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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Evaluation of Oral Food Provocation Test Results in Children Diagnosed with Food Allergy

Besin Alerjisi Tanılı Çocuklarda Oral Besin Provokasyon Testi Sonuçlarının Değerlendirilmesi

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ABSTRACT

Aims: Our study was conducted to evaluate the results of the oral food provocation tests in children with a diagnosis of food allergy and to examine the development of reactions in patients during the oral food provocation test.

Material and Method: This was a descriptive type of study. Children diagnosed with food allergy between the years 2020-2022, and who had an oral food provocation test were included in the study. The patient files were scanned retrospectively. Age, gender, allergy tests, total IgE, eosinophil values and reactions during treatment were evaluated.

Results: Oral food provocation test was applied to 40.5% (n=85) of the patients for diagnostic purposes and 59.5% (n=125) to determine the food tolerance. Of the patients who received oral provocation, 48.1% (n=101) received yoghurt, 39.0% (n=82) eggs, 5.7% (n=12) baked egg cake, 4.8% (n=10), baked yoghurt cake. Reaction was observed in 8.6% (n=18) of the patients who received oral food provocation test. Reactions were mostly urticaria. There was no statistically significant relationship between the development of the reaction and gender, the purpose of the provocation test, the age of onset of the first complaints and the age at which the provocation test was applied (p>0.05). The median specific IgE (milk) value was higher in patients who developed a reaction (p=0.034).

Conclusions: Reaction developed less than one in ten of the patients. Although the reactions are often mild such as urticaria, it is important to predict the development of the reaction in terms of the management of food allergies and the feasibility of the provocation test.

Keywords: Oral food provocation, children, food allergy

ÖZ

Amaç: Çalışmamız, besin alerjisi tanısı alan çocuklarda oral besin provokasyon testi sonuçlarını değerlendirmek ve oral besin provokasyon testi sırasında hastalarda reaksiyon gelişimini incelemek amacıyla yapılmıştır.

Gereç ve Yöntem: Çalışma tanımlayıcı tiptedir. 2020-2022 yılları arasında besin alerjisi tanısı alan ve oral besin provokasyon testi yapılan çocuklar çalışmaya dahil edildi. Hasta dosyaları retrospektif olarak tarandı. Yaş, cinsiyet, alerji testleri, total IgE, eozinofil değerleri ve tedavi sırasındaki reaksiyonlar değerlendirildi.

Bulgular: Hastaların %40,5'ine (n=85) tanı amaçlı, %59,5'ine (n=125) gıda toleransını belirlemek için oral gıda provokasyon testi uygulandı. Oral provokasyon uygulanan hastaların %48,1'ine (n=101) yoğurt, %39,0'una (n=82) yumurta, %5,7'sine (n=12) yumurtalı kek, %4,8'ine (n=10) fırınlanmış yoğurtlu kek verildi. Oral gıda provokasyon testi yapılan hastaların %8,6'sında (n=18) reaksiyon görüldü. Görülen reaksiyonlar çoğunlukla ürtikerdi. Reaksiyon gelişimi ile cinsiyet, provokasyon testinin yapılma amacı, ilk şikayetlerin başlama yaşı ve provokasyon testinin uygulanma yaşı arasında istatistiksel olarak anlamlı bir ilişki yoktu (p>0,05). Medyan spesifik IgE (süt) değeri reaksiyon gelişen hastalarda daha yüksekti (p=0,034).

Sonuç: On hastanın 1'inden daha az oranda reaksiyon gelişimi görüldü. Oral provokasyon testi sırasında gelişen reaksiyonlar genellikle ürtiker gibi hafif olsa da, gıda alerjilerinin yönetimi ve provokasyon testinin uygulanabilirliği açısından reaksiyon gelişiminin önceden tahmin edilmesi önemlidir.

Anahtar Kelimeler: Oral besin provokasyon testi, çocuklar, besin alerjisi

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INTRODUCTION

Food allergy is an immunological response to food proteins (1). Food allergies are most commonly seen against eggs, milk, nuts such as peanut, soy, wheat, shellfish, and fish (2, 3). The frequency of food allergy has been increasing in recent years and is more common in children than adults (4). Allergic reactions triggered by food can progress with various symptoms and disorders including the skin, gastrointestinal tract, and respiratory tract. These reactions occur by Immunoglobulin E (IgE)-mediated and non-IgE-mediated (cellular) mechanisms (5).

Confirming the diagnosis of a food allergy might be essential due to the subjectivity of findings associated with food allergies and the low positive predictive values observed in the skin prick test performed with food and specific IgE levels (6). In order to confirm the diagnosis of food allergies, it may be necessary to perform oral provocation tests with the suspect food (7, 8). In the oral provocation test, the suspected allergen food is given orally to the patient in a controlled and standardized environment (9). Another use of the oral food challenge test is to evaluate the tolerability of a food in a child with a previous food allergy (10).

Although the oral food provocation test is accepted as the gold standard for the diagnosis of food allergy, some adverse reactions may be seen during the test. Although these reactions are usually in the form of mild cutaneous allergic reactions such as urticaria, it should be kept in mind that life-threatening serious reactions such as anaphylaxis may also occur after oral food provocation test (11). There are few studies in the literature on the effectiveness, applicability and reliability of oral food provocation tests. In a study in the literature, it was reported that 18.8% of patients developed a reaction during oral food provocation tests (12).

The management of food allergies is extremely important especially for the pediatric patient group, since its prevalence is increasing. Examining provocation tests, which play a crucial role in allergy management, along with the characteristics of the tested patients, is necessary. In this context, our study was conducted to retrospectively evaluate the results of the oral food provocation tests in children with a diagnosis of food allergy and to examine the development of reactions in patients during the oral food provocation test.

MATERIAL AND METHOD

The study was carried out with the permission of University of Health Sciences, Ümraniye Training and Research Hospital Ethics Committee (Date: 22.12.2022, Decision No: 393). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This was a descriptive type of study. Children diagnosed with food allergy between the years 2020-2022, and who had an oral food provocation test were included in the study. The patient files were examined retrospectively, and all patients with a file were included in the study. The study had no exclusion criteria. Patients' age, gender, allergy tests, total IgE, eosinophil values and reactions during oral food provocation tests were evaluated within the scope of the study.

Oral Food Provocation Tests

In our clinic, oral food provocation tests were performed in the form of open oral food provocation tests, all anaphylaxis measures were taken and performed under the supervision of a physician. Consent was obtained from the parents before the test. The patients were examined before starting the oral food challenge tests and before each dose increase. Vital signs, respiratory and dermal examination findings were recorded after each dose. Adverse reactions that developed during the provocation test were also recorded. The patients were kept under observation for two hours after the last dose was given.

In open oral food provocation tests, the suspicious food is started at a low dose and dose increases are made at 15-minute intervals until the target dose is reached. The oral food provocation tests for each food are applied in accordance with the "Work Group Report: Oral Food Challenge Testing" guideline of the American Allergy and Immunology Committee (9).

Statistical Analysis

SPSS (Statistical Package for Social Sciences for Windows 25.0 program was used for the analysis and the recording of data. Descriptive data was presented wtih median, minimum, maximum values, numbers (n) and percentages (%). For the analysis of categorical data, Chi-square test was used. For the comprasion of continuous variables that non-normally distrubuted; Mann Whitney U test was used. The statistical significance level was set at $p<0.05$.

RESULTS

In the study, 43.3% (n=91) of 210 children who underwent oral food provocation test were female and 56.7% (n=119) were male. The median age of onset of the first complaint in children was 4.0 months (1.0-36.0). The median age at which the oral food provocation test was applied was 11.0 months (6.0-88.0).

When the first admission of the patients were examined, 66.2% (n=139) of the children had urticaria, 48.1% (n=101) had gastrointestinal system findings, 11.9% (n=25) had atopic dermatitis. Other accompanying clinical findings of the patients were reactive airway disease, allergic rhinitis and anaphylaxis (**Table 1**).

Table 1. Accompanying clinical findings of the patients

	n	%
Urticaria	139	66.2
Gastrointestinal system findings	101	48.1
Atopic dermatitis	25	11.9
Reactive airway disease	13	6.2
Allergic rhinitis	11	5.2
Anaphylaxis	9	4.3

Oral food provocation test was applied to 40.5% (n=85) of the patients for diagnostic purposes and 59.5% (n=125) to determine the food tolerance. Of the patients who received oral provocation, 48.1% (n=101) received yoghurt, 39.0% (n=82) eggs, 5.7% (n=12) baked egg cake, 4.8% (n=10), baked yoghurt cake. Of the patients 1.9% (n=4) had received goat yoghurt and 0.5% (n=1) had received baked goat yoghurt cake. Provocation test was performed in 52.5% (n=53) of the patients who were given yoghurt to confirm the diagnosis. In patients who were given eggs, the purpose of the provocation test was to detect the development of tolerance more frequently (n=50; 61.0%). The aim of the oral provocation test was to detect the development of tolerance in all those given goat yoghurt, baked egg, baked yoghurt, and baked goat yoghurt. In 7.9% (n=8) of the children given yoghurt, reaction development related to the provocation test was observed. Reactions developed in 8.5% (n=7) and 16.7% (n=2) of children given eggs and baked eggs, respectively. A reaction developed in 25.0% (n=1) of the children given goat yoghurt. No reaction occurred in those given baked yoghurt and baked goat yoghurt (**Table 2**).

Table 2. The foods applied in the oral provocation test, the purpose of the test and development of reaction

Foods	Total n (%)	For diagnosis (n=85) n (%)	For food tolerance (n=125) n (%)	Occurance of reaction n (%)
Yoghurt	101 (48.1)	53 (52.5)	48 (47.5)	8 (7.9)
Egg	82 (39.0)	32 (39.0)	50 (61.0)	7 (8.5)
Baked egg (cake)	12 (5.7)	0 (0)	12 (100.0)	2 (16.7)
Baked yoghurt (cake)	10 (4.8)	0 (0)	10 (100.0)	0 (0)
Goat yoghurt	4 (1.9)	0 (0)	4 (100.0)	1 (25.0)
Baked goat yoghurt (cake)	1 (0.5)	0 (0)	1 (100.0)	0 (0)

Reaction was observed in 8.6% (n=18) of the patients who received oral foodprovocation test. Of the patients 5.2% (n=11) had urticaria, 1.9% (n=4) had vomiting. Anaphylaxis was observed in 1.0% (n=2), and cough was observed in 0.5% (n=1) . The characteristics of 18 patients who had a reaction are given in **Table 3**.

Table 3. Features of patients with reactions during oral food provocation test

Patients	Gender	Age (months)	Aim of OPT	Tested food	Reaction	sIgE (kU/L) (milk)	sIgE (kU/L) (egg)
1	M	6	D	Yoghurt	Urticaria	0	-
2	M	8	D	Yoghurt	Urticaria	0	-
3	F	13	D	Yoghurt	Urticaria	0	-
4	F	26	D	Yoghurt	Urticaria	0.75	-
5	M	6	T	Yoghurt	Urticaria	0	-
6	M	8	T	Yoghurt	Vomiting	1.56	-
7	M	40	T	Yoghurt	Urticaria	4.19	-
8	M	26	T	Yoghurt	Anaphylaxis	0	-
9	F	49	T	Baked egg (cake)	Cough	-	2.57
10	F	8	D	Egg	Vomiting	-	0
11	M	8	D	Egg	Urticaria	-	0
12	M	11	T	Egg	Urticaria	-	0.32
13	F	15	T	Egg	Urticaria	-	0
14	F	14	T	Egg	Vomiting	-	0
15	F	44	T	Baked egg (cake)	Urticaria	-	0
16	M	9	T	Egg	Urticaria	-	0.11
17	F	14	T	Egg	Vomiting	-	0
18	F	45	T	Goat Yoghurt	Anaphylaxis	0.84	-

F: Female, M: Male, D:Diagnosis, T:Tolerance, OPT: Oral food provocation test, sIgE: specific Immunoglobulin E

A comparison was made between patients who exhibited a reaction and those who did not exhibit a reaction following the oral food provocation test. There was no statistically significant relationship between the development of the reaction and gender, the purpose of the provocation test, the age of onset of the first complaints and the age at which the provocation test was applied (p>0.05). For the laboratory values; the median specific IgE (milk) value was 1.56 kU/L (0.75-4.20) in patients who developed a reaction, and 0.35 kU/L (0.11-4.19) in those who did not (p=0.034). In terms of specific IgE (egg), eosinophil and total IgE values, there was no statistically significant difference between patients with and without reaction (p>0.05) (**Table 4**).

In order to prove the development of tolerance, the times between the first and last specific IgE measurements of the patients who received oral food provocation were evaluated. The median times between specific IgE first and last measurements of patients who were given eggs, yoghurt, and baked eggs in the provocation test were 4.0 months (1.0-14.0), 3.0 months (1.0-12.0), and 6.0 months (3.0-12.0), respectively. The times between two specific IgEs for patients given other foods are given in **Table 5**.

Table 4. Comparison of patients with and without reaction after oral food provocation test

	No reaction (n=192)	Reaction occured (n=18)	P value
Gender, n (%)			0.551*
Female	82 (90.1)	9 (9.9)	
Male	110 (92.4)	9 (7.6)	
Aim of the test, n (%)			0.518*
Diagnosis	79 (92.9)	6 (7.1)	
Tolerance	113 (90.4)	12 (9.6)	
Age of the onset of complaints (months) median (min-max)	4.0 (1.0-36.0)	4.5 (1.0-14.0)	0.215**
Age (months), median (min-max)	11.0 (6.0-88.0)	13.5 (6.0-49.0)	0.324**
sIgE (kU/L) (milk), median (min-max)	0.35 (0.11-4.19)	1.56 (0.75-4.20)	0.034**
sIgE (kU/L) (egg), median (min-max)	0.83 (0.10-2.98)	0.32 (0.11-2.57)	0.698**
Eosinophil (10^3/uL) (absolute), median (min-max)	280.0 (0-2220.0)	260.0 (10.0-590.0)	0.338**
Eosinophil (%), median (min-max)	3.35 (0-17.7)	3.1 (0.1-5.6)	0.564**
Total IgE (IU/mL), median (min-max)	18.0 (0-982.0)	46.5 (1.0-494.0)	0.267**

* Chi-square test, ** Mann-Whitney U test, p<0.05 is statistical significance level, sIgE: specific Immunoglobulin E

When the specific IgE first and last measurements of the patients who received oral food challenge to prove the development of tolerance were evaluated, the median value of the last measurements of specific IgE (egg), specific IgE (milk) and specific IgE (goat's milk) values was lowerin secondly measured values. The difference between the two measurements for specific IgE (egg) and sIgE (milk) was statistically significant (p<0.001 and p=0.017, respectively) (**Table 5**).

Table 5. The specific IgE first and last measurements of the patients who received oral food provocation test to prove the tolerance and the time between the two measurements

Time between sIgE measurements of each food (months)	Median	Min.	Max.
Egg (n=50)	4.0	1.0	14.0
Yoghurt (n=48)	3.0	1.0	12.0
Baked egg (cake) (n=12)	6.0	3.0	12.0
Baked yoghurt (cake) (n=10)	4.0	1.0	10.0
Goat yoghurt (n=4)	7.0	5.0	12.0
Baked goat yoghurt (cake) (n=1)	12.0	12.0	12.0
Specific IgE values (kU/L)	**Median**	**Min.**	**Max.**
sIgE (egg) first	2.78	0.00	39.40
sIgE (egg) last	0.87	0.00	2.98
P value*		<0.001	
sIgE (milk) first	0.88	0.00	6.68
sIgE (milk) last	0.46	0.00	4.19
P value*		0.017	
sIgE (goat milk) first	1.13	0.00	2.25
sIgE (goat milk) last	0.00	0.00	0.84
P value*		0.157	

* Mann-Whitney U test, p<0.05 is statistical significance level, sIgE: specific Immunoglobulin E

DISCUSSION

Food allergies are an important public health problem with an increasing frequency all over the world (13). Food allergies impair the quality of life of patients and may cause serious allergic reactions such as anaphylaxis (14). It is extremely important to diagnose food allergies and to treat patients with food allergies. In some patients with food allergies, oral food provocation tests are applied to confirm the diagnosis and detect food tolerance. For this reason, oral food provocation tests have an important place in the management of food allergies. In this context, the clinical characteristics of children who underwent oral food provocation test were evaluated in our study.

When the clinical presentations accompanying food allergy were examined in our study, urticaria, gastrointestinal system findings and atopic dermatitis were the most common ones, respectively. Other accompanying clinical findings of the patients were reactive airway disease, allergic rhinitis and anaphylaxis. In a study conducted in our country in pediatric patients with food allergy, the most common clinical diagnoses in children were reported as atopic dermatitis, gastrointestinal system diseases, and urticaria-angioedema, similar to our study (15).

In our study, oral food provocation test was applied to 40.5% of the patients for diagnosis and 59.5% to determine food tolerance. Similarly, in the literature, the oral food provocation test is most commonly used for determining the food tolerance (16). In our study, the most commonly administered foods for oral food provocation were yoghurt, eggs, and baked eggs. According to the literature, eggs were the most frequently used foods in oral food provocation tests (17).

Although it is considered the gold standard in the diagnosis of food allergiesfyo, some adverse reactions may be seen in patients during oral food provocation (18). In our study, reactions developed in 8.6% of patients who received oral food provocation. In a study conducted in our country, the frequency of reaction development after oral food provocation in children was reported as 20.6% (6). In a different study in the literature, the frequency of reaction development after oral food provocation in children was reported as 43% (19). In our study, the observed rate of reaction development was lower compared to findings in the literature. This discrepancy

may be associated with various factors, including the specific foods used in the provocation tests, the clinical characteristics of the patients, and their age. In our study, urticaria was observed most frequently in the patients with reaction, followed by vomiting. Anaphylaxis was observed in 1% of patients. Similar to the literature, the reactions seen after oral food provocation are mostly skin reactions (6, 12, 16). In another study, mild allergic reactions frequently developed during oral food provocation, and the percentage of anaphylaxis was reported as 2.4%, similar to our study (17).

In our study, we assessed the development of reactions based on food exposure during oral food provocation tests. While goat yoghurt and eggs showed the highest incidence of reactions, the reaction frequencies to different foods were relatively similar. Similarly, in a study in the literature, reaction development was observed mostly after oral food provocation with milk and eggs (19). In another study, 12.5% reaction was observed in children who were given eggs (6). This percentage is similar to the frequency of reactions developed during the oral food provocation test performed with eggs in our study (8.5%).

Factors that may be associated with reaction development during oral food provocation test were evaluated. In our study, no statistically significant relationship was found between gender, the purpose of the provocation test (diagnosis or tolerance), the age of onset of the first complaints, the age at which the provocation test was applied, total IgE and reaction development during the provocation. The specific IgE (milk) value was significantly higher in patients who developed a reaction. In a similar study conducted in pediatric patients in our country, factors associated with reaction development during oral food provocation were evaluated. Similar to our study, no relationship was found between age, gender, purpose of provocation, total IgE values and reaction development. In the same study, the induration diameter in the skin test was found to be significantly higher in those who developed a reaction (6). In future multicenter studies to be planned, there is a need to investigate the factors that may be associated with the development of the reaction during the provocation test.

When the specific IgE first and last measurements of the patients who were given oral food provocation test to prove the development of tolerance in our study, the final measurements of specific IgE (egg), specific IgE (milk) values were significantly lower than the first measurements. The decrease in the second measurements in specific IgE values suggests that tolerance to the foods has developed. Similarly, a study from the literature noted that a decline in food-specific IgE levels over time could be indicative of the emergence of clinical tolerance with regard to milk and egg allergies (20).

Limitations and Strengths

Our study was carried out on the results of the oral food provocation test performed in a tertiary hospital. The fact that the study was conducted on a single hospital database creates a limitation in terms of the generalizability of our results. On the other hand, the large number of study sample compared to similar studies in the literature is the strength of the study. In addition, presenting a wide range of data such as the clinical characteristics of the patients, laboratory values, and the change between specific IgE values is another strength of the study.

CONCLUSION

Oral food provocation test was applied to 40.5% of the patients in our study for diagnosis and 59.5% for determining the food tolerance. Reaction developed in 8.6% of the patients who received oral food provocation test. Most of the patients who developed a reaction had urticaria. Vomiting and coughing were other findings. Anaphylaxis was seen in only 2 patients. In our study, the specific IgE (milk) value was significantly higher in patients who developed a reaction than in those who did not.

As our study results show; although it has an important place in the diagnosis and management of food allergies, it is understood that it is necessary to be careful in terms of reaction development during oral food provocation tests. Although the reactions are often mild such as urticaria, it is important to predict the development of the reaction in terms of the management of food allergies and the feasibility of the provocation test. Therefore, in the light of our study findings, there is a need for further multicenter studies to evaluate the factors associated with reaction development in patients who underwent food provocation test.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences, Ümraniye Training and Research Hospital Ethics Committee (Date: 22.12.2022, Decision No: 393).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients for the study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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