

## Is it possible to predict the development of anaphylaxis before oral food challenge tests administered to evaluate tolerance in IgE-mediated food allergy in children?

Serdar Al<sup>1\*</sup>, Suna Asilsoy<sup>1</sup>, Dilek Tezcan<sup>1</sup>, Özge Atay<sup>1</sup>, Özge Kangallı<sup>1</sup>, Gizem Atakul<sup>1</sup>, Seda Şirin Köse<sup>2</sup>, Nevin Uzuner<sup>1</sup>, Özkan Karaman<sup>1</sup>

<sup>1</sup> Dept of Pediatric Allergy and Clinical Immunology, Dokuz Eylül University Faculty of Medicine, İzmir, TR  
<sup>2</sup> Dept of Pediatric Allergy and Clinical Immunology, Dr. Sami Ulus Child Disease Training and Research Hospital, Ankara, TR

\* Corresponding Author: Serdar Al E-mail: [drserdaral@gmail.com](mailto:drserdaral@gmail.com)

### ABSTRACT

**Objective:** Life-threatening anaphylaxis may occur in IgE-mediated food allergy. Oral Food Challenge (OFC) is the gold standard in demonstrating tolerance and diagnosing food allergy; however, these tests may cause anaphylaxis. Predicting the risk of developing anaphylaxis before performing OFC is valuable information in evaluating tolerance as in diagnosis. The present study aims to evaluate the effectiveness of the tests used in clinical practice in predicting the risk of anaphylaxis during OFC in IgE-mediated food allergy. To our knowledge, this is the first study evaluating skin prick tests in the prediction of anaphylaxis.

**Material and Methods:** In this descriptive cross-sectional study, the history, demographic, clinical and laboratory data of the patients, followed up with the diagnosis of IgE-mediated food allergy, on whom OFC was performed, were evaluated retrospectively.

**Results:** Of the 254 patients who underwent OFC, 133 were followed up with a diagnosis of IgE-mediated food allergy. The mean age was 21 months (12-120), and anaphylaxis occurred in nine (6.7%) of them during OFC. According to the frequency, the food responsible for IgE-mediated food allergy was determined as milk, egg and egg-milk combination. Age during the challenge and total IgE levels were higher in the group that experienced OFC-related anaphylaxis. The tests that could best determine the risk of anaphylaxis before the challenge was the skin prick test (SPT) and prick to prick (PTP) test for milk. Milk SPT and PTP test at the time of initial diagnosis and determination of milk sIgE and egg white sIgE before challenge were found to predict the risk of anaphylaxis. The negative predictive value was over 95% in tests that gave significant results for milk. There was no statistically significant finding associated with other allergenic foods.

**Conclusion:** In evaluating tolerance development, performing sIgE, SPT and/or PTP tests for milk before OFC is useful in predicting anaphylaxis. Studies with larger numbers of cases are needed to assess the risk of anaphylaxis caused by other foods.

**Keywords:** Food challenge in children, allergy in childhood, skin prick test, prick to prick test, specific IgE, anaphylaxis during provocation

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### INTRODUCTION

Food allergy is defined as an unexpected immunological response that develops after exposure (usually ingestion) to food and can be repeated after encountering the same food (1). Food allergy is a severe public health problem that affects society, especially children, with no known radical cure despite the risk of severe allergic reaction and even death, increasing in prevalence in our country and throughout the world (2). Although the prevalence varies according to countries, it was determined as 0.6-12% according to survey-based studies and 0.3-7.7% according to food allergy clinical practise (3). Food-related immunological reactions are classified as immunoglobulin E (IgE)-mediated, non-IgE and mixed type reactions (4).

IgE-mediated food allergies are reactions that typically begin within minutes to two hours after ingestion. Rash, urticaria-angioedema, pruritus, erythema, contact urticaria, vomiting, nausea, abdominal pain, nasal congestion, nasal itching, sneezing, hoarseness, wheezing, stridor, cough, respiratory distress, hypotension, somnolence, incontinence, convulsion, syncope and anaphylaxis with multi-organ involvement may occur (5,6). The food that causes IgE-mediated food allergy varies according to the nutritional habits of the population. The most common food-allergy type in our country is the allergies emerging after cow's milk and eggs (7,8). Milk and egg allergy in children is a common cause of anaphylactic reactions. Milk is also one of the most common causes of fatal food-borne anaphylactic reactions (9,10). The diagnosis of IgE-mediated food allergy is made by skin prick test (SPT), prick-to-prick test (PTP) or demonstration of IgE sensitivity via food-specific IgE and oral food challenge test (OFC) (11).

OFC is the gold standard in the demonstration of tolerance and in diagnosing food allergy. Restarting the responsible food that is thought to be allergic or starting the responsible food that is not consumed may cause the development of anaphylaxis in a patient with IgE-mediated food allergy. Generally, the recommended time to evaluate the tolerance to the responsible food is 12-18 months after the last reaction. Predicting whether a patient will experience anaphylaxis before oral food challenge in the evaluation of the tolerance as well as during diagnosis is valuable information from the point of deciding in which case OFC should or should not be performed. Yanagida et al. evaluated the relationship between anaphylaxis risk and sIgE during OFC (12). To our knowledge, there is not any research in the literature evaluating the risk of anaphylaxis with sIgE/total IgE, SPT and PTP during OFC. To our knowledge, this is the first study in the literature to evaluate the sIgE, sIgE/total IgE, SPT and PTP tests to predict the risk of anaphylaxis before OFC. This study aims to investigate whether it is possible to predict anaphylaxis that may develop during OFC to evaluate the development of tolerance in IgE-mediated food allergy and to determine which test is more valuable in showing the reaction that may develop.

## MATERIAL and METHODS

Patients who were followed up with the diagnosis of IgE-mediated food allergy and evaluated via OFC concerning tolerance development in the Pediatric Allergy and Clinical Immunology Department of Dokuz Eylul University Faculty of Medicine (DEU) between January 2016 and December 2020 were retrospectively included in the present study.

In our clinic, the diagnosis of food allergy is made utilizing history, examination findings, laboratory tests, and the elimination-provocation method. Furthermore, provocation tests are performed to evaluate the development of tolerance.

Gender, clinical findings, age of the first symptom, history of the atopic disease diagnosed by a physician in the family, allergen foods, presence of additional allergic disease, inhaled allergen sensitivity, reactions with food intake during the challenge test, allergic food-specific IgE levels, skin prick test, prick to prick test. Total IgE levels were obtained from the polyclinic files of the cases followed up due to food allergy and evaluated, and the factors that could help the prediction of the development of anaphylaxis during OFC were assessed. Those with the values of  $\geq 0.35$  kU/L for specific IgE and presence of an induration  $\geq 3$  mm wider than the negative control for skin prick test and prick to prick tests were considered positive. If the eosinophil count was greater than 500 per microliter of blood, it was considered eosinophilia. In the food challenge test, low-intermediate and full dose incremental food challenge protocols were applied (12). Tolerance was determined via a negative OFC test result according to PRACTALL (13). Data were checked by two independent researchers. This study was approved by the DEU non-interventional studies ethics committee (Approval no: 2020/12-45). Informed consent was obtained from all parents of the children enrolled in the study.

**Statistics:** The data were evaluated in the IBM SPSS Statistics 22.0 (IBM Corp. Armonk, New York, USA) statistical package program. Descriptive statistics were given as the number of units (n), percent (%), mean $\pm$ standard deviation ( $\bar{x}\pm sd$ ), median values, and minimum-maximum values. Numerical variables were evaluated with the normality test. Comparisons between groups were made with two independent samples t-test for normally distributed variables and Mann-Whitney U analysis for non-normally distributed variables. Logistic regression analysis was used as multivariate analysis to calculate odds ratios (ORs) and 95% confidence intervals (95% CI). Values pertaining to laboratory parameters that allow making a diagnostic decision in predicting anaphylaxis were analyzed using Receiver Operating Characteristics (ROC) curve analysis in anaphylaxis cases during OFC. The sensitivity, specificity ratios and areas under the curves (AUC) for these cut-off points were calculated in the presence of significant cut-off points. Chi-square, Yates correction (continuity correction) and Fisher's exact tests were used to assessing whether the categorical variables were dependent or not. A p-value of  $<0.05$  was considered statistically significant.

## RESULTS

Between January 2016 and December 2020, 254 patients underwent oral challenge tests with food. Of these, 133 were IgE-mediated food allergy patients to whom OFC was applied to assess food tolerance. Seventy-nine (59.4%) of them were male and the time of OFC for the evaluation of tolerance development was 21 months (12-120).

For the patients, the time to apply to the physician with the first complaint and/or findings was seven months (2-60 months) on average, while 62 (72.9%) of them had a cesarean section, 92 (86.8%) had a delivery at term, and the mean birth weight was 3300 g (1400-4400).

Eight (6.9%) had a family history of consanguineous marriages, and 86 (65.6%) had atopic disease diagnosed by a physician. Among the first-degree family members, 43 (32.8%) of them had a history of asthma, 36 (27.5%) had allergic rhinitis (AR), 19 (14.5%) had atopic dermatitis, 20 (15.3%) had a food allergy and five (3.8%) drug allergy. Except for food allergy, 84 (63.3%) cases had one or more additional atopic diseases. There was a history of atopic dermatitis in 59 (44.4%) of them, had recurrent wheezing/asthma in 31 (23.3%), AR in 10 (7.5%) and drug allergy in four (3%). Concomitant diseases were present in three (2.2%) cases (esophageal atresia and diaphragmatic hernia in one, Di-George syndrome in another and G6PD deficiency in the other).

Sixteen (12%) of the patients had a history of food-related anaphylaxis in the past. The clinical findings associated with food allergy in patients are summarized in **Table 1**.

When the distribution of food that causes food allergies was considered, a combination of milk and egg was the most common, followed by egg and milk. The distribution of allergic food is shown in **Figure 1**. Except for the combination of milk and egg, multiple food allergies were detected in 26 patients. Of these, 12 (46%) had an allergy to tree nuts, nine (34.6%) had a wheat allergy, and other cases had allergies to pulses, potatoes, kiwi, soy and chicken meat.

The median value of the eosinophil count of the patients was 500/mm<sup>3</sup> (0-4200), 72 (55.4%) of them had eosinophilia, and the total IgE level was 84 (2-2422) IU/mL. In 36 (27%) cases, two or more OFCs were performed 47 times in total, with the same food gradually or with different foods. In 52 (39%) of the cases, OFC was made with baked food containing milk and/or egg protein, in 48 (36%) of them with boiled eggs, in 19 (14.3%) with fermented milk products, in 18 (23.5%) with pasteurized milk, in two (1.5%) with tree nuts, in two pieces (1.5%) of bread, in one of the cases with potato and one with semolina.

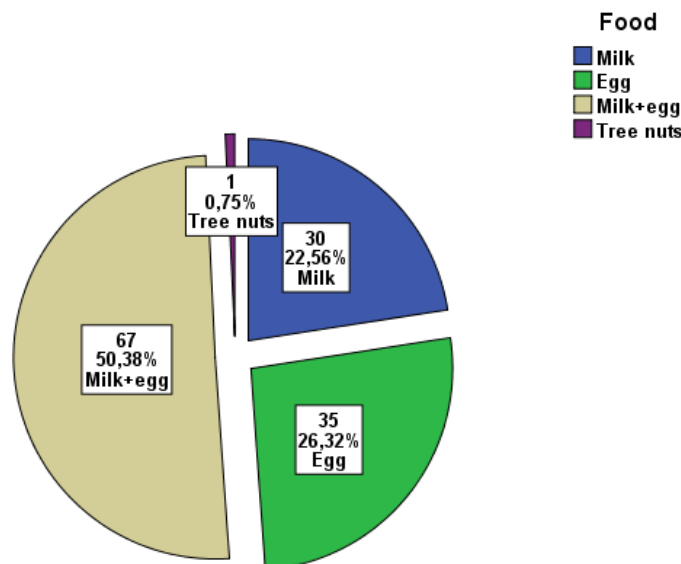
During these tests, reactions developed in 24 (18%) of the cases. While skin findings were observed in 21 (87.5%) cases, upper and/or lower respiratory tract findings were observed in 12 (50%) cases, GIS findings in seven (29.2%), while cardiovascular, neurological and other systemic symptoms were not detected in any of the patients. The reactions in nine (6.5%) cases were evaluated as anaphylaxis. 14 (10.5%) of the patients were administered medication for the developed reaction. Adrenaline injection was administered to seven (5.3%) of the patients, anti-histaminic to 12 (9%) of them, bronchodilator to five (3.8%), and systemic steroid to two (5%). None of the patients needed a second dose of adrenaline and fluid resuscitation. 122 (91.7%) of the patients were started on the tested food during OFC.

There was no difference between patients who had anaphylaxis and those who did not, concerning gender, birth history (term-preterm, normal-cesarean section, birth weight), atopic disease diagnosed by a doctor in the family, and the presence of atopic disease in addition to food allergy.

The nutritional sIgE, SPT, and PTP values of the patients were compared at the time of diagnosis and before OFC. It was detected that history of food-related anaphylaxis, age during the challenge, total IgE, milk sIgE, SPT, PTP at diagnosis, milk sIgE, SPT and PTP before the challenge, and egg sIgE, milk sIgE/total IgE differed between the group that experienced and the group that did not experience anaphylaxis during oral challenge test. A comparison of test results is shown in **Table 2**. ROC curves and cut-off points are shown in **Table 3**.

Cut-off points of tests were evaluated for anaphylaxis. The tests which had the best area under the curve in the ROC curves, that is, the tests which could determine the risk of anaphylaxis best, were SPT (AUC: 0.937-p: 0.001) and PTP (AUC: 0.928-p: 0.001), which were performed for milk before provocation.

Besides these, milk sIgE (AUC:0.760, cut-off:4.6 IU/mL, p:0.01), SPT (AUC:0.879, cut-off:4.5 mm, p<0.001), PTP (AUC:0.862, cut-off: 9.5 mm, p<0.001) during diagnosis and milk sIgE, the ratio of sIgE/total IgE before provocation had power to predict the risk of anaphylaxis (p<0.05). The negative predictive value of the tests that gave significant results for milk was over 95%. Although sIgE measurement for egg before provocation was significant, it predicted that moderate anaphylaxis might develop. The characteristics of children with anaphylaxis are shown in **Table 4**.



**Figure 1:** Distribution of food that causes food allergies

**Table 1:** Classification of clinical conditions seen in patients with food allergy

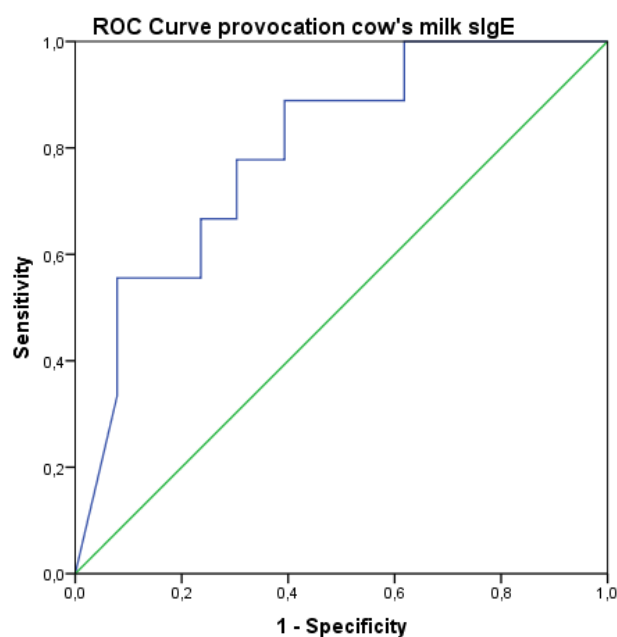
	Number	%
Rash-erythema	59	44.3
Atopic dermatitis*	54	40.6
Urticaria-angioedema*	22	16.5
Anaphylaxis	13	9.8
GIS findings	13	9.8
AR*	2	1.5

Patients other than those with anaphylaxis may have more than one clinical finding. (\*) three cases had a history of food-related anaphylaxis

**Table 2:** Comparison of anaphylaxis-related test results

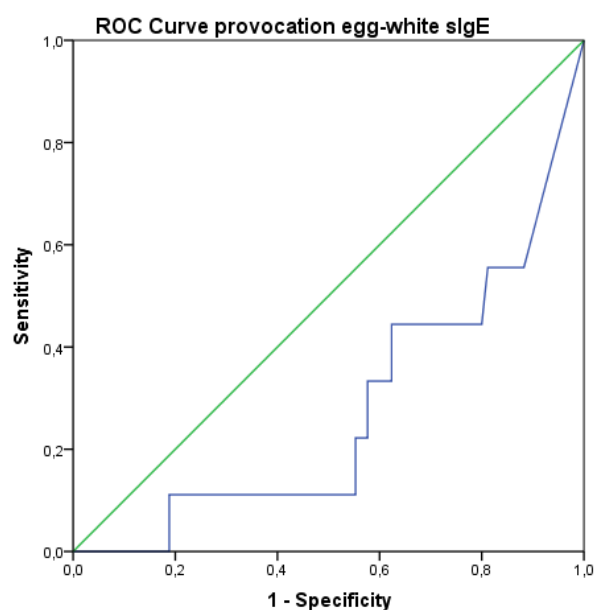
Variable°	Anaphylaxis via OFC (+) (n=9)	Anaphylaxis (-) (n=124)	p*
Age during challenge	47(12-96)	20 (12-60)	<b>0.006</b>
Total IgE (IU/mL)	173(73-800)	76.6(6-2000)	<b>0.013</b>
Eosinophil (cell/uL)	700(200-4000)	400(0-2300)	0.590
Anaphylaxis in history	5/9(55.5%)	11/124(0.8%)	<b>0.001</b>
<b>Tests performed during diagnosis.</b>			
sIgE milk	5(1-100)	1.020(0-100)	<b>0.007</b>
Milk sIgE/total IgE	0.065(0-0.200)	0.13(0-3.32)	0.189
Egg white sIgE	1.68 (0-17)	3.53 (0-100)	0.344
Egg white sIgE/total IgE	0.007(0-0.080)	0.37(0-1.97)	0.115
Egg yolk sIgE	0 (0-3)	0 (0-20)	0.771
Egg yolk sIgE/total IgE	0(0-0.03)	0(0-0.24)	0.615
SPT milk (mm)	7(5-9)	0(0-8)	<b>&lt;0.001</b>
PTP milk (mm)	9(5-13)	0(0-14)	<b>&lt;0.001</b>
<b>Tests performed before the oral food challenge.</b>			
sIgE milk	77.8(1.6-100)	0.48(0-100)	<b>0.003</b>
Milk sIgE/total IgE	0.075(0-1.080)	0.12(0-0.60)	<b>0.048</b>
Egg white sIgE	0.72 (0-18.40)	1.63(0-100)	<b>0.028</b>
Egg white sIgE/total IgE	0.008(0-0.080)	0.007(0-0.880)	0.921
Egg yolk sIgE	0 (0-3)	0(0-8)	0.417
Egg yolk sIgE/total IgE	0(0-0.01)	0.001(0-0.580)	0.357
SPT milk (mm)	5.5 (3-9)	0(0-7)	<b>&lt;0.001</b>
PTP milk (mm)	9(5-13)	0(0-8)	<b>&lt;0.001</b>

\*The significance data of the results which were determined as  $P < 0.05$  are demonstrated with bold numbers. \* The variables are given as median (min-max).

**Table 3:** ROC curves regarding anaphylaxis and cut-off points

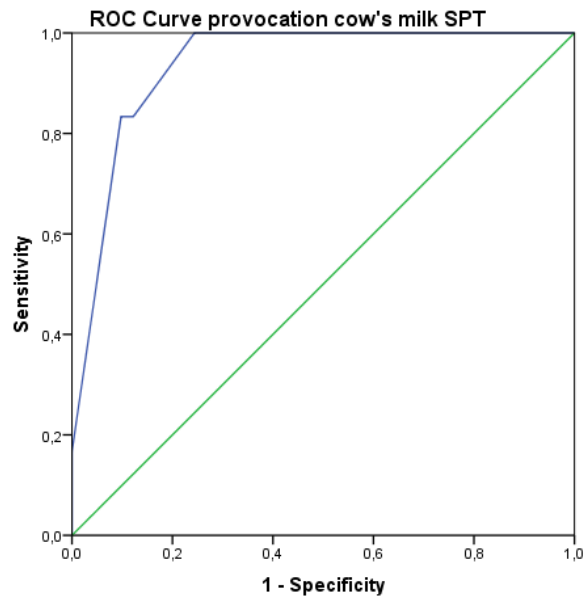
Diagonal segments are produced by ties.

Risk factor	AUC (95%)	Cut-off (IU/mL)	p	Sensitivity %	Specificity %	PPV %	NPV %
Provocation Milk sIgE	0.797 (0.661-0.934)	3.81	0.003	66.7	69.7	18.2	95.4



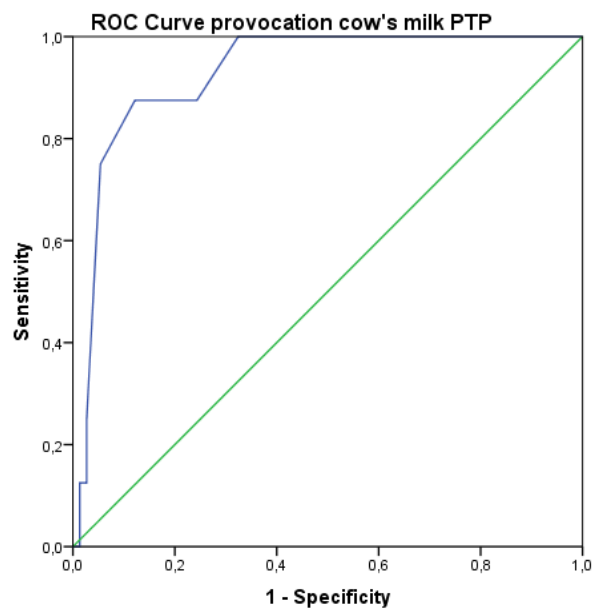
Diagonal segments are produced by ties.

Risk factor	AUC (95%)	Cut-off (IU/mL)	p	Sensitivity %	Specificity %	PPV %	NPV %
Provocation sIgE egg white	0.276 (0.105-0.448)	1.51	0.028	33.3	37.6	5.4	84.2



Diagonal segments are produced by ties.

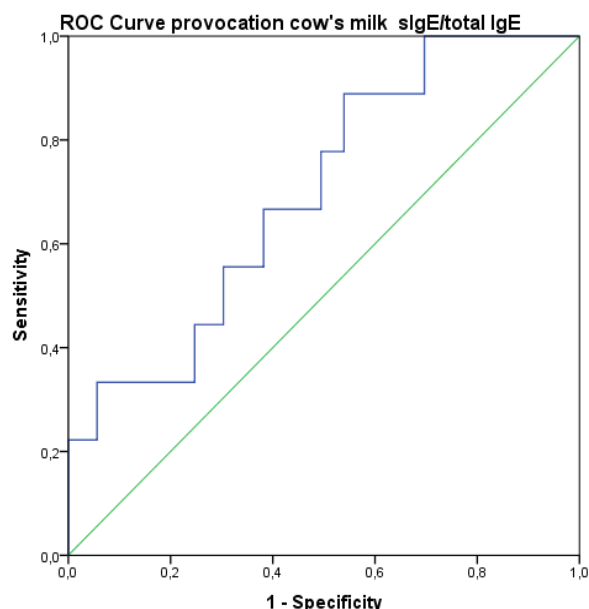
Risk factor	AUC (95%)	Cut-off (mm)	p	Sensitivity %	Specificity %	PPV %	NPV %
Provocation SPT milk	0.937 (0.864-1.000)	3.5	0.001	83.3	87.8	50	97.3



Diagonal segments are produced by ties.

Risk factor	AUC (95%)	Cut-off (mm)	p	Sensitivity %	Specificity %	PPV %	NPV %
Provocation Milk PTP	0.928 (0.857-1.000)	7.5	0.001	87.7	87.8	34	99





Risk factor	AUC (95%)	Cut-off	p	Sensitivity %	Specificity %	PPV %	NPV %
Provocation Milk sIgE/total IgE	0.698 (0.532-0.864)	0.0425	0.048	65.7	61.8	11	99

**Table 4:** Characteristics of children experiencing anaphylaxis

No	Diagnosis age (month)	Age during OFC (month)	Gender M/F	Sensitization	Food that causes anaphylaxis	Additional atopy	Familial atopy	Adrenaline	Anaphylaxis during OFC
<b>Individuals with a history of anaphylaxis, experiencing anaphylaxis during OFC</b>									
1	5	96	K	Milk+egg	Formula	Asthma	+	+	+
2	24	120	E	Milk+egg+wheat	Wheat	Asthma and AR	-	+	+
3	15	75	K	Milk	Fermented milk	Asthma	+	+	+
4	10	58	K	Milk+egg + pistachio nut	Baked milk	Asthma	+	+	+
5	7	96	E	Milk	Milk	-	+	+	+
<b>Those with no history of anaphylaxis but experienced anaphylaxis during OFC</b>									
6	7	60	E	Milk+egg	Baked milk	-	-	-	+
7	6	12	E	Milk+egg	Baked milk	Asthma	+	+	+
8	15	17	E	Milk+egg	Milk	-	+	-	+
9	6	36	E	Milk	Fermented milk	-	+	+	+

## DISCUSSION

There is a risk of anaphylaxis during challenge tests performed to evaluate food tolerance, as in provocations for diagnostic purposes. It is important to predict the risk of anaphylaxis before this test, performed in the evaluation of tolerance as in diagnosis. For this aim, we searched for markers that predict the risk of anaphylaxis during the oral challenge test performed to assess tolerance in our study. Anaphylaxis developed during OFC in 6.7% of our patients. In our patients who had anaphylaxis during OFC, while the tests that can best determine the risk of anaphylaxis were SPT and PTP performed before provocation for milk; milk sIgE, SPT, PTP during diagnosis, and sIgE, sIgE/total IgE ratio before provocation, were also found to be able to predict the risk of anaphylaxis.

The factors causing food allergies may differ according to the nutritional habits of the societies (14).

In studies conducted in Europe and our country, milk and egg seem to be the most common cause of IgE-mediated food allergy (15,16). In our country, the most common cause of anaphylaxis in infants is milk (17). In our study, while the most common cause of IgE-mediated food allergy was milk and egg, also milk was the most common cause of anaphylaxis in the OFCs performed to evaluate tolerance. Generally, the male gender is a risk factor for allergic diseases. There is also data showing that food allergies are more common in boys (18). Similarly, boys were more common in our study group (F:M=1:1.46).

In the literature, up to 88% of the groups with food allergies had additional allergic diseases (19). Especially for IgE-mediated food allergies, allergic diseases are common in close family members, such as parents and siblings (20,21). In most of our cases (65.6%), a history of allergic disease has existed in the family members. We think this will contribute to the early detection of children with risk factors.

In our findings, rash, erythema and atopic dermatitis were the most common findings of IgE-mediated food allergy. It has been reported that IgE-mediated food allergy can be seen up to 40% in patients with atopic dermatitis (22). In our patients with atopic dermatitis, erythema and rash frequently developed within the first two hours after exposure to food. Anaphylaxis developed in one patient.

In recent studies, the findings suggest that the application of gradual OFC may contribute to the development of earlier full tolerance and improvement of prognosis (12,23). It has been shown that 70% of children who have milk and egg allergies can tolerate baked milk and eggs (24,25). Cooking is a method that transforms cow's milk and eggs into a less allergenic form (25). In our cases, OFC was performed mostly with baked food containing milk and/or eggs, including gradually increasing doses of protein.

Our patients who experienced anaphylaxis were older, because we performed OFCs later, in the children with a history of anaphylaxis in the last year or those with severe anaphylaxis. Total IgE levels were higher in children who had anaphylaxis. We suggest that this is related to high allergic inflammatory activities. In our cases, milk was at the forefront as the cause of anaphylaxis.

PTP and SPTs are good indicators to rule out IgE-mediated food allergy (26). In a study conducted in Japan, the findings showed that high sIgE levels for food were associated with the risk of anaphylaxis (27). In another study, PPVs and NPVs were reported at levels similar to those in our study for SPT (9).

In Kwan et al.'s study, all of the individuals with a result of <8 mm, and 60% of those with a result of 8-14 mm in PTP tests, which was made with baked muffin slurry containing milk, tolerated OFC made with baked muffins containing milk without any problems (28). In our study, the induration diameter of <3.5 mm in SPT and the induration diameter of <7.5 mm in the pre-OFC PTP test were the best predictive test criteria for anaphylaxis, with an NPV of 99%. NPV was over 95% in general, in sIgE and skin tests performed for milk as the cause of anaphylaxis. In egg allergy, no significant result could be determined except for egg white sIgE. Four patients without a history of anaphylaxis experienced anaphylaxis during OFC performed to evaluate food tolerance.

In IgE-mediated food allergy, anaphylaxis may develop when food is reintroduced after elimination, even if patients without a history of anaphylaxis. Thus, we recommend that tests that will enable the evaluation of risky situations, especially SPT and PTP tests, to also be performed before OFC.

The retrospective nature of our study and the low number of patients who had anaphylaxis during OFC were important limitations. The patients were evaluated using basal tests in the allergy clinic, and further evaluations, such as molecular diagnostic tests, could not be performed.

## CONCLUSION

IgE-mediated food allergy is a clinical problem with an increasing prevalence. Appropriate diagnosis, treatment and follow-up should be dealt with by allergists. Milk and eggs are the most common responsible food in our country. Even if the first reaction is not anaphylaxis in patients which the responsible food has been eliminated due to food allergy, challenge tests to evaluate tolerance should be performed in centers specialized in anaphylaxis management. The tests that can best determine the risk of anaphylaxis before OFC in our patients were determined as DPT and PTP for pre-challenge milk. A personalized approach (e.g., baked product and fermented product) should be used to prepare the product to be selected for the provocation after evaluating the patient with the tests performed before the provocation (SPT, PTP, sIgE, sIgE/total IgE).

**Author Contributions:** All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Serdar Al, Gizem Atakul, Özge Atay, Özge Kangallı, Seda Şirin Köse, Dilek Tezer, Suna Asilsoy, Nevin Uzuner and Özkan Karaman. The first draft of the manuscript was written by Serdar Al, Suna Asilsoy and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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**Ethical approval:** The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. Approval was granted by the Ethics Committee of Dokuz Eylül University Non-Interventional Studies Ethics Committee (Approval no: 2020/12-45). Informed consent was obtained from all parents of the children enrolled in the study.



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