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The prevalence of sensitization to food allergens in children with atopic dermatitis

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Abstract
Introduction: Atopic dermatitis (AD) has a complex pathophysiology. The course of the disease is affected by both environmental factors and allergen hypersensitivities. Food and aeroallergens have a significant role in the pathogenesis and disease control.
Objective: In this study, it was aimed to determine the prevalence of food and aeroallergen sensitivity of children with AD.
Methods: Children under 18 years with AD who applied to pediatric allergy and immunology outpatient clinics were evaluated. All patients had a skin prick test (SPT) within most common food and aeroallergens.
Results: One hundred seventy three patients were studied. Most of the moderate and severe AD patients were boys (boys 64% vs. girls 47%). Symptoms started earlier and positive results in SPTs with food allergens were more common in patients with SCORAD (SCORing Atopic Dermatitis) >25 ($p < 0.0001$). Egg white (39%), egg yolk (31%), cow's milk (13%) and wheat flour (5%), were the most common allergens, respectively. The SCORAD scores were higher in multiple food sensitized patients' groups ($p < 0.001$). Although, food sensitizations were prevalent in patients who had higher SCORAD scores ($p = 0.001$), there was no significant difference in sensitization with aeroallergens. ($p = 0.392$).
Conclusion: Sensitizations to both food and aeroallergens are common in patients with AD. In addition, sensitization to these allergens and SCORAD severity in patients with AD have positive correlation.

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Introduction

Atopic dermatitis (AD) is a chronic, pruritic, inflammatory skin disease that occurs most frequently in children.[1] Xerosis is a cardinal feature in AD, caused by the impaired skin barrier function including loss of function mutations in the filaggrin gene.[2] The pathophysiology of AD is complex and involves a strong genetic predisposition, immune dysregulation, epidermal barrier dysfunction, skin microbiome abnormalities, and the neuroimmune system.[1]

Its prevalence in the pediatric population ranges from 5 to 20% and typically develops in infancy and affects up to 20% of children in the high-income countries.[3,4] Epidemiological studies on childhood and adulthood demonstrate an increasing prevalence of both AD and food allergy (FA).[5,6]

Children with AD are at higher risk of IgE-mediated type FA. Approximately 30–40% of children with moderate-to-severe AD have FA.[7-9] Many studies have investigated the role of food allergens in triggering or exacerbating the symptoms of AD patients. Epidermal barrier dysfunction in AD is leading to penetration of food allergens into stratum corneum, hence langerhans cells are activated and sensitization to food allergens develop.[10] The trigger foods in FA vary depending on each country; with hen's egg and cow's milk generally being the most common food allergies, followed by peanut, tree nuts, sesame, fish, soy, and wheat in Europe.[9] Many studies report that aeroallergens could trigger AD symptoms, besides food allergens. Sensitized to animal dander, house dust mites, grass pollens were more common in pediatric and adult patients with AD.[11]

In our study, it was aimed to determine the prevalence of food and aeroallergen sensitivity of children with AD.

Materials and Methods

Patients who applied to the pediatric allergy and immunology outpatient clinics due to AD between January 2021 and June 2022 have been evaluated for the purposes of this study. Six hundred forty two patients between the age of 0–18 with complaints related to AD applied to our clinics. Patients with allergic rhinitis or asthma—to avoid bias of allergen sensitivity—with chronic diseases and immunodeficiency were excluded from the study. As a result, 173 patients were included in our study. Pediatric allergologists diagnosed AD among patients by using the Hanifin and Rajka criteria.[12] Demographic characteristics, comorbid allergic diseases, and family history of atopy have been recorded. SCORAD (SCORing Atopic Dermatitis) index was used in order to determine the severity of AD.[13] Patients with SCORAD index lower than 25 were grouped as mild AD, whereas any index higher than 25 was classified as moderate and severe AD.

Skin prick tests (SPT) were performed in accordance with the guidelines of the European Academy of Allergy and Clinical Immunology (EAACI) using commercial extracts of the most common aeroallergens (ALK-Albello ®, Canada) such as house dust mite (*Dermatophagoides farinae, Dermatophagoides pteronyssimus*), grass pollen mix, tree pollen mix, mold fungus mix, cat and dog dander, cockroach allergen extracts and most common food allergens such as cow's milk, eggs, walnuts, hazelnuts, soy, peanuts, and wheat flour chicken meat, tomatoes, hazelnut, walnut, and fish mix. Such allergens were applied with a negative saline and positive histamine control (Histamindihydrochloride 0,1%).[14] Punctures were performed on the inner side of the forearm, on the allergen microdroplets using appropriate lancets. The reading was performed with a ruler graduated in millimeters after 15 minutes. The test result was considered negative with a wheal of <3 mm and positive with the wheal of ≥3 mm. If there was sensitivity to one food in the SPT, it was grouped as single, and if sensitivity to more than one food was detected, it was grouped as multiple.

The data obtained were analyzed with the SPSS 22.0 program. The Smirnov–Kolmogorov test was used in order to calculate the normality, and nominal variables were described as frequencies. Categorical variables were analyzed using the χ^2 and Fisher Exact tests test, Bonferroni correction was applied in multiple comparisons and numerical variables using the Mann-Whitney test. A value of $p < 0.05$ was considered significant for all analyses. The study was approved by the ethics committee of Fırat University Faculty of Medicine with the decision numbered 2022/09-43.

Results

One hundred seventy three patients aged between 2 months and 18 years with AD have been studied. Seven (4%) patients had a SCORAD score greater than 50. The detailed data and comparison of patients by the severity of dermatitis are shown in Table 1.

Food allergen sensitivity was determined in 54% of the patients in SPTs in the study group. The most common food allergens were egg white (67, 39%), egg yolk (54, 31%), cow's milk (22, %3), respectively. Unlike other foods, soy sensitization was more common in the mild dermatitis group (Table 2). The frequency of food sensitization was not different between girls and boys ($p > 0.05$). Patients with a family history of atopy were more likely to have multiple food sensitizations ($p > 0.05$). Food sensitizations were more common in patients who had higher SCORAD scores ($p = 0.001$), but no differences were found in sensitization with aeroallergens ($p = 0.392$). when the patients were compared according to the age groups, there was no significant difference in dermatitis severity and SPT results (Table 3).

There were no differences between the method of delivery, gender and the affected area of dermatitis in patients regardless of the existence of a food sensitization. Family history of atopy was more frequent (21% vs. 52%; $p = 0.005$) and dermatitis was more severe in those with food sensitized patients (30% vs. 60%; $p = 0.003$).

Discussion

In our study, children with AD were evaluated together with clinical severity score and food sensitization by SPT. As the clinical severity score increased, the presence of food sensitization increased. Sensitization to egg white, egg yolk and cow's milk were the most frequent food allergens in

Table 1 Comparison of the patients by severity of dermatitis.

Parameters	Total (n %)	SCORAD <25	SCORAD >25	p
Patients, n (%)	173 (100)	77 (45)	96 (55)	
Girls	86 (50)	46 (53)	40 (47)	**0.022**
Boys	87 (50)	31 (36)	56 (64)	
Age (month)[a]	12 (16)	13 (14)	11 (13)	**0.028**
Age of onset of AD (month)[a]	6 (8)	9 (12)	6 (7)	**<0.0001**
Family history of atopy, n (%)	73 (42)	18 (25)	55 (75)	**<0.0001**
Additional symptoms of food allergy				
None	152 (88)	71 (48)	81 (52)	>0.05
Urticaria	4 (2)	1 (25)	3 (75)	>0.05
Gastrointestinal symptoms[b]	17 (10)	5 (29)	12 (71)	>0.05
Affected area, n (%)				
Only face	84 (49)	45 (54)	39 (46)	**<0.05**
Only extremities	26 (15)	15 (58)	11 (42)	>0.05
Face and trunk	23 (13)	4 (17)	19 (83)	**<0.05**
Face and extremities	15 (9)	4 (27)	11 (73)	>0.05
Extremities and trunk	11 (6)	5 (45)	6 (55)	>0.05
All body areas	10 (6)	0	10 (100)	**<0.05**
Only trunk	4 (2)	4 (100)	0	**<0.05**
Skin prick test, n (%)				
Food allergens				
Positive	94 (54)	31 (34)	63 (66)	**0.001**
Negative	79 (46)	46 (58)	33 (42)	
Aeroallergens				
Positive	25 (15)	9 (36)	16 (64)	0.392
Negative	148 (85)	68 (46)	80 (54)	
Food sensitization, n (%)				
None	71 (41)	41 (58)	30 (42)	**<0.05**
Single	66 (38)	28 (42)	38 (58)	>0.05
Multiple	36 (21)	8 (22)	28 (78)	**<0.05**
Eosinophil (%) (median 25–75p; IQR)	2.1 (2.1–3.9; 2)	2 (2)	2.7 (3)	**0.012**
Eosinophil (#) (median 25–75p; IQR)	200 (200–400; 285)	200 (200)	280 (325)	**0.009**

[a]Median (interquartile range). [b]Bloody stools and diarrhea. AD, atopic dermatitis.

our study group. Patients with multiple food sensitization were more likely to have higher SCORAD scores, vice versa.

Food sensitizations are more common in children with AD than healthy children.[15] In a recent review, it was reported that food sensitization was six times higher in patient with AD.[16] We have found that 59% of our patients were sensitized to one or more food allergens. Similar results were obtained by other studies, on average, 50% of the children with AD were sensitized to common food allergens.[15,17,18]

We have reported that food sensitization is higher in patients with moderate and severe AD compared to those with mild AD. Numerous studies have shown an association between food allergen sensitization and AD severity.[19,20] Guidelines recommend investigating FA in moderate and severe dermatitis.[21] On the other hand, we have found food sensitivity in 34% of patients with mild dermatitis. Therefore, dermatitis severity should not be the sole parameter concerning FA researches and decisions. The presence of food sensitivity affects the clinical severity scores in our patients. The patients without food sensitivity more likely had mild AD, whereas patients with multiple food allergies had higher SCORAD scores. Concerning patients with single food sensitivity, the number of patients with moderate or severe dermatitis was higher than those with mild dermatitis, however, this difference was not statistically significant. It is known that allergen sensitization was more common in moderate and severe AD. The key point is, the severity of AD is a factor determining the subsequent development of allergic diseases.[3]

The most common food allergens were egg white, egg yolk and cow's milk in our study group, respectively. Most common food allergens identified as a trigger in AD are milk and milk products, peanuts, eggs, soy, wheat, seafood and shellfish.[22] The most common FA in AD is usually egg allergy. Patients with AD are six times more likely to have an egg allergy.[18] Hen's egg and cow's milk allergy are the most common food allergies, followed by peanut, tree nuts, sesame, fish, soy and wheat in Europe.[2]

We reported that clinical features began earlier in infants with moderate or severe AD. The presence of family history of atopy, eosinophilia and positive SPTs were more

common in these patients. Around 50–75% of all children with early-onset AD are sensitized to one or more allergens, such as food allergens, house dust mites, or pets, whereas those with late-onset AD are less often sensitized.[23] Approximately 70% of AD patients have a family history of atopic diseases. The odds ratio for the development of AD is 2–3 times higher in children with 1 atopic parent, and 3–5 times higher in children with 2 atopic parents. A maternal history of AD may be associated with a higher risk of developing AD.[3] The previous studies which show that AD is associated with a more severe FA phenotype and early development and persistent AD, are linked to FA.[23] In this regard, it is known that there is a strong association between severe AD with early onset of AD, sensitization with food allergens and FA.[24-26] Age of onset, white blood cell and eosinophil counts, serum C reactive protein and total IgE levels are the most important determinants when identifying the phenotype of AD.[27]

In the analysis of the relationship between food allergens and SCORAD level, we have found that the SCORAD of patient with egg allergy was higher, and interestingly, the SCORAD of children with soy allergy was lower. There was no relationship between aeroallergen sensitivity and SCORAD level. Although the relationship between egg allergy and the presence and severity of AD is better known, studies regarding the relationship between soy allergy and AD are limited. Savage et al. reported eczema in 11% of children with soy allergies in their study. However, its effect on the severity of eczema has not been analyzed.[28] Jarmila et al. observed positive results to soy in specific IgE, SPT or atopy patch test in 30% of AD patients. However, only a minority of these patients suffer from early allergic reaction after

Table 2 Frequencies of food and aeroallergens in skin prick test.

Allergens	Total, n (%)	SCORAD <25	SCORAD >25	p
Food allergens				
Egg white	67 (39%)	20 (30)	47 (70)	**0.003**
Egg yolk	54 (31%)	17 (31)	37 (69)	**0.020**
Cow's milk	22 (13%)	6 (27)	16 (73)	0.108
Wheat flour	9 (5%)	5 (55)	4 (45)	0.493
Peanut	8 (5%)	2 (25)	6 (75)	0.302
Chicken meat	8 (5%)	2 (25)	6 (75)	0.256
Soy	7 (4%)	5 (71)	2 (29)	0.244
Tomatoes	4 (2%)	0	4 (100)	0.130
Hazelnut	2 (1%)	1 (50)	1(50)	0.875
Walnut	3 (2%)	1 (33)	2 (67)	0.694
Fish mix	1 (1%)	0	1 (100)	>0.05
Aeroallergens				
Grass pollen	6 (3)	4 (67)	2 (33)	0.409
House dust mites	5 (3)	1 (20)	4 (80)	0.383
Mold	6 (3)	2 (33)	4 (67)	0.694
Cockroach	6 (3)	1 (17)	5 (83)	0.228
Cat	0(0)	0	0	
Dog	1 (1)	0	1 (100)	>0.05

Table 3 Comparison of frequencies by groups of ages.

Parameters	0–24 months n:143	24–48 months n:13	>48 months n:17	p
SCORAD				
<25	60 (78)	8 (10)	9 (12)	>0.05
25–50	76 (85)	5 (6)	8 (9)	>0.05
>50	7 (100)	0	0	>0.05
Skin prick test, n (%)				
Food allergens				
Positive	82 (87)	5 (5)	7 (8)	>0.05
Negative	61 (77)	8 (10)	10 (13)	
Aeroallergens				
Positive	12 (48)	2 (8)	11 (44)	>0.05
Negative	131 (88)	11 (7)	6 (4)	

the soy ingestion (as oral allergy syndrome and urticaria). Majority of patients are sensitized to soy without clinical symptoms after the soy ingestion, but they suffer from pollen or peanut allergy.[29] The positive skin test results with soy may not indicate clinically significant FA in our patients.

We knew that infants and young children with AD are more commonly sensitized to foods, and that children over 5 years and adults are more commonly sensitized to aeroallergens (dust mite sensitization is most prevalent in both children and adults).[15] In our patients, when SPT results were evaluated according to age groups, food allergen sensitizations were higher in 0–24 month-old infants compared to other ages, this difference was not significant. However, aeroallergen sensitization was significantly lower in this age group, and was significantly higher in patients who are older than 48 months. Our study confirms that sensitization to food allergens is common in infants with atopic eczema compared to aeroallergen sensitization and aeroallergen sensitivity in AD becomes more important after 4 years of age. Our patient group in the study consists of patients under 24 months-of-age mostly. Therefore, it does not allow to reach any definite conclusion regarding aeroallergens. Many studies, especially in adolescents and adults, have shown that aeroallergens also have an effect on AD, especially on exacerbations.[24,30]

Conclusion

We have found that 54% of our patients had food sensitivity, and 15% of our patient had aeroallergen sensitivity in SPT. Positive results in SPT with both food allergens and aeroallergens are more common in patients with AD than in the general population. Therefore, we are of the opinion that patients with AD, especially with moderate-to-severe AD, should be evaluated by pediatric allergists for possible allergen sensitivities. According to our results, aeroallergens are not significant triggers for AD and have no effect on AD severity in children with AD under 2 years of age.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this article.

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