

Proven Food-Induced Acute Urticaria and Predictive Factors for Definitive Diagnosis in Childhood

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Keywords

Childhood · Food allergy · Urticaria

Abstract

Background: Urticaria can be the only sign of a food allergy or can be seen together with other signs and symptoms of a food allergy. **Objective:** To determine the demographic, etiologic, and clinical features of food-induced acute urticaria in childhood. **Methods:** Patients suspected of food-induced acute urticaria were included in this prospective cross-sectional multicenter study.

Results: Two hundred twenty-nine urticaria cases were included in this study. Seventeen patients who did not meet the inclusion criteria of the study were excluded. Of the 212 included cases, 179 (84.4%) were diagnosed with definitive food-induced acute urticaria. The most common foods causing acute urticaria were cow's milk, hen's eggs, and nuts in 56.4, 35.2, and 19% of cases, respectively. The positive predictive value of a history of milk-induced acute urticaria together with a milk-specific IgE >5

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kU/L for cow's milk-induced acute urticaria was 92% (95% CI: 81–96%). A history of cow's milk-induced and/or hen's egg-induced acute urticaria was consistent with a definitive diagnosis of food-induced urticaria (Chen's kappa: 0.664 and 0.627 for milk and eggs, respectively). Urticaria activity scores were higher in patients with food-induced acute urticaria ($p = 0.002$). **Conclusion:** Cow's milk, hen's eggs, and nuts were the most common allergens in the etiology of childhood food-induced acute urticaria. Although the urticaria activity score provides guidance for diagnosis, an oral food challenge is often essential for the definitive diagnosis of a patient with a history of food-induced acute urticaria.

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Introduction

The prevalence of food allergies has increased dramatically in recent years [1, 2]. Food allergies can cause a wide range of clinical symptoms, including itching, flushing, urticaria, angioedema, and exacerbations of atopic eczema after food intake. Skin involvement is the most common presentation of food allergies [3, 4]. Several studies have reported that food-induced urticaria is the most common skin finding both in food-induced anaphylaxis series and during oral food challenge tests [2, 5–8]. The foods most frequently reported to cause urticaria in children are milk, eggs, peanuts, and tree nuts [9, 10]. Urticaria may appear rapidly within minutes or up to 2 hours after consumption of the offending food. Flushing, pruritus, and a morbilliform rash may precede the development of urticaria. The shapes and sizes of wheals may vary from millimeters to a few centimeters, and some may merge to form giant lesions with raised borders.

Although food-induced anaphylaxis, atopic dermatitis, and non-IgE food allergies have been extensively discussed in various studies, food-induced urticaria has not been dominantly addressed. However, urticaria can be seen as the only sign of a food allergy or together with other signs and symptoms of a food allergy. The aim of the present study was to determine the demographic, etiologic, and clinical features of food-induced acute urticaria in childhood.

Methods

Patients and Questionnaire

A total of 225 patients suspected of food-induced acute urticaria were included in the present study. This prospective cross-sectional study was carried out between July 2019 and February

2020 with the participation of 13 pediatric allergy and immunology centers throughout Turkey. The parents of the patients were interviewed face-to-face, and a previously prepared questionnaire was filled out. This questionnaire inquired about the demographic and clinical features of the patients. These features included age, gender, dietary habits, history of concomitant atopic diseases, presence of other food allergies, familial history of atopic diseases and food allergies, sensitization to food allergens, clinical manifestations, urticaria activity score, laboratory findings, and open food challenge (OFC) test results.

Definitions

Recurrent wheeze was defined as a previous history of 2 or more wheeze episodes. *Rhinitis* was defined as a nasal symptom, including anterior or posterior rhinorrhea, sneezing, nasal blockage, and/or itching of the nose. These symptoms must occur over 2 or more consecutive days for more than 1 h on most days.

Atopic eczema was defined as a chronic or recurrent inflammatory skin disease that is itchy and localized according to age. Urticaria activity score entailed the documentation of wheal numbers and itch intensity, which resulted in daily wheal and pruritus subscore values ranging from 0 (no wheals, no itch) to 3 (many wheals, severe itch), yielding a total of 6 points [11].

Laboratory

Serum food allergen-specific and total IgE levels and blood eosinophil counts were measured. A specific IgE level >0.35 kUA/L for a food was considered positive. A total percentage of blood eosinophils greater than 4% of white blood cells was considered eosinophilia.

Skin-Prick Test

Skin-prick tests were performed for standard commercial extracts, and the skin prick-to-prick technique was performed for non-available extracts. These techniques were performed on the volar surface of the forearms or on the back of the body with a 1-mm lancet in accordance with the European Academy of Allergy and Clinical Immunology (EAACI) guidelines [12]. A positive SPT was defined as a mean wheal size of 3 mm or larger than the negative control. Histamine (10 mg/mL) and saline were used as the positive and negative controls, respectively. The commercial food allergen extracts (Abello-ALK, Madrid, Spain) used for the skin-prick test were cow's milk, hen's egg (white and yolk), beef, chicken meat, fish mix, wheat, rice, soybean, lentil, hazelnut, walnut, peanut, and pistachio.

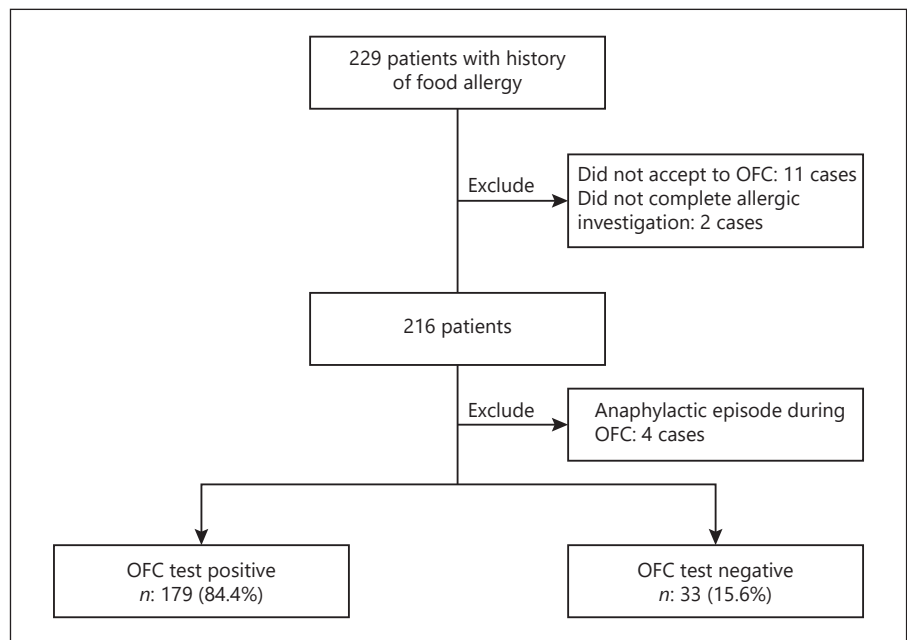
OFC Test

OFC tests were conducted in accordance with EAACI guidelines [13, 14]. All foods for the OFC test were prepared and administered by the institutional staff in increasing doses in accordance with these guidelines. All participants were observed for 2 h after the OFC and were followed up for late reactions for 7 days by telephone.

Diagnostic Procedure

All the children were suspected of having a diagnosis of food-induced acute urticaria. The parents were asked to report any previous adverse reactions to foods in interviews. Then, the follow-up test procedures were carried out. First, SPT and/or food-specific IgE were investigated. Standardized oral food challenges

Fig. 1. Study flow chart. OFC, open food challenge.



were then performed for all suspected foods in accordance with EAACI guidelines [13, 14]. The diagnosis of food-induced acute urticaria was confirmed when objective symptoms (e.g., flushing, urticaria, and/or angioedema) occurred during the food challenge.

The exclusion criteria of this study were as follows: (1) previous diagnosis of chronic urticaria, (2) immunosuppressive treatment, (3) urticarial lesions triggered by factors other than foods (e.g., infections, drugs, or venoms), and (4) urticaria with coexisting anaphylaxis.

Statistical Analysis

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS) 21.0 (SPSS Inc., Chicago, IL, USA) and Microsoft Office Excel (Microsoft Corporation, Redmond, WA, USA). Normality was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive statistics were expressed as frequencies and percentages for categorical variables or as medians (min–max) for non-normally distributed quantitative data. Categorical variables were compared using a Pearson χ^2 test or Fisher's exact test, and quantitative variables were compared using a Mann-Whitney U test. Cohen's kappa coefficient was used to assess between-rater agreement (i.e., a history of food-induced acute urticaria and definitive diagnosis). Strength of agreement was categorized as poor (<0.00), slight (0.00–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), or almost perfect (0.81–1.00) [15]. Sensitivity, specificity, and predictive values were calculated for history of milk-induced acute urticaria together with milk-specific IgE >5 kU/L. These values were also calculated for history of egg (white)-induced acute urticaria together with egg (white)-specific IgE >2 kU/L. A two-sided $p < 0.05$ was considered statistically significant.

Table 1. Skin-prick test results and specific IgE levels for food allergens

Foods allergen	Skin-prick test		Specific IgE test	
	<i>n</i>	median (min–max)	<i>n</i>	median (min–max)
Cow's milk	98	6 (3.8–10)	92	5.6 (1.1–15.9)
Egg				
Egg white	62	7 (4–10)	18	18 (6–100)
Egg yolk	61	3 (0–5.5)	7	0 (0–80)
Nuts				
Peanut	7	5 (3–7)	5	2.8 (1.8–3.9)
Hazelnut	13	10 (8–17.5)	7	6.4 (1–20.6)
Walnut	9	5 (3.5–6.5)	8	3.2 (2.4–10.2)

Results

Demographics

The demographic data of the patients are summarized in Table 2. Two hundred twenty-nine urticaria cases were included in the present study. Seventeen cases were excluded from the study: 11 did not accept the OFC, 4 experienced anaphylaxis during the OFC, and 2 did not complete the allergic investigation (Fig. 1). The median age of the patients was 14 months (min: 4, max: 192) and 120 patients (56.6%) were male. Of the 212 included cases, 179 (84.4%) were diagnosed with definitive food-in-

Table 2. Demographic and clinical features of patients diagnosed with food-induced acute urticaria

Variables	Age group, <i>n</i> (%)			
	total	≤12 months (<i>n</i> = 152)	>12 months (<i>n</i> = 27)	<i>p</i> value
Gender (male)	103 (57.5)	86 (56.6)	17 (63)	0.684
Age at admission, median (min–max), months	13.7 (4–192)	12.5 (4–84)	58 (6.5–192)	<0.001
Age at urticaria onset, median (min–max), months	6 (1–180)	6 (1–12)	30 (13–180)	<0.001
Allergy to foods				
Cow's milk	101 (56.4)	98 (64.5)	3 (11.1)	<0.001
Egg	63 (35.2)	61 (40.1)	2 (7.4)	<0.001
Peanut	7 (3.9)	3 (2)	4 (14.8)	0.011
Nuts	34 (19)	16 (10.5)	18 (66.7)	<0.001
Hazelnut	13 (7.3)	9 (5.9)	4 (14.8)	0.112
Walnut	12 (6.7)	5 (3.3)	7 (25.9)	<0.001
Pistachio	3 (1.7)	0	3 (11.1)	0.003
Cashew	2 (1.1)	0	2 (7.4)	0.022
Sesame	6 (3.4)	4 (2.6)	2 (7.4)	0.224
Wheat	3 (1.7)	3 (2)	0	1
Beef	3 (1.7)	1 (<1)	2 (7.4)	0.060
Lentil	3 (1.7)	2 (1.3)	1 (3.7)	0.390
Fish	1 (<1)	0	1 (3.7)	0.152
Feeding pattern at the time of diagnosis				
Breastfeeding	15 (8.4)	14 (9.2)	1 (3.7)	0.341
Formula feeding	19 (10.6)	19 (12.5)	0	0.082
Complementary feeding	160 (89.4)	133 (87.5)	27 (100)	0.082
Allergy to multiple foods	23 (12.8)	21 (13.8)	2 (7.4)	0.376
Urticaria accompanied by angioedema	54 (25.5)	43 (23.8)	11 (35.5)	0.166
Concomitant atopic disease				
Recurrent wheeze	24 (13.4)	17 (11.2)	7 (25.9)	0.038
Chronic rhinitis	17 (9.5)	12 (7.9)	5 (18.5)	0.083
Atopic eczema	46 (25.7)	45 (29.6)	1 (3.7)	0.005
Family history of atopy	56 (31.3)	45 (29.6)	11 (40.7)	0.250
Family history of food allergy	28 (15.6)	23 (15.1)	5 (18.5)	0.655
Serum total IgE >100 kU/L (<i>n</i> : 131)	57 (43.5)	44 (40.4)	13 (59.1)	0.168
Eosinophil >4%	95 (53)	83 (55)	12 (44.4)	0.313

Statistically significant *p* values are printed in bold.

duced acute urticaria. The median age of the onset of food-induced acute urticaria was 6 months (min: 1, max: 180), and the median time between the age of onset and the age of diagnosis was 6 months (min: 0, max: 81). Among the definitive food-induced acute urticaria cases, urticaria lesions appeared during the complementary feeding period in 160 cases (89.4%), and 72 cases (40.2%) had concomitant atopic diseases other than food allergies. The parents of 28 patients (15.6%) reported histories of food allergies. The most common foods causing acute urticaria were cow's milk, hen's eggs, and nuts in 56.4, 35.2, and 19% of the cases underwent the OFC. In the etiology of food-induced acute urticaria, cow's milk, and hen's eggs were found to be causative before 1 year of age in the

majority of cases, while nuts were primarily causative after 1 year of age (Fig. 2). The median urticaria activity score of the food-induced acute urticaria cases was 3 (min: 0, max: 6). The median induration diameters produced by food allergens in skin-prick tests for milk, egg whites, and peanuts were 6, 7, and 5 mm, respectively. The median levels of serum-specific IgE for milk, egg whites, and peanuts were 5.6, 18, and 2.8 kUA/L, respectively (Table 1). Eosinophilia was detected in 95 patients with food-induced acute urticaria (53%).

Results of the OFC

Of the 216 challenges performed, 4 cases experienced anaphylactic reactions and required epinephrine during

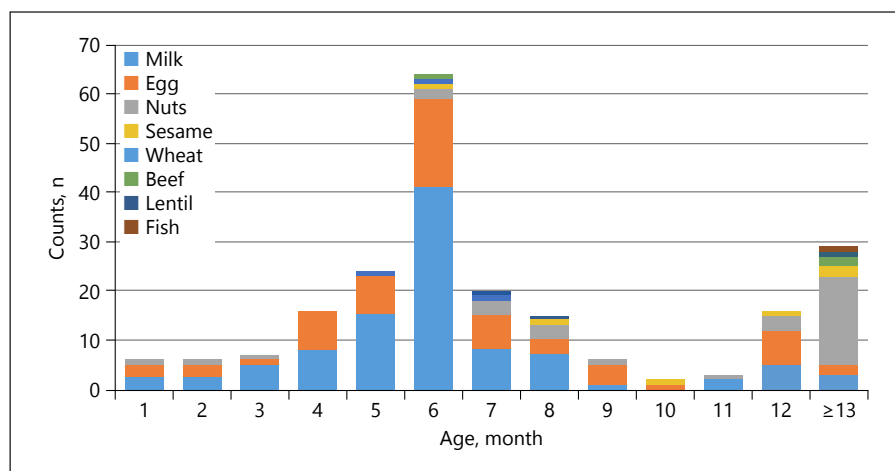


Fig. 2. Etiology of food-induced acute urticaria according to age.

Table 3. PPV and NPV, sensitivity, and specificity for the definitive diagnosis of food allergies

	Sensitivity	Specificity	PPV	NPV
The history of cow's milk-induced urticaria and cow's milk-specific IgE level >5 kU/L	50	96	92	70
The history of egg-induced urticaria and egg white-specific IgE level >2 kU/L	61	97	92	83

PPV, positive predictive value; NPV, negative predictive value.

the OFC; these cases were excluded from the study. One hundred seventy-nine patients (84.4%) had reactions during the OFC, while 33 (15.6%) had no reactions. Of the 179 patients who had reactions, 122 (68.2%) had only urticaria, 53 (29.6%) had urticaria with angioedema, and 4 (2.2%) had urticaria with an exacerbation of atopic eczema.

Predictive Factors of Positive OFC Outcomes among Children Suspected of Acute Food-Induced Urticaria

The positive predictive value (PPV) of a history of milk-induced acute urticaria together with milk-specific IgE >5 kU/L for cow's milk-induced acute urticaria was 92% (95% CI: 81–96%). The PPV of a history of egg (white)-induced acute urticaria together with egg (white)-specific IgE >2 kU/L for egg (white)-induced acute urticaria was 91.7% (95% CI: 61–99%; Table 3).

The presence of milk-induced or egg-induced acute urticaria in the patient history showed substantial agreement with the definitive diagnosis of food-induced urticaria (Cohen's kappa: 0.664 and 0.627 for milk and egg, respectively). Urticaria activity scores were higher in patients with food-induced acute urticaria ($p = 0.002$). No statistically significant differences were found between the patients with food-induced acute urticaria and the re-

maining patients in terms of gender, age of symptom onset, feeding, multiple food allergies, history of previous urticaria caused by the same food, concomitant atopic disease, urticaria accompanied by angioedema, parental history of atopic disease and food allergies, eosinophilia, or high levels of total IgE ($p > 0.05$ for all; Table 4).

Discussion

Numerous studies have evaluated the role of food allergens in the etiologies of allergic diseases, such as anaphylaxis, atopic dermatitis, allergic proctocolitis, enterocolitis, and eosinophilic esophagitis [16–19]. However, a limited number of studies have examined food-induced acute urticaria. Several food allergens can induce urticarial lesions, which may vary with age. In the present study, the demographic characteristics, clinical presentation, and etiology of proven food-induced urticaria in childhood were exhaustively discussed. It was determined that food-induced urticaria was mostly triggered by cow's milk and hen's eggs prior to 1 year of age and primarily triggered by nuts after 1 year of age. In addition, the high urticaria activity scores of the patients with histories of

Table 4. Predictive factors associated with food-induced acute urticaria

Variable	Food-induced urticaria, n: 179, n (%)	Non-food-induced urticaria, n: 33, n (%)	p value
Gender (male)	103 (57.5)	17 (51.5)	0.52
Age of symptoms at onset, median (min–max), months	6 (1–72)	6 (1.5–54)	0.93
Urticaria activity score, median (min–max)	3 (0–6)	2 (1–6)	0.002
Feeding pattern at the time of diagnosis			
Breastfeeding	15 (8.4)	2 (6.1)	0.65
Formula feeding	19 (10.6)	3 (9.1)	0.79
Complementary feeding	160 (89.4)	29 (87.9)	0.80
Allergy to multiple foods	23 (12.8)	0 (0)	nc
Urticaria with same food >2 episodes in the history	142 (79.3)	23 (69.7)	0.31
Urticaria accompanied by angioedema	50 (27.9)	4 (12.1)	0.06
Concomitant atopic diseases	72 (40.2)	10 (30.3)	0.28
Recurrent wheeze	24 (13.4)	3 (9.1)	0.49
Chronic rhinitis	17 (9.5)	5 (15.2)	0.33
Atopic eczema	46 (25.7)	5 (15.2)	0.19
Family history of atopic disease	56 (31.3)	9 (27.3)	0.65
Family history of food allergy	28 (15.6)	5 (15.2)	0.94
Serum total IgE >100 kU/L (n = 150)	57 (43.5)	6 (31.6)	0.33
Eosinophils >4%	95 (53)	13 (39.4)	0.24

food-induced urticaria were found to predict that the present urticaria was triggered by food.

Urticaria was the most common finding both in cases of food-induced anaphylaxis and during oral provocation tests with the foods under investigation [2, 5–8]. Chan et al. [20] reported that out of 916 patients who had undergone OFC tests at 1 year of age, 539 tested positive. Urticaria, which was followed by angioedema, developed in 83.3% of the patients with positive OFC tests. Furthermore, Mankad et al. [21] reported cutaneous reactions in 68% of children with positive OFC results. Similar to these researchers, we found that urticaria and angioedema were the leading symptoms of food-related skin involvement in the present study.

Patients who have been diagnosed with food-induced acute urticaria may develop other atopic diseases simultaneously or at a later time. Therefore, when food-induced acute urticaria is diagnosed, other atopic diseases (e.g., atopic eczema, allergic rhinitis, and asthma) should be evaluated as well. In a study by Mankad et al. [21], 62% of OFC-positive patients were also found to have atopic eczema, 34% were found to have allergic rhinitis, and 28% were found to have asthma. These rates were lower in the present study. This discrepancy might have been due to the younger age of the patients enrolled in the present study. One of the first signs of atopic march is food al-

lergy, and other atopic diseases occur depending on the age. Consistent with this knowledge, recurrent wheezing was significantly higher in patients over 1 year of age in the present study. These results indicate that patients diagnosed with food-induced acute urticaria should be evaluated and monitored for other atopic diseases.

The etiology of IgE-mediated food allergies may vary according to geographical region and age of onset. When we evaluated the prevalence of childhood allergies by region, cow's milk allergy was found to be more common in Europe and America, while egg allergy was found to be more common in Asia [22]. With respect to age, milk, and egg allergies are more common in the early stages of life, while nut allergies are predominant at later ages [23]. Since urticaria was the most common form of IgE-mediated food allergy, the frequency of food in the etiology of urticaria according to age was similar in the present study. Two-thirds of the patients with cow's milk-induced urticaria were younger than 1 year of age, and two-thirds of the patients with nut-induced urticaria were older than 1 year of age.

IgE-mediated food allergies are mostly seen after 6 months of age. Ferrari and Eng [23] aimed to identify the most frequent food allergens causing immediate hypersensitivity reactions in Swiss children of different age-groups. In their study, 29.8% of children diagnosed with IgE-mediated food allergy were infants and 43.9% were

toddlers. With complementary feeding after 6 months of age, infants are exposed to various food allergens; thus, the frequency of allergies tends to increase. In line with the results of this previous study, urticaria was observed at the time of the complementary feeding period in approximately 90% of patients in the present study.

Skin-prick testing and measurements of serum-specific IgE have limitations in the diagnosis of food allergies because IgE sensitization often occurs without any symptoms [24, 25] and, a substantial number of food allergies are non-IgE-mediated [26–28]. Therefore, oral food challenges are recommended for the diagnosis of food allergies [29]. The level of specific IgE correlates with the likelihood of a clinically significant reaction to a food trigger. Based on a study of more than 100 children in which tests were correlated with the gold standard oral food challenges, Sampson [30, 31] drew up values of serum-specific IgE for the most common allergens that had a PPV of 95% for the diagnosis of food allergies. Sampson [30, 31] reported that if a patient's specific IgE level for cow's milk is >5 kUA/dL before the age of 1 year or >15 kUA/dL after the age of 2 years, the PPV for diagnosis is 95%. For hen's egg, if the specific IgE level for cow's milk is >2 kUA/dL before the age of 2 years, the PPV for diagnosis is 95%. Similarly, the median age of the patients in the present study was 13 months, and the serum-specific IgE values for cow's milk and hen's egg were above 5 and 2 kUA/dL, respectively. The PPVs for diagnosis were found to be 92 and 91.4% for cow's milk and hen's egg, respectively, in the present study. The results of these studies showed that if the serum-specific IgE value is >5 or 2 kUA/dL for cow's milk or hen's egg, respectively, diagnosis can be considered without any need for an OFC in patients with histories of food-induced acute urticaria during childhood.

In the present study, a high urticaria activity score was found to be a predictive factor for food-triggered urticaria. This might have been due to the absorption and systemic effect of food allergens after oral food intake. However, factors such as concomitant atopic diseases, feeding attitudes, histories of previous urticaria episodes due to the same food, and food allergies among family members did not predict that the present episode of urticaria was related to food. Therefore, although urticaria activity scores and serum-specific IgE levels provide some guidance for diagnosis, OFCs are often required for definitive diagnosis of patients with histories of food-induced acute urticaria in childhood. These results may imply that the likelihood that a child has a food allergy correlates with their parent's assessment of their reaction severity.

The present study has a few limitations. First, PPV and Cohen's kappa analyses were performed for cow's milk and hen's egg, which played a role in the etiology of acute urticaria, but could not be performed for other foods due to the low number of subjects. The use of open OFC instead of DBPCFC for certain diagnosis was another limitation of this study.

In conclusion, cow's milk, hen's eggs, and nuts were found to be the most common foods in the etiology of food-induced acute urticaria in childhood. Although urticaria activity scores provide some guidance for diagnosis, OFCs are often required for the definitive diagnosis of patients with histories of food-induced acute urticaria. However, patients who have cow's milk-specific IgE levels >5 kUA/dL or hen's egg-specific IgE levels >2 kUA/dL together with histories of food-induced acute urticaria may not require OFCs for diagnosis.

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Statement of Ethics

All parents provided their written informed consent. The study was performed according to the Declaration of Helsinki, and the procedures were approved by the Ethical Committee of Non-Invasive Clinical Research of Kocaeli University. The approval date and number are February 8, 2019 and 2019/14, respectively.

Conflict of Interest Statement

There are no conflicts of interest statement for each author.

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M.A., E.T., P.U., O.C., Z.H.D, C.A., N.Y., S.A., E.A., I.E.S., F.K., M.A., E.Y., M.T.C., Z.T., N.G., Y.Y., S.C., N.S., H.C., A.K., N.C.G., T.T., and F.O. collected data. M.A., O.O., and C.O. edited the manuscript. M.A., Z.T., N.G., N.S., H.C., F.O., O.O., and C.O. supervised the study. E.T. wrote the manuscript. H.C.U. and M.S.E. conducted statistical analysis.

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