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Research article

Investigation of clinical characteristics of children with food allergy and factors associated with tolerance development

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Abstract: Objective: Food allergies, an immune reaction to food, affects 2–8% of children in developed countries, thereby presenting with symptoms ranging from anaphylaxis to gastrointestinal issues. This study explores the clinical and tolerance development aspects of pediatric food allergy cases at our clinic. Methods: This retrospective study included 187 pediatric patients with diagnosed food allergies from a pediatric allergy and immunology outpatient clinic at a training and research hospital. The patient files were retrospectively analyzed based on symptoms, improvements upon food removal from diets, food-specific IgE measurements, and skin prick tests. Results: This study included 187 pediatric patients diagnosed with food allergies, which were predominantly affected by eggs (66.8%) and cow's milk (54.5%). Tolerance developed in 73.3% of patients, with no significant differences based on age, gender, or comorbidities. Most patients with egg (72.8%) and milk (76.5%) allergies eventually developed a tolerance. While tolerance developed in 31.4% (n = 43) of patients with multiple allergies, tolerance developed in 68.6% (n = 94) of patients with an allergy to a single food. Conclusions: Our study of 187 pediatric patients highlighted egg and cow's milk as predominant allergens, with onsets typically in infancy. Tolerance developed in 73.3% of patients, with multiple allergies hindering tolerance acquisition. The median ages for tolerance were 12 months for cow's milk and 13 months for egg allergies, which indicates a relatively early resolution. The development of tolerance was found to be lower in patients with multiple food allergies than in patients with a single food allergy.

Keywords: cow milk; egg; food allergy; IgE-mediated; oral tolerance

1. Introduction

A food allergy is an immune-mediated reaction to food, and its prevalence is increasing. Currently, the prevalence of food allergies affects 2–8% of children in developed countries. Food allergies may present as anaphylaxis, skin, and respiratory or gastrointestinal (GI) symptoms. Food allergy-related diseases that cause gastrointestinal symptoms and signs are classified in three groups according to the immune mechanisms involved: Immunoglobulin E (IgE) mediated, delayed T cell mediated (non-IgE), and mixed (mixed, IgE/non-IgE mediated) types. In cases where a food allergy is suspected, a specific IgE and/or skin prick test (DPT) is helpful in the diagnosis of IgE-mediated (type I) diseases, and a patch test is helpful in the identification of suspicious foods in diseases where delayed cell-mediated mechanisms are involved [1–3]. In IgE-mediated food allergies, symptoms are observed shortly (minutes-2 hours) after food intake [4]. The skin, the GI system, the respiratory system, and the cardiovascular system are affected and anaphylaxis may occur [5,6]. The reaction time in non-IgE-mediated food allergies varies between 1 hour and 7 days [5]. Non-IgE-mediated food allergies include food protein-related enterocolitis, enteropathy, proctitis/proctocolitis, celiac disease, dermatitis herpetiformis, and pulmonary haemosiderosis [6]. IgE-mediated and non-IgE-mediated responses coexist in mixed-type food allergies [5]. Contact dermatitis, atopic dermatitis (AD), allergic eosinophilic oesophagitis, asthma, and gastroenteritis are examples of mixed type food allergies [6]. The diagnosis of non-IgE and mixed-type food allergies primarily relies on clinical evaluations. Unlike IgE-mediated food allergies, symptoms in these cases typically manifest with a delayed onset and may progress chronically, which can obscure their association with the allergen [4]. Furthermore, there is a lack of laboratory tests to aid in the diagnosis. In most instances, non-IgE-mediated food allergies are diagnosed based on consistent symptoms and the observation that symptoms resolve upon eliminating the suspected food, only to recur upon reintroduction [7].

Oral tolerance refers to systemic unresponsiveness or hyporesponsiveness to food antigens, thus representing the innate physiological immune response. In cases of food allergies, individuals may naturally develop a tolerance to food antigens if they overcome the allergy, a process known as natural resolution [8]. Oral tolerance arises from the intestinal immune system's ability to appropriately respond to external stimuli. A healthy intestinal immune system eliminates pathogens, tolerates harmless environmental antigens such as food proteins and peptides, and maintains a balanced bacterial flora, all while minimizing tissue inflammation. Food allergies are most commonly observed in infancy [9], and several factors can predispose infants to an impaired oral tolerance. Although early introduction has been demonstrated to be a highly effective intervention in the prevention of food allergies, it may not be enough. There may be a role for an ongoing regularity of ingestion in the prevention of food allergy; in fact, the regularity of ingestion may play as significant a role as the timing of introduction. For some allergens such as eggs, the form in which the allergen is introduced may play a role [10]. The intestinal barrier is still developing during infancy [11], and an inadequate secretion of gastric acid and proteolytic enzymes may increase the exposure to allergenic antigens. While IgA deficiency may potentially elevate the risk of food allergies, the current clinical evidence remains inconclusive [11,12]. A failure to establish a proper Th1/Th2 balance due to genetic and/or environmental factors can also contribute to the development of allergies.

In this study, clinical and laboratory characteristics and the tolerance development processes of patients who presented to our pediatric allergy and immunology polyclinic and were diagnosed with food allergy were investigated.

2. Materials and methods

This retrospective study included 187 patients who underwent follow ups in the pediatric allergy and immunology outpatient clinic of a training and research hospital and were diagnosed with food allergies between January 2023 and January 2024. The patient files were retrospectively reviewed. The diagnosis of food allergies was based on symptoms (IgE-mediated, non-IgE-mediated, mixed type) that occured upon food consumption, symptom improvement upon the removal of the food from the diet, skin prick tests and food-specific IgE measurements. Data including age, gender, diagnosis, the presence of comorbidities (allergic rhinitis, asthma, asthma and allergic rhinitis), the total IgE levels, tue eosinophil percentage, the absolute eosinophil count, and results of food-specific IgE measurements and skin prick tests (if available). Patients who consumed eggs and cow's milk without any problems for one week after oral provocation were considered tolerant.

2.1. Laboratory measurements

We utilized ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden) for allergen-specific IgE measurements. Specific IgE levels for cow's milk, egg whites, and a food mix (including milk, egg white, wheat, peanut, soya, and fish) were assessed. A specific IgE level of 0.35 kU/L or higher was classified as positive. Skin prick tests were conducted using egg white, egg yolk, cow's milk, wheat, peanut, red meat, chicken and nuts. Antihistamine medication was discontinued 10 days prior to testing, with histamine (10 mg/mL) serving as the positive control and saline as the negative control. A positive test result showed an induration of 3 mm or more in the absence of induration or dermographism in the negative control.

2.2. Ethics

The study was conducted with the ethical approval of the ethics committee of our hospital with the decision numbered 3, dated 11/01/2024. This study was conducted in accordance with the Declaration of Helsinki and informed consent was obtained from all participants.

2.3. Statistical analysis

The SPSS 25.0 software was used for data recording and analysis. The descriptive data were presented with median, minimum, and maximum values, number (n), and frequency (%). In the analysis of the data, the Chi-square test was used for categorical variables. The normal distribution of the data was evaluated by the Kolmogorov-Smirnov/Shapiro-Wilk tests and histograms. The Mann-Whitney U test was used for a comparison of continuous variables that did not fit the normal distribution. $P < 0.05$ was set as the statistically significant level.

3. Results

A total of 187 patients were included in the study, of whom 87 were female (46.5%) and 100 were male (53.5%). The median age at the time of diagnosis of food allergy was 9 months (range: 1–190 months).

The most frequently identified food allergens were as follows: egg (66.8%), cow's milk (54.5%), nuts (11.8%), chicken (8.0%), red meat (1.1%), and wheat, which was rarely observed (0.5%). The presenting symptoms of food-allergic patients included a rash (61.5%), bloody stools (12.8%), anaphylaxis (6.4%), pruritus (5.9%), cough and wheezing (4.8%), vomiting (4.3%), diarrhea (1.6%), mucous stools (1.6%), growth retardation (0.5%), and restlessness (0.5%) (Table 1).

Table 1. Frequency distribution of food allergens and clinic of the patients.

Allergens	n	%
Egg	125	66.8
Milk	102	54.5
Nuts	22	11.8
Chicken	15	8.0
Red meat	2	1.1
Wheat	1	0.5
Clinical features	n	%
Rash	115	61.5
Bloody stools	24	12.8
Anaphylaxis	12	6.4
Itching	11	5.9
Cough, wheeze	9	4.8
Vomiting	8	4.3
Diarrhoea	3	1.6
Stools with mucus	3	1.6
Growth retardation	1	0.5
Restlessness	1	0.5

A tolerance to the offending food developed in 137 patients (73.3%), while 50 patients (26.7%) did not develop tolerance to any of the food allergens. There were no statistically significant differences between the tolerant and intolerant groups in terms of the age at diagnosis, gender distribution, family history of atopy, or the presence of comorbid conditions ($p > 0.05$). Tolerance developed in 94 patients (68.6%) with a single food allergy, while only 43 patients (31.4%) with multiple food allergies achieved tolerance.

Among the most prevalent allergens, the median age of tolerance development was 12 months (range: 6–131 months) for the cow's milk allergy and 13 months (range: 6–96 months) for the egg allergy. There was no statistically significant differences in the age of tolerance acquisition based on the allergen type ($p = 0.074$). However, the presence of multiple food allergies had a statistically significant negative impact on the development of tolerance ($p = 0.005$) (Table 2).

Among the 70 children with multiple food allergies, the most frequent combination was milk and egg allergies (n = 34, 48.6%). Of those who did not develop tolerance, 62.5% had an egg allergy, 33.3% had a milk allergy, 26% had a nut allergy, and 13.9% had a chicken allergy. As shown in Table 3, there were no significant differences in the eosinophil counts or the total IgE levels between the tolerant and intolerant groups ($p > 0.05$).

Table 2. Characteristics of patients with and without tolerance.

		Tolerance		P value
		None (n = 50)	Present (n = 137)	
Age at diagnosis (months), median (min-max)		8.0 (1.0–190.0)	9.0 (1.0–87.0)	0.767
Gender, n (%)	Female	22 (44.0)	65 (47.4)	0.676
	Male	28 (56.0)	72 (52.6)	
Family history of atopy, n (%)	None	50 (100)	134 (97.8)	0.576
	Present	0 (0)	3 (2.2)	
Comorbidity, n (%)	None	38 (76.0)	111 (81.0)	0.450
	Present	12 (24.0)	26 (19.0)	
Presence of multiple allergies, n (%)	None	23 (46.0)	94 (68.6)	**0.005**
	Present	27 (54.0)	43 (31.4)	
IgE-mediated allergy	None	10 (25.0)	30 (75.0)	0.779
	Present	40 (27.2)	107 (72.8)	

Table 3. Laboratory values of patients with and without tolerance.

	Tolerance		P value
	None (n = 50)	Present (n = 137)	
Eosinophils (10^3 cells/μL), median (min-max)	0.4 (0.04–1.4)	0.3 (0.0–4.6)	0.456
Eosinophils (%)	3.7 (0.6–14.8)	3.3 (0.1–65.9)	0.542
IgE	27.0 (1.0–1815.0)	40.0 (0.0–1132.0)	0.950

Among our patients, 72.8% of the children with an egg allergy developed a tolerance, while 27.2% still have not developed a tolerance; 76.5% of the children with a milk allergy developed a tolerance, while 23.5% still have not developed a tolerance; and 100% of the children with a red meat allergy developed a tolerance (Table 4 and Figure 1).

Table 4. Tolerance development status according to food allergy types.

	Tolerance			
	None (n = 50)		Present (n = 137)	
	n	%	n	%
Egg allergy	34	27.2	91	72.8
Milk allergy	24	23.5	78	76.5
Nut allergy	10	45.5	12	54.5
Chicken allergy	7	46.7	8	53.3
Red meat allergy	0	0.0	2	100.0
Wheat allergy	1	100.0	0	0.0

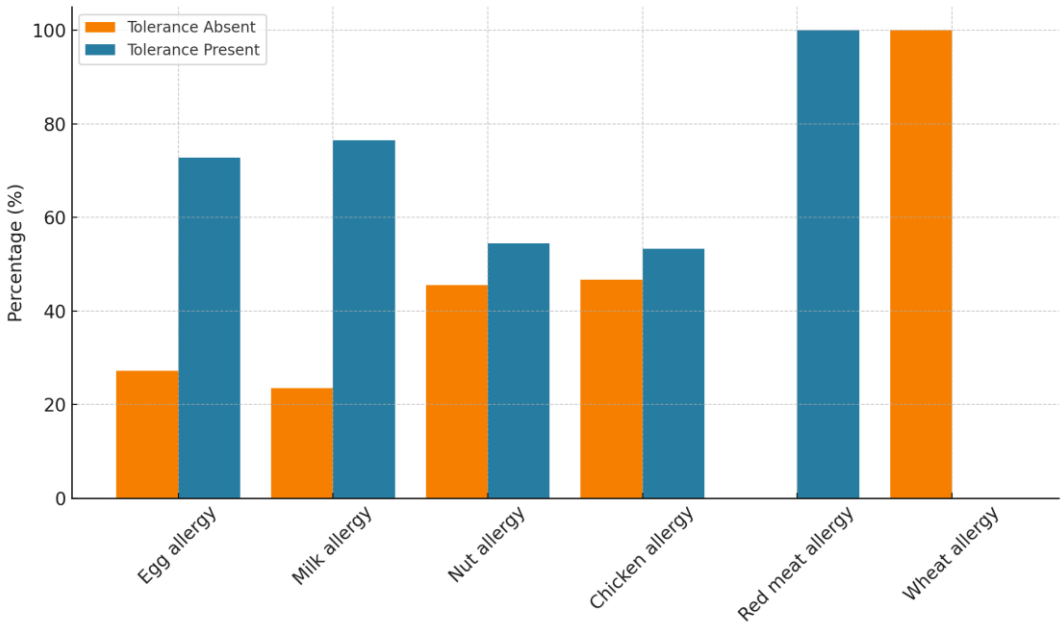

Figure 1. Tolerance development by food allergy type.

4. Discussion

Food allergies are a major global health concern that affect millions of individuals and significantly impairs the quality of life [13]. Over the past three decades, a steady increase in its prevalence has been observed [14]. Most food allergies emerge within the first two years of life, with reported prevalence rates of 6–8% during infancy and 3–4% in later childhood [15]. In pediatric care, food allergies pose a particular challenge, with symptoms and tolerance development playing a critical role in disease management. This study analyzed the clinical course from diagnosis through follow-up in a cohort of 187 children diagnosed with food allergies.

The median age at diagnosis in our cohort was 9 months. Although our sample size was limited, this finding aligns with previous studies which indicated that most food allergies are identified during the first year of life. The early timing of diagnosis may reflect the rapid onset of symptoms and an increased awareness among both parents and healthcare providers.

Eggs (66.8%) and cow's milk (54.5%) were the most frequently identified allergens in our study. This is consistent with previous literature, where eggs (57.8%) and milk (55.9%) were similarly reported as the most common allergens among children with food allergies [16]. Additionally, children with one food allergy are known to have an elevated risk of developing multiple food allergies [14]. In our cohort, 70 children (37.4%) were allergic to more than one food, with the most common combination being eggs and milk. Similar associations were reported in a study by Can et al., where egg and milk allergies frequently co-occurred [17].

While cutaneous symptoms such as a rash (61.5%) and pruritus (5.9%) were common, more severe manifestations, including anaphylaxis (6.4%), were also observed. These findings underscore the potential of food allergies to cause systemic symptoms beyond the GI tract. Other studies similarly highlight skin symptoms as predominant, followed by GI complaints [9,18–20].

In terms of tolerance development, 73.3% of patients achieved tolerance, while 26.7% did not. These findings suggest that tolerance may develop over time in a substantial proportion of children, thus reinforcing the importance of long-term follow-up. Notably, the presence of multiple food allergies appeared to hinder tolerance development: 54% of children with multiple allergies failed to develop a tolerance, whereas 68.6% of those with single-food allergies did. This observation aligns with the findings of Ersözlü et al. [21], who reported that 80.9% of children who achieved tolerance within the first year were allergic to a single food. Their data also showed that these patients developed tolerance at higher rates compared to those with multiple food allergies. Similarly, in our study, tolerance was less likely to develop in patients with a nut allergy (45.5%), which suggests a greater persistence or severity of nut-related allergies. No statistically significant association was found between tolerance development and laboratory parameters such as eosinophil counts or the total IgE levels. This finding is consistent with clinical observations and implies that laboratory data alone may not be sufficient to predict the likelihood of tolerance. Therefore, a clinical evaluation and patient history remain essential components of assessment. This highlights the growing need for more sensitive and specific diagnostic tools in food allergy evaluations. Component-resolved diagnostics (CRD) is one such emerging method. By measuring specific IgE antibodies to individual allergenic molecules using fast and reliable *in vitro* assays, CRD allows for a more detailed evaluation of sensitization profiles [22,23]. Another advanced tool is the basophil activation test (BAT), which assesses the functional immune response to allergens *in vitro* [24]. BAT evaluates the ability of allergens to trigger basophil activation and degranulation from patient samples [25]. Both CRD and BAT may reduce the reliance on oral food challenges, which are time-consuming, costly, and carry the risk of severe reactions. No significant difference in the tolerance rates was observed between IgE-mediated and non-IgE-mediated food allergies. Among patients with an egg allergy, 72.8% developed a tolerance, while 76.5% of those with a milk allergy did so. Shek et al. [26] found that tolerance developed in 28 of 66 children with an egg allergy and in 16 of 33 with milk allergy. The median age of tolerance acquisition in their study was 12 months for a milk allergy and 13 months for an egg allergy. Sicherer et al. [27] reported that 49.3% of children with an egg allergy achieved tolerance, with a mean age of 72 months. Chong et al. [28] found that 81.8% of children with a cow's milk allergy developed a natural tolerance by age 6. Compared to these studies, the earlier age of tolerance observed in our cohort may reflect a timely diagnosis and early referral to pediatric allergy specialists.

Among patients who did not achieve tolerance, 62.5% had an egg allergy, 33.3% had a milk allergy, 26% had a nut allergy, and 13.9% had a chicken allergy. In a retrospective study, Dias [29] reported that 44% of children with a cow's milk allergy remained allergic at age 10. Similarly, Savage et al. [30] observed a slower-than-expected tolerance development for an egg allergy.

Previous research emphasizes that an early diagnosis and consistent follow-up are key determinants of long-term health outcomes in food-allergic patients. Additionally, both the number of allergens and the specific allergen types significantly influence the likelihood of developing a tolerance. These findings are consistent with our results and reinforce the importance of a multidisciplinary approach to food allergy management. Oral immunotherapy (OIT) has emerged as a promising strategy to manage food allergies [31,32]. However, its long-term safety and efficacy remain under investigation, and the underlying immunological mechanisms are not yet fully understood. A detailed understanding of the immune responses mediated by OIT is essential to optimize its application as a definitive therapeutic approach. OIT typically consists of an initial dose-escalation (acute

desensitization) phase followed by a maintenance (consolidation) phase [33,34]. Continuous allergen exposure during this process can lead to the successful desensitization of mast cells, thereby promoting the development of an allergen-specific tolerance [35].

Since the relationship between the development of tolerance and age was removed from the conclusion, the statement here was removed and no source was added. This study has several limitations that should be taken into account. First, its retrospective design inherently limits data control and relies on the accuracy and completeness of the medical records. As a single-center study conducted in the pediatric allergy clinic of a tertiary hospital, the findings may not be generalizable to wider pediatric populations. Furthermore, potentially influential variables such as breastfeeding duration, dietary patterns, family history of atopy, and environmental exposures were not included in the analysis.

5. Conclusions

In our study, we found that food allergies regressed in most cases and multiple allergies were an important factor that negatively affected the development of a tolerance. We found that the development of a tolerance was limited especially in cases of a nut allergy. Factors such as the presence of multiple allergies, the allergen type, and clinical symptoms should be taken into consideration in the management of food allergies. Future studies could potentially provide insights into strategies aimed at enhancing tolerance development in individuals with food allergies. In conclusion, this study provides a valuable basis to strengthen clinical practice in food allergy management and to promote tolerance development. Future studies are expected to develop more effective treatment strategies by either extending or validating these findings.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflict of interest

The authors declare that there is no conflict of interest in the preparation and publication of this article.

Author contributions

Conceptualization, S.Ç., M.Y.Ö. and U.A.; methodology, M.Y.Ö., Z.M.A., U.A.; validation, M.Y.Ö. and S.Ç.; formal analysis, S.Ç., U.A.; investigation, M.Y.Ö. and U.A.; resources, M.Y.Ö., S.Ç., and U.A.; data curation, S.Ç. and Z.M.A.; writing—original draft preparation, Z.M.A., S.Ç. and U.A.; writing—review and editing, M.Y.Ö. and S.Ç.; visualization, Z.M.A. and U.A.; supervision, M.Y.Ö and S.Ç. All authors have read and agreed to the published version of the manuscript.

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