

# Factors Affecting Tolerance Development in Children with Food Allergies

*Besin Alerjisi Tanılı Hastalarda Tolerans Gelişimi ve Toleransa Etki Eden Faktörler*

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## Abstract

Although the prevalence of food allergy (FA) is unknown, it is estimated to have increased in recent years. In general, food allergies are more common in the pediatric age group than in adults. In our study, we aimed to determine the development of tolerance and the factors affecting it in children with food allergies. Medical records of cases followed up for FA were retrospectively reviewed between 2013 and 2016. Gender, age of first symptom, duration of breastfeeding, family history of atopy, multiple food allergies, concomitant allergic diseases and clinical evidence of the cases were evaluated. In addition, prick test results, total IgE and specific IgE levels, food challenge test results and tolerance development were evaluated. Of 319 patients 57.7% (184) were male. The average age of onset of symptoms was 3 months. The most common symptoms were related to the gastrointestinal system (69.9%), the skin (22.3%) and the respiratory system (6.3%). When the tolerance development rates were investigated by years, it was found that the tolerance developed 87.1% in the first year, 5.9% in the second and 2.8% in the third year. The most common allergens are cow's milk (71.3%), eggs (17.6%), peanuts (2.8%), nuts (2.04%) and other foods such as strawberries, cocoa, peaches. The mother's smoking status was significantly associated with the development of tolerance. The rate of development of tolerance in the first year was significantly higher in non-Ig E-mediated allergies and single food allergies.

**Keywords:** Food allergy, Prognosis, Tolerance

## Özet

Besin alerjisinin prevalansı bilinmemekle birlikte son yıllarda giderek arttığı tahmin edilmektedir. Genel olarak besin alerjileri pediatrik yaş grubunda erişkine oranla daha sık görülür. Çalışmamızda; polikliniğimizde gıda alerjisi tanısı olan hastalarımızın, doğal seyri, tolerans gelişimi ve toleransa etki eden faktörleri belirlemeyi hedefledik. Ocak 2013-Ocak 2016 yılı arasında polikliniğimizde Besin Alerjisi tanısı alan hastaların dosyaları retrospektif olarak incelendi. Hastaların cinsiyetleri, ilk semptom yaşı, anne sütü alma süresi, ailede atopi öyküsü, çoklu besin alerjisi, ek alerjik hastalık varlığı ve klinik bulguları değerlendirildi. Hastaların prik test sonuçları, total IgE, spesifik IgE, düzeyleri ve tolerans geliştirme durumları değerlendirildi. 319 hastanın 184'ü erkek (%57.7) idi. Hastaların 127'sinde (%39.8) ailede atopi öyküsü ve 71'inde (%22.3) çoklu besin alerjisi mevcuttu. Hastalarda görülen en sık semptom, %65.8 gastrointestinal sistem, %21 cilt bulguları, %6.3 solunum bulgularıydı. Hastaların semptom yaşı  $5.8 \pm 9.7$  ay; tanı yaşı  $6.6 \pm 9.08$  aydı. Hastaların yıllara göre tolerans geliştirme oranları; Birinci yıl 287 (%87,1) ikinci yıl 19'unda (%5,9) üçüncü yıl 9'unda (% 2,8) olarak saptandı. En sık alerjen gıda inek sütü (%71,3), yumurta (%17,6), fıstık (2,8), fındık (%2,04) olmakla beraber diğer gıdalar çilek, kakao, şeftali, buğday, soya, balık olarak saptandı. Çalışmamızda ilk yılda annenin sigara kullanımı ile besin alerjilerinde tolerans gelişimi arasında anlamlı fark saptanmıştır. Non Ig E aracı besin alerjisi olanlar ve tek besine karşı alerjen olan hastalarda ilk yılda tolerans gelişimi anlamlı oranda fazla saptanmıştır.

**Anahtar Kelimeler:** Besin alerjisi, Prognoz, Tolerans

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## 1. Introduction

There is a significant increase in childhood allergic diseases worldwide. The prevalence of these diseases varies from country to country and even in different regions of the same country (1). Since these changes cannot be explained by genetic factors alone, environmental factors are also blamed.

The main allergenic foods are cow's milk, chicken eggs, soybeans, wheat in childhood, peanuts, shellfish, fish and nuts in adults. Other allergenic foods include legumes, vegetables, fruits, beef, lamb, pork, chicken, and turkey meat (2-7). Sensitization with food antigen can occur not only by ingestion of food but also after inhalation and skin contact. In addition, cross-reactions can occur with allergens such as birch pollen, profilins, latex, and lipid transfer protein (8,9).

The healthy immune system maintains unresponsiveness towards to potential food allergens. Various hypotheses such as integration of vitamin D deficiency, hygiene and dual allergen exposure hypothesis have been proposed to explain the increase in FA. Most recently investigated hypothesis is dual allergen hypothesis. Randomised controlled trials recommend including possible common food allergies such as peanuts and eggs in complementary foods nutritional regimens starting at approximately 6 months but not before 4 months. National Institutes of Health recommendations promotes the early introduction of peanut for the prevention of peanut allergy(46). Oppositely the study Enquiring about tolerance (EAT) suggest that early introduction of allergenic food in sufficient quantity from 3 months of age may be able to help prevent food allergies developing in children(47). Future advances understanding oral tolerance in human subjects will largely determine treatment.

In our study; we aimed to determine the factors that affect the natural course, development of tolerance and tolerance of our patients diagnosed with food allergy.

## 2. Materials and Methods

Between January 2013 and January 2016, the files of the patients diagnosed with Food Allergy in the outpatient clinic of Eskişehir Osmangazi University Faculty of Medicine, Department of Pediatrics, Allergy-

Immunology Department were retrospectively analyzed according to the questionnaire form prepared. Local ethical committees approved all studies.

Food allergy was diagnosed by clinical history, allergy tests, elimination of cow's milk from the diet and food challenge test. The diagnosis of non-IgE mediated food allergy was made in the presence of clinical symptoms, the disappearance of symptoms with elimination diet and the occurrence of symptoms when suspected food was given again. From the polyclinic files of the children who were followed up with a diagnosis of food allergy, gender, first symptom age, breastfeeding time, age at starting additional foods, family history of atopy, multiple food allergy, presence of additional allergic disease, inhaled allergen sensitivity, and clinical findings were obtained. The time interval between milk protein intake and reaction formation and the pattern of milk protein intake were evaluated. Prick test, prick to prick test results with pasteurized milk, total IgE, milk and casein specific IgE levels and reactions food challenge test were evaluated. Tolerance development status of the patients was evaluated according to the results of the loading test performed both at home or in clinic and information received from the families.

In statistical analysis, chi-square test was used in comparison of categorical data, T test (Student's T test) in independent groups in case of assumptions in comparison of numerical measurements, and MannWhitney U test if assumptions were not provided. Mann Whitney U test was used for comparing two independent groups, while Pearson chi-square and Fisher's chi-square tests were used for comparison of categorical variables. Two ratio tests were used in the frequency distribution test (f) and chi-square analysis was used in the test of cross tables. A value of  $p < 0.05$  was considered statistically significant in all tests.

## 3. Results

Between January 2013 and December 2016, 416 children who were followed up with a diagnosis of food allergy were found. Forty-three children with a diagnosis of food allergy

excluded during their follow-up and 16 patients with a diagnosis of inflammatory bowel disease were excluded from the study. 17 patients whose ICD codes were entered incorrectly and 21 patients whose follow-up data could not be accessed were excluded from the study. A total of 319 patients were included in the study. The characteristics of

the patients included in the study are shown in Table 1.

According to immunological mechanisms, 220 of the patients (69.9%) had non-IgE-mediated, 48 (15%) had Ig E-mediated, and 51 (16%) had mixed disease. The clinical findings of the patients are summarized in Table 2.

**Table 1.** Characteristics of patients with food allergies

<b>Gender</b>	<b>n</b>
Male	184 (57,7%)
Female	135 (42,3%)
<b>Age of first symptom (months)</b>	<b>3 (2-6)</b>
<b>Breastfeeding time (months)</b>	<b>12 (9-17,25)</b>
<b>Additional food starting age (months)</b>	<b>6 (5-6)</b>
<b>Family history of atopy</b>	<b>127 (39,8%)</b>
<b>Presence of multiple food allergies</b>	<b>72 (22,6%)</b>
<b>Prematurity</b>	<b>24 (7,5%)</b>
<b>Presence of additional allergic diseases</b>	<b>101 (31,3%)</b>
Asthma	9/101
Rhinitis	18/101
Atopic dermatitis	74/101

**Table 2.** Clinical findings of patients with food allergies

<b>Clinical finding</b>	<b>n (%)</b>
<b>Skin manifestations</b>	71 (22,3)
Urticaria	7 (9,9)
Atopic dermatitis	60 (84,5)
Angioedema	4 (5,6)
<b>GIS findings</b>	223 (69,9)
Bloody stool	61 (27,35)
Mucus stool	72(32,28)
Bloody mucus stool	41(18,3)
Vomiting	12 (5,38)
Abdominal pain	10 (4,48)
Diarrhea	11 (4,93)
Constipation	14 (6,27)
Bloody vomiting	2 (0,9)
<b>Respiratory symptoms</b>	20 (6,3)
Rhinitis	3 (15)
Wheezing	9 (45)
Cough	8 (40)
Anaphylaxis	5 (1,6)

The most common symptoms in children with food allergy were GIS findings in 223 (69,9%) patients, skin findings in 71 (22,3%) patients, and respiratory system findings in 20 (6,3%) patients. It was determined that five (1,6%) of the patients developed anaphylaxis after consuming food which is an allergen.

When the patients were separated according to food allergens, the most common allergen was

cow's milk (71,3%). Other common allergens were eggs (17,6%), peanuts (2,8%), and hazelnuts (2,04%).

In the first year controls while tolerance development was observed in 278 (87,1%) of patients, it did not develop in 40 (12,5%) of patients (Table 3). Tolerance did not develop in 22 patients at the second year and in 13 patients at the third year follow-up.

**Table 3.** Distribution of tolerance development by years

Tolerance development	First year	Second year	Third year
No	41 (12,8%)	22 (6,8%)	13 (4%)
Yes	278 (87,1%)	19 (5,9%)	9 (2,8%)
Total	319	41 (12,8%)	22 (6,9%)

In tolerance development; gender, family history of atopy, social environment, prematurity, breastfeeding time, starting month of supplementary food, eosinophilia, total and specific IgEs, food prick test were not significant. The mothers of 267 (96%) of 278 (87,1%) patients with tolerance development in the first year were non-smokers ( $p < 0.01$ ). In patients who developed tolerance in the second year and in the third year, the history of smoking in the mother was lower than those who did not develop tolerance, but the difference was not statistically significant.

While 225 (91,1%) of 278 (87,1%) children with tolerance development at the end of the first year showed an allergic reaction to a single food; 53 (19,1%) of them are allergic to multiple foods. Those who are allergic to a single food develop more tolerance than patients with multiple food allergies, which is statistically significant ( $p < 0.01$ ). All children with tolerance development in the second year had a single food allergy. Tolerance did not

develop in those with multiple food allergies ( $p < 0.001$ ).

When allergen types are classified as cow's milk, egg and other; 209 (75,2%) of the children with tolerance development in the first year were allergic to cow milk, 15 (5,4%) to eggs, 54 (19,4%) to other foods ( $p < 0.01$ ). Only 1 (5,3%) of 19 children who developed tolerance in the second year were allergic to eggs ( $p < 0.01$ ). 2 (22,2%) of 9 children with tolerance development in the third year were allergic to eggs ( $p = 0.544$ ). The development of tolerance in cow's milk allergy was found to be significantly higher than other allergens. When the characteristics of 13 patients without tolerance development in the third year were examined, 7 (53,8%) were male and 6 (46,2%) were female. 12 (92,3%) were living in the urban area. The mothers of 10 (76,9%) were not smoking. 6 (46,1%) of them had non Ig E mediated disease. Twelve (92,3%) of them had multiple food allergies. Variables affecting tolerance development are summarized in Table 4.

**Table 4:** Variables affecting tolerance development

		First year tolerance development			Second year tolerance development			Tertian year tolerance development		
		No	Yes	<i>p</i> value	No	Yes	<i>p</i> value	No	Yes	<i>p</i> value
Smoking	No	28 %68,3	267 %96	<b>&lt;0,01</b>	17 %77,3	11 %57,9	>0,05	10 %76,9	7 %77,8	>0,05
	Yes	13 %31,7	11 %4		5 %22,7	8 %42,1		3 %23,1	2 %22,2	
Immune mechanism	Ig E	14 %34,1	34 %12,5	<b>&lt;0,01</b>	9 %40,9	5 %26,3	>0,05	4 %30,8	5 %55,6	>0,05
	NonIgE	21 %51,2	199 %71,6		9 %40,9	12 %63,2		6 %46,2	3 %33,3	
Number	Mixed	6 %14,6	45 %16,2		4 %18,2	2 %10,5		3 %23,2	1 %11,1	
	Multiple food	19	53	<b>&lt;0,01</b>	19	0	<b>&lt;0,01</b>	12	7	>0,05

	%46,3	%19,1		%86,4		%92,3	%77,8	
Single food	22 %53,7	225 %80,9		3 %13,6	19 %100	1 %7,7	2 %22,2	
Cow milk	16 %39	209 %75,2	<b>&lt;0,01</b>	0	16 %64,2	0	0	>0,05
Egg	2 %4,9	15 %5,4		2 %9,1	1 %5,3	0	2 %22,7	
Other	23 %56,1	54 %19,4		20 %90,9	2 %10,5	13 %100	7 %77,8	

Bold entries are statistically significant p values

#### 4. Discussion

In many Western countries, diseases such as asthma and atopic dermatitis and allergic rhinitis have been increasing in the last 50-60 years and constitute a significant burden on the society and health systems (11-15). It is thought that the frequency of food allergy has increased in the past 10-20 years with atopic diseases and this situation is due to many different risk factors (16-20).

When studies on food allergies in the literature are examined, the most common finding is skin reactions, followed by gastrointestinal findings (14-18). GIS symptoms have been reported as 30.3% (22) in France, 49.3% (23) in the UK, 20.9% (24) in Lithuania, and 27.6% (21) in the European country. Skin reactions were followed by gastrointestinal system finding(23). In our study, the most common symptoms in children with food allergy were related to the gastrointestinal system (GIS) (69.9%). This was followed by skin findings in 22.3% of patients and respiratory system symptoms in 6.3% of patients. The reason for our different findings can be attributed to the difference in the patient population referred to as our hospital, a top-level healthcare institution.

When the children were categorized according to food allergens, the most common allergen was cow's milk (71.3%). This was followed by egg (17.6%), peanut (2.8%), and hazelnut (2.04%). Strawberry, cocoa, peach, wheat, soy and fish were other responsible food allergens. In the study conducted by Orhan et al. (20) in children aged 6-9 years, the most common allergenic foods were red meat (31,8%), cow's milk (18,1%), cocoa (18,1%), chicken egg

(13,1%) and kiwi (13,6%) respectively has been reported. However, foods that cause allergies change with age. In our study, we attribute the difference of the foods most frequently responsible to food allergies from other studies conducted in our country to the age group evaluated. Egg and milk are the most common causes of food allergy in all countries (1,21,23,24).

Most of the patients develop tolerance to foods in advanced ages (28,29). In our study, tolerance developed in 87.5% of the children in the first year, 6.8% in the second year, and 2.8% in the third year. Shek (28) showed that 28 of 66 children with egg allergy and 16 of 33 children with cow's milk allergy developed tolerance over time. Similarly, Dannaeus et al. (30) found that 4 out of 12 children with cow's milk allergy, 20 out of 55 children with egg allergy, 5 out of 32 children with fish allergy developed tolerance, but none of the cases with peanut and tree nut allergy developed tolerance. Dias (19) reported in a retrospective study that 44% of 79 children with cow's milk allergy were still allergic by the time they reached the age of 10. In a study conducted in Sweden, it was found that 50% of children with egg allergy passed their allergies by the age of 3 (32). In another study, 52% of children with egg allergy developed tolerance at the age of 3 and 66% at the age of 5 (33). Savage (34) found that the development of tolerance to egg allergy was slower than predicted. The results of this study suggest that, contrary to what was previously known, egg allergy is not a food allergy that usually occurs at school age, but a food allergy that is

likely to persist in later life. Sicherer (35) showed in his multicenter observational study that age of tolerance is not as high as suggested by Savage. The different results of these studies on tolerance developmental ages seem to be influenced by many different factors such as genetic and phenotypic characteristics of the studied population and inclusion criteria.

Although passive smoking is known to be a risk factor for asthma, there is no information about whether it increases the risk of food allergy (25,36,37). There are publications indicating that smoking during pregnancy increases the prevalence of allergic diseases (38,39). Avoiding smoking during pregnancy is recommended for primary prevention from allergic diseases (40). In our study, the mothers of 96% of the patients with tolerance development in the first year were not smoking. Only 4% of their mothers were smoking. A significant relationship was found between the mother's smoking and the development of tolerance in the first year. The mothers of the children with tolerance development in the second and third years smoked at a higher rate than the mothers of the children who developed tolerance in the first year. The smoking rates of the mothers of the children with and without tolerance in the second and third years were not statistically different.

The majority of patients (80.9%) who developed tolerance at the end of the first year had allergies to a single food. These patients develop a higher rate of tolerance than those who are allergic to more than one food. In a study, it was reported that 18% of patients who developed tolerance until the age of 4 were also allergic to other foods and that multiple food allergy had no effect on the development of tolerance (41). Multiple food allergies have been reported in 3.5% of children under 2 years of age and 30.5% of children over 2 years of age with persistent cow's milk allergy (42). In the same study, the presence of allergies to other foods was reported as a risk factor for persistent cow's milk allergy. In a study investigating the differences between single food allergy and multiple food allergy, although not statistically significant, food allergy remission at 2 years of age was found to be less in those with multiple food allergies. In accordance to

our study another multicenter study revealed multiple food allergy is a risk factor for late tolerance. Although different results were reported in the literature, it was observed in our study that multiple food allergies had no effect on the development of tolerance. In our study, we think that the effect of multiple food allergies on the development of tolerance may change after the patients are exposed to other food allergens in the next follow-up period.

191 (68.7%) of 278 children who had tolerance development in the first year started to consume complementary feeding after the 4th month. 87 of them (31.3%) switched to additional food before 4 months. All 19 children with tolerance development in the second year and all 9 children with tolerance development in the third year switched to additional foods after the 4th month. A statistically significant relationship was not found between the age of starting the supplementary food and the development of tolerance. It was suggested that families with a high risk of allergic diseases should not give additional food to their atopic children in the first six months. It was recommended to postpone dairy products until the 12th month, eggs until the 24th month, peanuts, hazelnuts, fish and seafood until the 36th month. However, after 2008, European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the American Academy of Pediatrics (AAP) are recommended to start supplementary foods in the first 4-6 months (29,34).

When the allergen types are classified in 3 groups as cow's milk, egg and others; Of the 278 patients with tolerance development in the first year, 209 were allergic to cow's milk, 15 to eggs, and 54 to other foods. Tolerance development was higher in those with cow's milk allergy than those allergic to eggs and other foods. There have been several studies of natural history of cow's milk allergy and predictors of remission. The largest multicentre European case series in food allergy, EuroPrevall study, in which standardized evaluation including DBPCFC, population with DBPCFC, 57% confirmed cow's milk allergy developed tolerance within 1 year (48).

199 (71.6%) of 278 (87.1%) allergy diagnosed patients who developed tolerance in the first year is non Ig E, 45 (16.2%) of the sample is

mixed. 34 (12.2%) of them are food by Ig E-mediated mechanisms. Likely others we found Ig E mediated allergies are more resistant to tolerance. Of %21 Children aged 16 in which had increased cow's milk specific IgE were

notified non- tolerated (49). The strict elimination diet resulted in improvement of symptoms and tolerance to allergic food usually with in 1 year (43).

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#### Ethics

**Ethics Committee Approval:** The study was approved by Eskişehir Osmangazi University Noninterventional Clinical Research Ethical Committee (Number: 24, Date: 14.11.2016).

**Informed Consent:** The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.



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