European Journal of Therapeutics

DOI: 10.54614/eurjther.2022.21009

Original Article

Food Allergy and Philagrine Mutation in Children with Atopic Dermatitis

Gülşah Duyuler Ayçin

Department of Pediatric Allergy Immunology, Adana City Training and Research Hospital, Adana, Turkey

ABSTRACT

Objective: To determine the frequency and type of food allergy in patients having atopic dermatitis and to show the presence of mutations genetically.

Methods: Patients diagnosed as having atopic dermatitis according to the Hanifin Rajka criteria were evaluated retrospectively. Eosinophils, total immunoglobin E, milk-specific immunoglobulin E, egg-specific immunoglobulin E, wheat-specific immunoglobulin E, and filaggrin gene mutation results were recorded. Nutrient elimination was performed for 1 month in patients who were thought to have food allergy owing to skin prick test and milk-specific immunoglobulin E results. The diagnosis was confirmed through a food loading test for the patients who benefited from the elimination.

Results: Of the 66 patients included in the study, 42 (63.63%) were male. Food allergies were detected in 40 patients (60.6%). According to the Scoring of Atopic Dermatitis index, 9 out of 16 patients aged 40 years and over had food allergy and 31 out of 50 patients aged under 40 years had food allergy. There was no significant difference between the groups ($P = .56$). All patients included in the study were examined for filaggrin. Only 1 patient with a Scoring of Atopic Dermatitis index below 40 and milk allergy was found to have p.R501 * and c.2282-2285delCAGT mutations.

Conclusion: Atopic dermatitis food allergy was found to be 60.6%. The most common improvement was egg allergy and egg elimination. There was no difference between atopic dermatitis severity and food allergy and laboratory tests. Severe atopic dermatitis was found to be 24.2%.

Keywords: Child, atopy, allergy

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease that usually starts in infancy and early childhood occurring as a result of the interaction of genes and environmental factors and can be triggered by various allergens.[1] The frequency of AD is 15-20% in children living in developed countries, whereas it is between 1% and 3% in adults, and the lifetime frequency is 17.3%.[2] It is known that AD is associated with food allergies. However, a relationship between AD and food allergy has been shown in only one-third of patients with moderate-to-severe AD.[3] Although AD has a mild clinical course in 70-84% of patients, approximately 20% of patients present with a severe clinical course.[4,5] Filaggrin (FLG) plays a critical role in epidermal barrier function. The importance of FLG mutations was first noticed in 2006 with the discovery of dysfunctional mutations in patients with ichthyosis vulgaris.[6] Studies have shown that the FLG mutation is community-specific. The R501X and 2282de14 mutations, which were found frequently, and S3247X and R2447X mutations, which were found rarely, were found in 7-10% of the Caucasian European population in studies.[7] The relationship between AD and food allergy has been brought to the agenda again because FLG mutations have been considered as a possible mechanism in the development of AD in recent years. Changes in this gene are thought to play a key role in cutaneous exposure to food allergies, by increasing the permeability of the skin to proteins.[8]

Food allergies often accompany AD, which is very common in children. It is known that genetic factors play a role. In our study, we aimed to show the frequency, type, and effect of FLG mutations in patients who were diagnosed as having AD and evaluated the severity using the Scoring of Atopic Dermatitis (SCORAD) index.

METHODS

Patients diagnosed as having AD according to the criteria of Hanifin Rajka[9] in the pediatric allergy immunology outpatient clinic between March 2018 and October 2018 were evaluated retrospectively. The study was approved by the Ethics Committee of Erzurum Regional Training and Research Hospital Clinical Research Ethics Committee (Date: November 5, 2018, Decision No: 2018/17-167). Patients' age at admission, symptom onset age, symptom frequency, spreading area of dermatitis,

Cite this article as: Duyuler Ayçin G. Food allergy and philagrine mutation in children with atopic dermatitis. *Eur J Ther* 2022;28(1):57–61.

Corresponding author: Gülşah Duyuler Ayçin, e-mail: drduyu@gmail.com

Received: January 20, 2021 **Accepted:** May 25, 2021

SCORAD index, food prick, inhaler prick, eosinophil count, total immunoglobin E (IgE), milk-specific immunoglobulin E (sIgE), egg sIgE, wheat sIgE, peanut sIgE, fish sIgE, food provocation tests, and FLG gene mutation results were examined and recorded from medical records. The patients were followed up and evaluated by the same allergy immunologist throughout the study. The SCORAD index was calculated according to the formula: A (prevalence)/5 + B (density) × 7/2 + C (subjective symptoms; itching severity + loss of sleep). If the score was <15, AD was considered to be mild, if it was between 15 and 40, AD was considered to be moderate, and if it was >40, AD was considered to be severe.[10] The patients were divided into 2 groups as mild-moderate and severe AD, and the groups were compared in terms of food allergy, susceptible allergen sensitivity, and laboratory results. Skin test results of eggs, sIgE milk, wheat, peanuts, and fish were examined, and those with values ≥0.35 IU/mL were considered positive. The allergen solutions of Allergopharma® (Reinbek, Germany) with standard activity and concentrations including standard food allergens belonging to milk, egg yolk, egg white, wheat, hazelnut, peanut, lentil, sesame, walnut, fish, soybean were used while evaluating skin prick tests (SPT). Skin prick tests with 12 standard aeroallergens were performed (Allergopharma) with *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria*, *Cladosporium*, *Aspergillus*, *Candida albicans*, tree pollen mixture 1, tree pollen mixture 2, grass pollen mixture, weeds, cockroach, and 10 mg/mL histamine phosphate as positive control and 0.9% saline as negative control. Those with sIgE values >0.35 IU/mL and above in blood were considered positive. Prick test result 3 mm and above from negative control was accepted as positive. Food elimination was performed for 1 month in patients who were diagnosed with AD and who were thought to have food allergy with prick test and sIgE results. The diagnosis was confirmed by performing an oral food challenge (OFC) test in patients who benefited from elimination. Oral food challenge tests were performed in the form of open provocation about 4-6 hours after fasting early in the morning while the patients were completely healthy and their eczema was completely under control. Drugs containing antihistamines that could mask early allergic reactions and develop in the OFC were discontinued for 2 weeks before the OFC. The families of the patients were informed before the OFC. All risks were explained, and the patients signed an informed consent form. Foods to be used in the OFC were prepared freshly and the test started with 0.1 mL of cow milk, 1 g of egg, wheat, lentil, sesame, and 125 mg of walnut. The doses were doubled at 15-minute intervals, and the patients were examined after each dose. The doses were increased up to 100 mL milk, 50 g eggs, 50 g wheat, and lentils in patients without reactions. In the OFC, the test was considered positive in patients with type 1 hypersensitivity reactions such as urticaria and angioedema, and anaphylaxis within the first 4-6 hours. Some of these patients had a rash only during the test, whereas some had an exacerbation in the eczema within a few days and their test was considered positive. Foods were freed in the diet if no reaction was observed.[11] Filaggrin mutation analyses were performed in the genetic diseases diagnosis center. In this study, a new-generation sequence analysis was performed for the common R501X and 2282de14 mutations. The study was planned retrospectively: 13 patients who were thought to have food allergy according to OFC, SPT, and/or food sIgE results but could not be tested for provocation were excluded from the study. Forty patients with food allergies were tested with a total of 78 different foods because some patients had more than 1 food allergy, 68 of which were positive. The families of the patients were informed about the food challenge test and signed an informed consent form. The statistical analysis of the study was performed using the Statistical Package for the Social Sciences (SPSS) version 18.0 (IBM Inc, Chicago, IL, USA) program. For descriptive statistics of the study data, continuous data are given as mean ± standard deviation, median, and minimum–maximum, and categorical variables are given as numbers and percentages. Pearson's chi-square and Fisher's exact tests were used in comparisons.

Main Points

- It is a known fact that atopic dermatitis (AD) is associated with food allergies. However, a relationship between AD and food allergy was shown in only 1/3 of patients with moderate to severe AD.
- Food allergy was detected in 40 (60.60%) of the samples. We found egg allergies to be the most common. Egg sensitivity was observed in 35 patients (53.03%) in total, and the diagnosis was confirmed by elimination and loading.
- No significant correlation was found between the severity of AD and food allergy and laboratory tests. Severe AD was found to be 24.2% (16). In our study, the rate of FLG mutations was found to be 1.51%.

RESULTS

Of the 66 patients included in the study, 42 (63.63%) were boys and 24 (36.3%) were girls. The average age at admission was 17.9 ± 19.4 (min: 4, max: 98) months. Symptom onset age was 5.5 ± 8.4 (min: 1, max: 48) months. The most common symptoms were erythema, edema/papulation, and dryness in 53 (80.3%) patients, whereas in 13 (19.6%) patients, the most common symptom was skin irritation/crusting, excoriation, and lichenification.

Table 1. Clinical Features of Patients with Atopic Dermatitis

Male/female, n (%)	**42 (63.6%)/24 (36.3%)**
Symptom onset age (months) (min–max)	5.5 ± 8.4 (1–48)
Age at admission, months (min–max)	17.9 ± 19.4 (4–98)
Average IgE, IU/mL (min–max)	81.0 ± 181.46 (1–1182)
Average eosinophil count, mm^3 (min–max)	489.6 ± 406.3 (10–2340)
Patients with food allergy	40 (60.6%)
SCORAD index average (min–max)	28.2 ± 11.2 (15–60)

IgE, immunoglobulin E; SCORAD, Scoring of Atopic Dermatitis.

Table 2. Comparison Between Patients with Mild–Moderate Atopic Dermatitis and Patients with Severe Atopic Dermatitis

	SCORAD <40	SCORAD ≥40	*P**
Total IgE average, IU/mL (min–max)	81.98 (1–980)	77.25 (15–1182)	.664
Average eosinophil count, mm^3 (min–max)	451.16 (10–2340)	610.0 (10–1500)	.241
FLG mutation, n	1	0	.758
Food allergy, n (%)	31 (62)	9 (56.2%)	.560
Inhalant allergen sensitivity, n (%)	6 (12)	3 (18.7%)	.67

n, number of patients; mild–moderate atopic dermatitis, SCORAD<40; severe atopic dermatitis, SCORAD>40.
**P*: Fisher's exact test.
IgE, immunoglobulin E; SCORAD, Scoring of Atopic Dermatitis; FLG, filaggrin.

The mean total IgE level was 81.0±181.46 (min: 1, max: 1182) IU/mL, and the mean eosinophil count was 489.6 ± 406.3 mm^3. The mean SCORAD index was 28.2 ± 11.2 (min: 15, max: 60) (Table 1). In 21 (31.8%) patients, lesions were observed on the cheek and head, in 19 patients (29.7%) on cheek + trunk + limb, in 16 patients (24.2%) on cheek + trunk, and in 10 patients (15.1%) on cheek + extremity. A SCORAD index ≥40 was considered as severe AD. In this study, the SCORAD index of 40 patients (24.24%) was ≥40 and <40 in 50 (75.75%) patients. Forty-nine (74.2%) patients with a SCORAD index of 15-40 were evaluated as having moderate AD, and 1 patient (1.51%) with a SCORAD index of <15 was considered as having mild AD. Patients with mild and moderate AD were grouped together. A comparison was made between patients with mild-moderate and severe AD. The mean total IgE and eosinophil counts were compared and no significant difference was found between the 2 groups (*P* = .664, *P* = .241, respectively) (Table 2). In 16 (24.24%) patients with a SCORAD index ≥40, 9 (56.2%) had food allergy, and in 50 (75.75%) patients with SCORAD index <40, 31 (62%) had food allergy. There was no significant difference between the groups (*P* = .56). Allergen sensitivity was detected in 9 (13.6%) patients. Inhaler allergen sensitivity was detected in 6 (12%) patients with a SCORAD index <40 and in 3 (18.7%) patients with a SCORAD index >40 (*P* = .67) (Table 2). Filaggrin was investigated in all patients included in the study and p.R501X and c.2282del4 mutations were detected in only 1 (1.51%) patient who had a SCORAD index <40 and milk allergy. There was no difference between the 2 groups (*P* = .785) (Table 2).

According to the SPT and/or food sIgE result, OFC was performed in 46 of 66 patients. Forty-six patients with food allergies underwent OFCs with different foods 78 times in total (egg: 39, milk: 30, wheat: 5, sesame: 1, lentil: 2, walnut: 1). As a result, 68 OFCs were positive in 40 patients due to multiple food allergies. Food allergy was not found in 26 (39.39%) patients. Milk and egg allergy in 18 patients (27.27%) diagnosed with food elimination and loading, milk + egg + sesame allergy in 1 (1.51%) patient, milk + egg + walnut allergy in 1 patient, egg allergy in 12 patients (18.1%), milk allergy in 4 patients (6.06%), milk + egg + wheat allergy in 2 patients (3.03%), and wheat allergy in 1 patient (1.51%) were observed. Multiple food allergies were observed in 24 patients (Table 3).

When patients who were found positive in specific IgE and/or SPTs and confirmed by food elimination and challenge tests were evaluated, egg allergy in 35 (53%) patients, milk allergy in 27 (40.9%) patients, wheat allergy in 3 (4.5%) patients, sesame allergy in 1 (1.5%), lentil allergy in 1 (1.5%), and walnut allergy in 1 (1.5%) patient were detected (Table 4). These foods were eliminated from the diet for 1 month and clinical improvement was observed. The diagnosis of food allergy was confirmed through an OFC. Food allergy was detected in 40 (60.60%) patients. Egg allergy was the most frequently encountered allergy.

DISCUSSION

In our study, the rate of boys (63.6%) was higher. In a study involving 110 infants with AD, it was found that 70% were male.[12] In our study, food allergy was found in 60.60% of patients with AD. In a study conducted in Korea, food allergy was found in 37.1% of infants with AD aged 0-5 months and in 38.5% of infants aged 6-11 months.[13] In genetically susceptible individuals, AD is accompanied by an IgE-mediated food allergy ranging from 30% to 60% in infancy.[14] In our study, the most common allergies were milk + eggs (31.8%), eggs (18.1%), milk (6.06%), milk + egg + wheat (3.03%), and wheat (1.51%). Egg allergy was detected in 35 (87.5%) of 40 patients in whom food allergy was confirmed through food elimination and OFC. In an international cohort study, 64% of 2184 infants with AD aged 11.8-25.4 months were reported to develop IgE-mediated food sensitivity to egg and/or cow milk and/or peanut before the age of 3 months.[15]

In our study, the mean SCORAD index was found to be 28.2 ± 11.2, and the most common sIgE and/or SPT test positivity was observed for egg. There was no difference between SCORAD index ≥40 and <40 in terms of total IgE and eosinophil counts. In a study evaluating the relationship between SCORAD index and atopy patch tests in patients with AD, the mean SCORAD index was 37.3 ± 12.13 (range: 15.1-66.0), the fresh prick test with food was found positive in 32.5%, and in the atopy patch test, the highest positivity was for egg (54.1%). In this study, no relation was observed between SCORAD index and prick test positivity, total IgE, and serum eosinophil count.[16] These results were similar to our results. In a study in which 236 patients with AD were examined, food allergen sensitization was positive in 31% of patients, and the most common food allergies were

Table 3. Food Challenging Test Results

Number of patients who underwent food provocation test, n (%)		**46 (69.6)**
Mean age of patients who underwent food provocation test (min–max)		8 (6–72)
Number of food provocation tests performed		78
Foods used in food provocation test (%)	Egg	39 (59.09)
	Milk	30 (45.4)
	Wheat	5 (7.5)
	Sesame	1 (1.51)
	Lentil	2 (3.03)
	Walnut	1 (1.50)
Number of patients with positive food provocation test result, n (%)		40 (60.6)
Distribution of patients with food allergy, n (%)	Egg + milk	18 (27.27)
	Egg + milk + lentil allergy	1 (1.51)
	Egg + milk + sesame allergy	1 (1.51)
	Egg + milk + walnut allergy	1 (1.51)
	Egg	12 (18.1)
	Milk	4 (6.06)
	Milk + egg + wheat	2 (3.03)
	Wheat	1 (1.51)

found against egg, cow's milk, and peanuts. In that study, the patients were divided into 2 groups according to the severity of AD as mild and medium-severe AD, and no difference was found between the 2 groups in terms of age at symptom onset, sex, family history of atopy, IgE level, eosinophil count, and inhalant allergen sensitization. It was found that food allergy was significantly more common in the medium-severe AD group.[17] In our study, there was no difference between the groups, and food allergy was also observed in the mild AD group.

Inhalant allergen sensitivity was detected in 9 (13.6%) patients, and SPTs with inhalant allergens gave sensitive results. In a study conducted in 64 patients with AD, foods were responsible for allergy in children aged under 2 years, food and inhalant allergens between the ages of 2-10 years, and inhalants above 10 years of age.[18]

Table 4. Foods with Positive Provocation Test

Food type	Number of patients, n = 40 (%)
Egg allergy	35 (53)
Milk allergy	27 (40.9)
Wheat allergy	3 (4.5)
Sesame allergy	1 (1.5)
Lentil allergy	1 (1.5)
Walnut allergy	1 (1.5)

In our study, p.R501X and c.2282del4 mutations were detected in only 1 (1.51%) patient who had a SCORAD index <40 and had milk allergy. There was no difference between the 2 groups. In a study, the relationship between peanut allergy and p.R501X and c.2282del4 mutations was investigated, and it was shown that there was a relationship between peanut allergy and FLG mutations.[19] In a study of 249 Japanese patients with AD, 14 FLG mutations and sensitivity to 15 different allergens were investigated and at least 1 FLG mutation was detected in 25.7% of patients. At least 1 allergen susceptibility was detected in 47.7% of patients. However, only a relationship between peanut allergy and carrying the FLG mutation was found, no relationship was found between the FLG mutation and other allergens.[20] In a study conducted in Indian children, the p.R501X mutation, which was common, was investigated and detected in 5.5% of 90 children with allergy; none of the 81 patients in the control group had these mutations.[21] Surprisingly, although p.R501X and c.2282del4 FLG mutations were common in Europe, these mutations were not found to be significant in a study conducted in the Italian population.[22] In our study, the rate of FLG mutations was found as 1.51%. The FLG mutation was detected in a patient with milk allergy in our study. The limitation of our study was that only the R501X and 2282de14 mutations were investigated, which are common among FLG mutations.

CONCLUSION

The rate of food allergy confirmed through OFCs in patients with AD was 60.6% in our study. Egg allergy was found most frequently in patients with AD. As a result of this study, it could be said that even if the SCORAD index is not high in pediatric patients with AD, it is necessary to investigate food allergy and to decide on elimination in this way. It was thought that the failure to find a relationship with the FLG mutation might be related to social differences or types of food allergy.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Erzurum Regional Training and Research Hospital Clinical Research Ethics Committee (Date: November 5, 2018, Decision No: 2018/17-167).

Informed Consent: Informed consent obtained from parents of participants.

Peer-review: Externally peer-reviewed.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Boguniewicz M, Leung DYM. Atopic dermatitis. In: Adkinson NF, Bochner BS, Burks AW, et al., eds. *Middleton's Allergy Principles and Practice*. 8th ed. Philadelphia: Saunders Elsevier; 2014:540-564.
2. Cookson WO, Moffatt MF; The genetics of atopic dermatitis. *Curr Opin Allergy Clin Immunol*. 2002;2(5):383-387. [CrossRef]
3. Sampson HA. The evaluation and management of food allergy in atopic dermatitis. *Clin Dermatol*. 2003;21(3):183-192. [CrossRef]
4. Kato A, Fukai K,Oiso N, Hosomi N, Murakami T, Ishii M. Association of SPINK5 gene polymorphisms with atopic dermatitis in the Japanese population. *Br J Dermatol*. 2003;148(4):665-669. [CrossRef]
5. Leung DY, Boguniewicz M, Howell MD, Nomura I, Hamid QA. New insights into atopic dermatitis. *J Clin Invest*. 2004 ;113(5):651-657. [CrossRef]
6. McGrath JA. Profilagrin, dry skin and atopic dermatitis risk: size matters. *J Investigative Derma.ens*. 2012 ;132:10-11.
7. Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. *N Engl J Med*. 2011;365(14):1315-1327. [CrossRef]
8. Worth A, Sheikh A. Food allergy and atopic eczema. *Curr Opin Allergy Clin Immunol*. 2010;10(3):226-230. [CrossRef]
9. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Dermatol Venerol Stockh*. 1980;92:44-47.
10. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. *Dermatology*. 1993;186(1):23-31. [CrossRef]
11. Yum HY, Yang HJ, Kim KW, et al. Oral food challenges in children. *Korean J Pediatr*. 2011;54(1):6-10. [CrossRef]
12. Şengül Emeksiz ZŞ, Cavkaytar Ö, Aksoy İ, Daller Y, Soyer Ö. Food hypersensitivity in atopic dermatitis during infancy: skin prick testing for whom? *Asthma Allergy Immunol*. 2017;15(1):32-37 .[CrossRef]
13. Kwon J, Kim J, Cho S, Noh G, Lee SS. Characterization of food allergies in patients with atopic dermatitis. *Nutr Res Pract*. 2013;7(2):115-121. [CrossRef]
14. 14. Eigenmann PA, Calza AM. Diagnosis of IgE-mediated food allergy among Swiss children with atopic dermatitis.*Pediatr Allergy Immunol*. 2000;11(2):95-100.[CrossRef]
15. Hill DJ, Hosking CS, Benedictis FM, et al. Confirmation of the association between high levels of immunoglobulin E food sensitization and eczema in infancy: an international study. *Clin Exp Allergy*. 2008;38;15:161-168.
16. Kutlu A, Aydın E, Karabacak E, et al. Relationship between atopy patch test with foods and SCORAD. *Türkderm*. 2013;47;16:99-102.
17. Beken B, Çelik V, Gökmirza P, Süt N, Yazıcıoğlu M. Food sensitization and food allergy in atopic dermatitis. *Osmangazi J Med*. 2019;41:405-412.
18. Escarrer Jaume M, Muñoz-López F. Role of aeroallergens in the etiopathogenesis of atopic dermatitis. *Allergol Immunopathol (Madr)*. 2002;30(3):126-134. [CrossRef]
19. Brown SJ, Asai Y, Cordell HJ, et al. Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy. *J Allergy Clin Immunol*. 2011;127(3):661-667. [CrossRef]
20. Li M, Liu JB, Liu Q, et al. Interactions between FLG mutations and allergens in atopic dermatitis. *Arch Dermatol Res*. 2012;304(10):787-793. [CrossRef]
21. Chauhan A, Panigrahi I, Singh M, Attri SV, Agarwal A, Singh M. Prevalence of filaggrin gene R501X mutation in Indian children with allergic diseases. *Indian J Pediatr*. 2020;21(8):587-590. [CrossRef]
22. Giardina E, Paolillo N, Sinibaldi C, Novelli G. R501X and 2282del4 filaggrin mutations do not confer susceptibility to psoriasis and atopic dermatitis in Italian patients. *Dermatology*. 2008;216(1):83-84. [CrossRef]