPTs to beef were negative but open food challenge and subsequent DBPCFC were positive are not included.

SPT, skin prick test; DBPCFC, double-blind, placebo-controlled food challenge.

26.2% of 9-year-old children ($P = 0.527$) (Table 1) and by gender revealed that 45.8% of boys and 54.2% of girls reacted to SPT with foods ($P = 0.537$).

The most frequently reported symptoms in food SPT-positive children were cutaneous ($n = 37$, 90.2%), gastrointestinal ($n = 31$, 75.6%), bronchial ($n = 22$, 53.6%), nasal ($n = 21$, 51.2%), and ocular ($n = 13$, 31.7%). In 30 (62.5%) children, the reaction was reported to involve more than one organ system.

A total of 36 (36/145, 24.8%) children in the parental-reported group were sensitized to one or more of the aeroallergens tested. SPTs to Dp were found to be positive in 26 (26/36, 72.2%) children, to Df in 14 (38.8%), to grasses and weeds in nine (25.0%), to *Alternaria* in three (8.3%), and to trees in one (2.7%). When food SPT-positive children were

compared with food SPT negatives, the rates of familial atopy were 22.9% (11/48) and 7.2% (7/97) ($P=0.007$), sensitizations to one or more of the aeroallergens tested were 41.6% (20/48) and 16.5% (16/97) ($P=0.001$), and the rates of having any of the atopic diseases were 41.6% (20/48) and 19.5% (19/97) ($P=0.008$), respectively.

Of the 48 children with positive SPTs, 41 (85.4%) were challenged in a double-blind fashion. The remaining seven children refused an oral challenge. None of the children failed to undergo DBPCFC because of a recent major reaction. A total of 83 DBPCFCs were carried out in this group of children. Twenty-two DBPCFCs in 20 children were assessed as positive. The outcomes of positive DBPCFC are summarized in Table 3. Foods that led to positive reactions were beef in five (5/22, 22.7%) children, cow's milk and cocoa in four (18.1%) each, hen's egg and kiwi in three (13.6%) each, and fish, tomato, and black pepper in one (4.5%) each (Table 2). None of the confirmed beef-allergic children were allergic to cow's milk. Of the five children sensitized to both cocoa and cow's milk, two had confirmed allergy to both these foods. DBPCFCs were negative to both foods in children sensitized to cocoa and hazelnut, and to cocoa and peanut. Sixty-one DBPCFCs were negative; these included 19 challenges to hen's egg, nine to cocoa, six to milk, four to kiwi fruit, three each to beef, fish, and black pepper, and two each to peanut,

hazelnut, walnut, corn, chickpea, banana, and tomato. The clinical reactions to DBPCFC were urticaria ($n=19$, 86.3%), oral allergy syndrome ($n=2$, 9.1%), gastrointestinal (nausea and/or vomiting) symptoms ($n=4$, 18.1%), and cough ($n=1$, 4.5%). Multiple reactions were observed in four challenges (urticaria and gastrointestinal symptoms in three children and urticaria and cough in one). The severities of challenge reactions were minimal in 11 children, mild in eight, and moderate in one child. None of the children reacted severely to any food challenge. All children with a positive reaction were given an antihistamine. Other medications (i.e. epinephrine, corticosteroids) were not necessitated. None of the DBPCFC-negative children showed a clinical reaction to the following open challenge. Analysis of the reactivity to DBPCFC by age groups revealed that 0.82% of 6-; 0.78% of 7-; 0.64% of 8-; and 0.70% of 9-year-old children ($P=0.982$), and by gender that 0.78% of boys and 0.68% of girls reacted to DBPCFC ($P=0.901$).

When the DBPCFC-positive children were compared with the DBPCFC-negatives, the rates of familial atopy were 30.0% (6/20) and 19.0% (4/21) ($P=0.650$), sensitizations to one or more of the aeroallergens tested were 70.0% (14/20) and 28.5% (6/21) ($P=0.008$), and the rates of having any of the atopic diseases were 65.0% (13/20) and 28.5% (6/21) ($P=0.02$), respectively.

Table 3. Summary of positive double-blind, placebo-controlled food challenge

No	Age (years)/sex	Food(s)	SPT (mm)	Total dose given	Total time to reaction (min)	Symptoms
1	6/M	Cocoa	6	8 g	35	Urticaria
2	6/M	Beef	5	25 g	50	Urticaria
3	6/F	Beef	6	10 g	40	Urticaria, nausea, vomiting
4	6/F	Black pepper	6	0.1 g	10	Urticaria
5	7/F	Cow's milk	6	280 mL	80	Nausea, vomiting
		Cocoa	5	3 g	20	Urticaria
6	7/F	Kiwi	8	0.4 g	20	OAS
7	7/F	Beef	5	50 g	65	Urticaria
8	7/F	Beef	4	10 g	40	Urticaria
9	7/F	Tomato	5	0.4 g	20	Urticaria
10	7/F	Kiwi	6	0.4 g	20	OAS
11	8/M	Cow's milk	5	130 mL	65	Urticaria, nausea, vomiting
		Cocoa	7	8 g	40	Urticaria
12	8/M	Cocoa	4	3 g	25	Urticaria
13	8/M	Hen's egg	7	1 g	40	Urticaria
14	8/M	Hen's egg	6	2.5 g	55	Urticaria
15	8/M	Fish	8	25 g	50	Urticaria
16	8/M*	Beef	0	50 g	70	Urticaria
17	8/F*	Beef	0	100 g	80	Urticaria
18	9/M	Kiwi	8	1 g	40	Urticaria, vomiting
19	9/M	Cow's milk	7	55 mL	40	Urticaria
20	9/M	Beef	8	3 g	20	Urticaria, cough
21	9/F	Hen's egg	6	0.4 g	20	Urticaria
22	9/F	Cow's milk	6	55 mL	55	Urticaria

*DBPCFC is performed following a positive open food challenge.

OAS, oral allergy syndrome; DBPCFC, double-blind, placebo-controlled food challenge.

Of the 97 children with negative SPTs, 32 (32.9%) were challenged in an open fashion. We could not reach 16 children and the remaining 49 refused the challenge. A total of 40 open oral challenges were carried out. A positive reaction occurred in only three children, and the responsible food was beef. Among them, allergy to beef was confirmed in two children (one girl, both 8 years old) with a subsequent DBPCFC. The pattern of reaction in these children was urticaria, and reaction severity was minimal in both.

The foods ($n=85$) reported to cause a positive reaction in SPT-negative children ($n=49$, 22 boys) who did not consent to undergo a food challenge were chocolate in 24 (24/85, 28.2%) children, hen's egg in 19 (22.3%), beef in 13 (15.3%), cow's milk in eight (9.4%), hazelnut in five (5.8%), tomato in four (4.7%), corn, fish, chickpea, and strawberry in two (2.3%) each, and peanut, walnut, banana, and potato in one (1.2%) each. Twenty-six (53.0%) children were reported as having one FA, while 14 children (28.5%) had two, six (12.2%) had three, two (4.1%) had four, and one (2.0%) had five FAs. The most frequently reported clinical manifestations were cutaneous ($n=40$, 81.6%), followed by gastrointestinal ($n=14$, 28.5%) and nasal ($n=1$, 2.0%). In six (12.2%) children, the reactions were reported to involve more than one organ system and were all mild in nature.

Based on the data of the 22 children with reactions proven by DBPCFC, the prevalences of IgE-mediated FA calculated according to age groups were 0.82% in 6-, 0.78% in 7-, 0.90% in 8-, and 0.70% in 9-year-olds ($P=0.978$) (Table 1); for gender were 0.85% in boys and 0.75% in girls ($P=0.927$); and the overall prevalence of IgE-mediated FA calculated for 6–9-year-old urban schoolchildren in the eastern Black Sea region of Turkey was 0.80% (95% CI, 0.47–1.13%) (Table 1).

The rate of reported IgE-mediated FA was significantly more than clinically confirmed FA by means of DBPCFC (OR, 7.46; 95% CI, 4.67–12.01; $P<0.0001$).

Seven children in the SPT-positive group and 65 children in the SPT-negative group did not undergo food challenges. If we apply the same rates of positive challenge to these groups, three children in the SPT-positive and four children in the SPT-negative group could be estimated as having FA, increasing the overall prevalence of IgE-mediated FA in our study group to 1.0%.

Discussion

This is the first population-based study conducted in Turkey that investigates the prevalence of parentally reported and clinically confirmed IgE-mediated FA in 6–9-year-old schoolchildren. We found that, although the reported prevalence was 5.7%, the overall prevalence of clinically confirmed FA to any food allergen was 0.8% in our study group.

Epidemiologic studies on FAs are relatively rare when compared with studies on asthma, allergic rhinitis, and atopic dermatitis [3, 38]. Available surveys are generally focused on the prevalence in certain age groups, in certain diseases such as atopic dermatitis and asthma, or to certain food items. Only two studies reported the prevalence of FAs in childhood, all ages included. The study by Roehr et al. [17] in Germany was based on a questionnaire given to 2354 children aged between 0 and 17 years, followed by SPT, specific serum IgE, and DBPCFC. Although the response rate to the questionnaire was considerably low (31.4%), they found the prevalence of FA confirmed by DBPCFC to be 3.5%. Osterballe et al. [16], in Denmark, used a similar methodology and estimated the prevalence of FA to be 3.3% in 0–22-year-old individuals.

Most studies in assessing the prevalence of FA have been based on perceived (self- or parent-reported) symptoms, sensitization to food allergens using SPT, specific serum IgE, or any combination of these methods [5–13]. The actual prevalence of FA, however, is even up to 10-fold lower than that perceived by the population, and this situation has been clearly demonstrated in studies using DBPCFC [14–25]. Bock [39] found a self-reported prevalence of food hypersensitivity of 28% in a prospective survey of selected children followed up to the third year of life, where 3.9% was confirmed by a blinded challenge. Pereira et al. [21] found the prevalence of reported food hypersensitivity among the 11- and 15-year-old cohorts to be 11.6% and 12.4%, respectively. By means of an objective assessment, however, they showed the prevalence of food hypersensitivity to be 2.3% for both 11- and 15-year-old children. In accordance with the previous studies, we established a sevenfold decline between reported (5.7%) and clinically confirmed (0.8%) FA in our study group.

The methodology and the age group of our study population limit, to a great degree, comparison of our results with those of previous studies. Regarding parental-reported prevalence of FA in this age group, our results are comparable only to the results of the study conducted in France by Rance et al. [11]. They estimated the point prevalence of FA in children aged 6–10 years to be 6.8%, which is slightly higher than that estimated in the present study (5.7%). However, we are not able to find comparable studies in this age group regarding sensitization assessed by SPT and FA confirmed by DBPCFC. The only study that is available for comparison was performed by Venter et al. [23] in 6-year-old children, which found that 11.8% of their study group reported a problem with a food or a food ingredient and 15.7% of these symptomatic children, according to the questionnaire, were sensitized to any food as assessed by SPT. When compared with this study, we realized that the rates of reported adverse events with foods as a whole and in 6-year-old children were lower in our study group (5.7% and 4.9%, respectively), but the

sensitization rates (33.1% and 40.9%, respectively) were clearly higher than the rates found in the aforementioned study. This might be attributed to the fact that we included only children with a suggestive history of IgE-mediated FA, but Venter et al. [23] included all children who reported any food-related adverse events. Confirmed FA, on the other hand, was found to be 1.6% in 6-year-old children in the same study [23], which was two times higher than we demonstrated in our 6-year-old children (0.82%).

We think that the order of allergenic foods as demonstrated in our study group can be considered somewhat unique to the eastern Black Sea region. We found beef to be the major cause of IgE-mediated FA in our study population, with cocoa and cow's milk the second most common causes. It has been suggested that many factors, such as cultural or dietary habits (i.e. cooking methods) [40], exposure to new allergenic products early in life by early introduction of the food and heavy consumption [41], genetic factors, and probably others, may be unidentified factors, alone or in combination, that may contribute to the order of specific food allergens in different populations. While peanut is a very common food allergen in the United Kingdom [8], France [26], and North America [27], fish allergy is common in Mediterranean [28], sesame in Israel [13], and bird's nest in Singapore [29]. Fishery and hazelnut agriculture are not only the two leading occupations at which wide populations in the eastern Black Sea region earn their living, but fish and hazelnut products are widely consumed in this region. Thus, we would expect that fish and hazelnut would be the most common food allergens in our study group. However, we found fish allergy in only one child, whereas none of the children in the study group reacted to hazelnut. Another striking finding in contrast with the situation in western countries was that peanut caused no allergic reactions in our study group.

Chocolate was the most commonly reported allergenic food in our study group. Although allergic reactions to chocolate are reported in some previous studies [6], to our knowledge, it has never been investigated in detail. In the present study, all children who reported a reaction with chocolate were skin prick tested not only with cocoa and milk but also with hazelnut, almond, and peanut, as these are widely used additives in marketed chocolate in Turkey. We found cocoa to be the second most common food that caused sensitization and the second most common food, with cow's milk, that caused IgE-mediated FA as confirmed by DBPCFC.

Genetic factors, at least in part, might play an important role in determining beef as the major allergenic food in the eastern Black Sea region. In a previous study, Orhan and Şekerel [42] reported the clinical characteristics of 12 beef-allergic patients who were under follow-up at the Hacettepe University Pediatric Allergy and Asthma Unit,

which is a referral centre with a broad spectrum of patients from all regions of the country, and they demonstrated that all beef-allergic patients were from the eastern Black Sea region, with many of them relatives. They concluded that although the sample size was small, their results revealed a familial tendency and a susceptibility to beef allergy in people living in the eastern Black Sea region.

Our results also revealed the fact that the order of allergenic foods demonstrated in our study does not correspond to the panel of foods recommended for use in screening tests that were extrapolated from the FA screening panels used in western countries.

As both cow's milk and beef contain bovine serum albumin, bovine γ -globulin, and other proteins in significant quantities, a higher prevalence of beef allergy might be expected among children allergic to cow's milk, and vice versa. In a previous study, eight of the 11 children who reacted to beef (73%) were documented to be allergic to cow's milk in a previous DBPCFC. In contrast, only 20% of cow's milk-allergic patients had positive DBPCFC to beef even though 84% had a positive SPT to beef [43]. Our results, however, do not correlate with these findings. Of the seven children confirmed to have beef allergy, only two (28.5%) were sensitized to cow's milk, whereas none of them had positive DBPCFC with cow's milk. Of the four children with confirmed cow's milk allergy, none of them were sensitized to beef.

In our study, the rates of aeroallergen sensitization and atopic diseases were significantly high in food-allergic children confirmed by DBPCFC. It is known that children with atopic diseases tend to have a higher prevalence of FA [1]; about 35% of children with moderate-to-severe atopic dermatitis have IgE-mediated FA [44]. It has also been shown that children with FAs have a higher prevalence of allergic diseases. Arshad et al. [45] showed that the prevalences of any allergic disease in children with peanut and egg allergy are 54.5% and 75.0%, respectively.

A weakness of our study could be that we did not perform SPT in all children, including asymptomatics. Thus, we cannot make an exact estimation of the prevalence of food sensitization in our study group. This also eliminates the potential for further follow-up regarding whether or not clinical FA would develop in any of the children.

Another weakness of our study is that a high number of patients with negative SPT refused the oral challenge. Although this may be due to anxiety regarding the reactions they might experience, the reactions in this group were reported to involve more than one organ system in only 12.2% and all were mild in nature. Therefore, the reasons for the refusal of the oral challenge could be threefold: parents and children may have considered a negative SPT sufficient; they may have considered the oral challenge a waste of their time; or the importance of

FA may not have taken into consideration by these patients/parents.

Although DBPCFC is considered the gold standard for the diagnosis of FA, its positive predictive value has been suggested to be around 90%, at least in peanut allergies [46], suggesting that a minority may still have allergies to the food challenged. Therefore, a cautionary approach should be adopted particularly in patients with a negative DBPCFC but with a consistent history and positive SPTs.

In conclusion, our study demonstrates a discrepancy between parental-reported and confirmed FA. Overall, 5.7% children presented possible IgE-mediated FA, whereas the prevalence of confirmed IgE-mediated FA by DBPCFC was 0.8% in 6–9-year-old urban schoolchildren. The order of allergenic foods was different and somewhat unique to our region, when compared with western countries, with beef, cocoa, and cow's milk identified as the most prevalent food items in the eastern Black Sea region. Genetic factors rather than cultural and dietary factors might be more important in this situation. Therefore, a reevaluation of the list in different countries is required instead of the use of the panel of foods recommended in screening tests in western countries.

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