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Original Research

Food Sensitivity in Children Diagnosed with Atopic Dermatitis in The First 2 Years: How Many of These Patients Are Truly Allergic?

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ABSTRACT

Objectives: In this study, it was aimed to examine food sensitivity in patients with atopic dermatitis (AD) and to investigate the frequency of food allergy in patients with food sensitivity.

Methods: Patients aged 0–2 years who were followed up with the diagnosis of AD were included in the study. The characteristics of demographic and clinical and laboratory findings of the patients were recorded retrospectively. Patients were classified as mild, moderate, and severe using the SCORing AD index according to the severity of AD. The presence of food sensitivity was evaluated by skin prick test and serum-specific immunoglobulin (Ig)E results. Food allergy was diagnosed by oral food challenge (OFC) test.

Results: Of the 72 patients included in the study, 62.5% (n=45) were male, and the mean age was 9±4.8 months. When the disease severity was evaluated, it was mild in 40 patients (55.6%); moderate/severe AD was present in 32 patients (44.4%). The frequency of moderate/severe AD was higher in patients who were younger (p=0.01), whose symptoms started in the first 6 months (p=0.03), who had a family history of allergic disease (p=0.001), who breastfed for <6 months (p=0.01), who had a higher median serum total IgE level, and a higher percentage of serum eosinophils (p=0.005 and p=0.01, respectively). Food sensitivity in 45.8% of patients; food allergy was detected in 41.7% of them. The most common sensitivities and allergies were eggs white/yolk and cow's milk, respectively. The rate of food sensitivity was found to be higher in male gender (p=0.03) and breastfed patients (p=0.03), whereas it was similar in patients with mild and moderate/severe AD.

Conclusion: In the investigation of food sensitivity in patients with AD, it is important to evaluate other demographic and clinical characteristics such as gender and breastfeeding, apart from the severity of disease. The OFC test should be performed to confirm the food allergy in patients with food sensitivity before the recommendation of an elimination diet.

Keywords: Atopic dermatitis, childhood, food allergy, food sensitivity

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Atopic dermatitis (AD) is the most common inflammatory skin disease of childhood characterized by chronic, itchy, and recurrent lesions.^[1] It has been reported to affect approximately 20% of children in developed countries.^[2] Findings are mostly seen in early infancy and often in the first 6 months of life.^[3] The interaction of genetic, immunological, and environmental factors that cause skin barrier disorder and chronic inflammation in the skin play an important role in the pathophysiology of AD.^[4,5]

It has been reported that food and inhalant allergens entering the body through the skin as a result of skin barrier defect in AD patients cause sensitization by creating a Th2 response and these individuals are more likely to develop other allergic diseases such as food allergy and asthma.^[6] Sensitivity to food allergens is mostly seen in children with moderate/severe AD in the first 2 years of age; sensitivity to inhalant allergens occurs in patients with age.^[7] Foods that cause allergic reactions vary according to age. While eggs, cow's milk, wheat, and soy constitute 75–90% of reactions in young children, nuts, fish, and shellfish cause allergies more frequently in older children and adults.^[8] Especially, patients with early-onset and severe AD should be evaluated for food allergies. In patients with food sensitivity determined through skin prick test and food-specific immunoglobulin (Ig)E value, food allergy should be investigated clinically with oral food challenge (OFC) test before starting an elimination diet with the sensitive food.^[9,10]

In this study, it was aimed to investigate food sensitivity in patients aged 0–2 years with AD and the frequency of food allergy in AD patients with food sensitivity.

Methods

Patients aged 0–2 years who were followed up with the diagnosis of AD between July 2020 and May 2021 were included in the study. The age at which patients consult a doctor, time of onset of complaints, gender, family history of allergic disease and AD, duration of breastfeeding, severity of AD, serum total IgE and eosinophil levels, skin prick tests, food sptgE, and OFC tests results were recorded retrospectively from patient files. The diagnosis of AD was made according to the diagnostic criteria of Hanifin and Raika.^[11] Severity of AD was evaluated according to the SCORing AD (SCORAD) index.^[12] Patients with a SCORAD index <25 were classified as mild; patients with a range of 25–50 were classified as moderate; and those with >50 were classified as severe AS. During the comparison of the findings, the patients were evaluated in two groups as “mild” and “moderate/severe” according to the severity of AD.

Food sensitivity was evaluated according to the skin prick test and serum food sptgE results. In the skin prick test, a

panel containing standard food allergens (ALK-Albello®, Canada) of cow's milk, egg white, egg yolk, wheat, hazelnut, peanut, cashew, sesame, chicken meat, beef, fish, soy, peach, and apple was applied. Furthermore, 0.9% of sodium chloride was used as negative control and 10 mg/mL histamine (ALK-Albello®, Canada) was used as positive control. Detection of an induration diameter of 3 mm and/or larger than the negative control against the food allergens was considered positive.^[13] Food sptgE levels were measured with the ImmunoCAP (PhadiaAB, Uppsala, Sweden) system, values above 0.35 kUA/l were considered positive. To determine the relationship between the suspected food and AD exacerbation in patients with sensitivity to food allergens, an open OFC test with the suspected food was performed for the diagnosis of food allergy after 2–4 weeks of elimination diet.^[14] The OFC tests were applied to mothers in patients exclusively breastfed. In addition, in patients with symptoms during complementary feeding, the challenge tests were applied only to the patient. The amount of starting the challenge test for each food for which sensitivity was detected and the amounts planned to be consumed daily were determined according to the Turkish National Food Challenge Tests guideline.^[15] After the OFC test, the patients were kept under observation for 2–4 h. The test was considered positive in patients with objective symptoms (skin findings such as eczema, urticaria, angioedema; gastrointestinal system findings such as vomiting; respiratory tract findings such as cough, wheezing, and cardiovascular system findings such as hypotension) during or after the test, and symptomatic treatment was administered. Patients who did not have any symptoms during or after the test were asked to consume the food given during the test for 7 days in terms of delayed reactions and were followed up in terms of findings. During this period, the challenge test was considered positive in patients with exacerbation of eczema.

This study was conducted in accordance with the Declaration of Helsinki and ethics committee approval was obtained for the study from the Clinical Research Ethics Committee of Sisli Hamidiye Etfal Training and Research Hospital (Date: April 27, 2021, decision no: 1881).

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (Chicago, IL, USA) version 21.0. Descriptive statistics of evaluation results; numbers and percentages for categorical variables, mean, standard deviation, minimum, and maximum for numerical variables were given. Comparisons of numerical variables between two independent groups; Student's t test was compared with normal distribution condition and Mann–Whitney U test when normal distribution condition was not met. Differences between cat-

egorical variables were tested with Chi-square analysis. Statistical significance level was accepted as $p < 0.05$.

Results

Seventy-two patients aged 0–2 years who were followed up with a diagnosis of AD were included in the study. 62.5% ($n=45$) of the patients were male, mean age was 9 ± 4.8 months. When the patients were grouped according to the age of complaints onset, it was observed that starting time of symptoms was at 0–6 months in 59.7% of the patients ($n=43$); 6–12 months in 34.7% ($n=25$); 12–24 months in 5.6% ($n=4$). While 33% ($n=24$) of the patients had a family history for allergic diseases, 22% ($n=16$) had AD in the family members. About 77.8% of the patients were still breastfeeding. Mean breastfeeding duration was 7.9 ± 3.5 months. The mean age of starting solid food was 5.9 ± 0.21 months.

The median serum total IgE level was 26.2 (IU/mL) (range: 0.28–885 IU/mL) and the median serum eosinophil percentage was 3.1% (range: 0.10–17.7%). When the severity of AD was evaluated according to the SCORAD index, it was mild in 40 patients (55.6%), and also 32 patients (44.4%) had moderate/severe AD.

When the clinical and laboratory characteristics of the patients were compared according to the severity of AD, the moderate/severe AD frequency was found to be higher in patients with a high median serum total IgE level and a high median serum eosinophil percentage ($p=0.005$, $p=0.01$, respectively). In addition, the frequency of moderate/severe AD was higher in patients who were younger ($p=0.01$), whose complaints started in the first 6 months ($p=0.03$), who had a family history of allergic disease ($p=0.001$), and who were breastfed for a shorter period of time ($p=0.01$) (Table 1).

Table 1. Comparison of demographic and clinical characteristics of patients according to the severity of atopic dermatitis

	Mild n (%)	Moderate and severe n (%)	p
Gender			
Male	25 (62.5)	20 (62.5)	1*
Female	15 (37.5)	12 (37.5)	
Age at diagnosis (month)			
Median (min-max)	9.5 (2–22)	6.5 (3–19)	0.01 [†]
Age at the onset of symptoms (month)			
0–6	19 (47.5)	24 (75)	0.03 *
6–12	17 (42.5)	8 (25)	
12–24	4 (10.0)	0 (0)	
Family history of allergic disease			
Yes	7 (17.5)	17 (53.1)	0.001 *
No	33 (82.5)	15 (46.9)	
Family history of atopic dermatitis			
Yes	9 (22.5)	7 (21.9)	0.94*
No	31 (77.5)	25 (78.1)	
Status of breastfeeding			
Yes	29 (72.5)	27 (84.4)	0.22*
No	11 (27.5)	5 (15.6)	
Duration of breastfeeding (month)			
Median (min-max)	9 (2–15)	6 (1–19)	0.01 [†]
Food sensitization			
Yes	16 (40)	17 (53.1)	0.26*
No	24 (60)	15 (46.9)	
Food allergy			
Yes	14 (35)	16 (50)	0.20*
No	26 (65)	16 (50)	
Serum total IgE (IU/mL)			
Median (min-max)	21 (0.28–885)	45 (5.36–700)	0.005 [†]
Serum eosinophil level (%)			
Median (min-max)	2.8 (0.10–16.50)	4.5 (0.40–17.70)	0.01 [†]

*: Chi-square test; †: Mann-Whitney U test was applied.

Table 2. Frequencies of foods which detected sensitivity and allergy in patients

Sensitized food allergens	Patient number n (%)	Allergic foods	Patient number n (%)
Egg White and egg yolk	30 (41.7)	Egg White and egg yolk	21 (29.2)
Cow's milk	16 (22.2)	Cow's milk	17 (23.6)
Wheat flour	7 (9.7)	Cashew	1 (1.4)
Chicken meat	7 (9.7)		
Beef meat	3 (4.2)		
Apple	2 (2.8)		
Peach	2 (2.8)		
Cashew	1 (1.4)		

To determine food sensitivity, skin prick test was measured in 27.8% (n=20) of the patients, and food sptgE level was measured in 93.1% (n=67) of the patients. Accordingly, food sensitivity was detected in 33 patients (45.8%). A total of 42 OFC tests were applied to the patients who were found to have food sensitivity and received informed consent, separately for each food. Food allergy was diagnosed in 30 patients (41.7%) with the OFC test. Sensitivity and allergy-detected foods are shown in Table 2. In 11% of the patients with food allergy, multiple food allergies (milk and egg in seven patients; milk, egg, and cashew in one patient) were present. Demographic and clinical characteristics of patients with and without food sensitivity were compared and food sensitivity was found more frequently in male (p=0.03) and currently breastfed patients (p=0.03). No statistically significant correlation was found between food sensitivity and patient age, age at onset of complaint, duration of breastfeeding, severity of AD, serum total IgE level, and percentage of serum eosinophils. According to the results of OFC tests performed with egg and cow's milk, the most sensitive foods in the study, allergy detection rates were determined as 55.2% and 50%, respectively.

Discussion

In this study, food sensitivities and the frequency of allergy to foods that were found to be sensitive in infants with AD between 0 and 2 years of age were investigated. It is known that the skin barrier defect, which plays an important role in the pathogenesis of AD, contributes to the development of sensitivity to food allergens.^[16] With the "dual allergen exposure hypothesis" supported by the results of many studies in recent years, it has been stated that early allergen exposure through the skin leads to the development of food sensitivity and food allergy; it has been argued that early oral exposure supports tolerance.^[17] In our study, the rate of sensitivity to food allergens was found to be 45.8%. In the previous studies, the rate of food sensitivity in patients with AD was found to be between 30% and 40%, and similar to

our results, it was shown that sensitivity to egg, cow's milk, and wheat most frequently developed.^[18-20] In our country, Beken et al.^[21] evaluated food sensitivity and food allergy in 236 AD patients aged 0–18 years; food sensitivity rate was found to be 31%. In the same study, the rate of food allergy diagnosed with a food challenge test was reported to be 30.8%. In our study, the rate of food sensitivity in patients with AD was found to be higher than in the literature. This result can be explained by the fact that our study group included the 0–2 age patients who have a higher prevalence of food allergy and both skin prick and sptgE methods were used to determine the sensitivity. Similarly, in another study conducted in Turkey, Ciğerci Günaydın et al.^[22] reported a high rate of food sensitivity as 65.4% in children with AD between 2 and 70 months. In Thailand, Yuenyongviwat et al.^[23] studied the risk factors of food sensitivity; the food sptgE results of 119 patients with AD diagnosed between 2 months and 5 years of age were examined retrospectively and food sensitivity was found to be 60%.

In the previous studies investigating the relationship between AD and food allergy, severe and early-onset AD has been shown to be associated with the development of food sensitivities and food allergy at an early age.^[24-27] In a systematic review of studies on the association of AD and food allergy, it was shown that the development of food sensitivity in children with AD at 3 months of age was 6 times higher than in healthy controls.^[28] In a recent study conducted in our country, food sensitivity was found to be significantly higher in children with moderate/severe AD, and it was reported that the SCORAD index was higher in patients with food allergy.^[29] In our study, it was found that the rate of moderate/severe AD was more frequent in patients with early-onset AD (0–6 months). However, the rate of food sensitivity was found to be similar between patients with mild and moderate/severe AD (respectively, n=16 and n=17). In addition, no significant correlation was found between the age of onset of symptoms and food sensitivity. In international guidelines, it is recommended

to investigate food sensitivity in children under 5 years of age, especially with moderate/severe AD that does not respond to topical treatment.^[30,31] The results of our study show that the severity of AD and the age of onset of symptoms are not sufficient to investigate food sensitivity, and the patient should be evaluated together with other clinical findings and history.

In the previous studies, it was reported that the rate of food sensitivity was found to be high in AD patients, but the rate of food allergy confirmed by food challenge tests was lower and food allergy was mostly detected in patients with severe AD.^[32,33] In the results of the Danish allergy research cohort, it was shown that sensitivity to food allergens was detected in approximately 53% of AD patients aged 6 months–6 years, and food allergy was confirmed in 15% of them.^[8]

The OFC test, which is the gold standard in the diagnosis of food allergy, is strongly recommended to prevent unnecessary food elimination and to diagnose true food allergy, especially in AD patients with food sensitivity.^[31] In our study, the OFC test was performed in 33 patients with food sensitivity, and as a result of the OFC tests, food allergy was diagnosed in 30 patients (41.7%). We thought that the reason for the high rate of food allergy in our study compared to the literature could be explained by the fact that we included not only early type reactions but also mixed type reactions (delayed type) that occur as eczema exacerbations as positive reactions. In addition, the fact that our study group consisted of patients in the first 2 years of age, which is the age group in which AD symptoms and food allergy are most common, may have contributed to this result.^[34] Consistent with our findings in studies conducted in our and the other countries, the frequency of food allergy was found to be high, ranging from 33% to 39%, especially in patients with severe AD.^[24,35-37]

In our study, sensitivity to egg white/yolk, cow's milk, wheat, and chicken meat was found most frequently. In addition, while food allergy was confirmed in half of the patients with egg and cow's milk sensitivity, food allergy was not confirmed in any of the patients with wheat and chicken meat sensitivities. According to our findings, it has been shown that the rate of confirmed food allergy was higher in patients with sensitivity to egg and cow's milk, which are the most common allergenic foods in infancy, similar to other studies in the literature.^[24,38,39]

In a study examining 110 AD patients younger than 1 year old, serum total IgE and serum eosinophil levels were found to be higher in the food sensitive group, and it was reported that the serum total IgE and serum eosinophil level elevations provided a prediction for food sensitivity in patients with severe AD.^[40] In our study, on the contrary, no

statistically significant correlation was found between the severity of AD, serum total IgE level, percentage of eosinophils, and food sensitivity. Ciğerci Günaydın et al.^[22] reported in their study that there was no difference between food sensitivity and total serum IgE and serum eosinophil levels, similar to our results.

In our study, food sensitivity was detected more frequently in male gender and breastfed patients. Yuenyongviwat et al.^[23] found in their study that the rate of food sensitivity is higher in infants who have been breastfed for more than 6 months. They explained this result with the concern of parents of children who are prone to develop food sensitivities or food allergies and their intention to breastfeed longer than the normal population. We thought that the reason for the higher rate of sensitivity in children who are still breastfed may be related to the longer exposure to the allergen food in mother's diet. The high rate of susceptibility in males may be associated with an increase in the prevalence of atopic diseases in males, as stated in the literature.^[41]

In our study, when the severity of AD was compared with the clinical and demographic characteristics of the patients, the frequency of moderate/severe AD was found to be higher in patients who were younger, had early-onset AD, had a family history of allergic disease, had a higher serum total IgE level, and a higher percentage of serum eosinophils. Similar to our findings, Cansever and Oruç^[29] reported that moderate/severe AD was associated with a family history of atopy, high serum eosinophil level, and early-onset symptoms in their studies.

The limitations of our study are that it is a retrospective study and the skin test cannot be applied to all patients. Although the results of a limited number of patients were examined, the combined use of skin prick test and sIgE measurements to determine sensitization and the OFC test for all patients with sensitivity is the strength of our study.

Conclusion

As a result, the rate of food sensitivity was 45.8% and the rate of food allergy was 41.7% in patients diagnosed with AD at the first 2 years of age, and it was observed that the most common foods with sensitivity and allergy were egg and cow's milk, respectively. In addition, food sensitivity was found at a similar rate in patients with mild and moderate/severe AD. In our study, the importance of evaluating other demographic and clinical characteristics such as gender and breastfeeding, apart from the severity of AD, was emphasized in the investigation of food sensitivity in patients with AD. The OFC test should be performed to confirm the food allergy in patients with food sensitivity before the recommendation an elimination diet.

Disclosures

Acknowledgement: Sevgi Sipahi Cimen and Belgin Usta Guç contributed equally to the study.

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences Türkiye, Sisli Hamidiye Etfal Training and Research Hospital (No: 1881, dated 27.04.2021).

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Conflict of Interest: None declared.

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