DOI: 10.24938/kutfd.1466473 Kırıkkale Üniversitesi Tıp Fakültesi Dergisi 2024;26(2):194-200
Original Article *Özgün Araştırma*

EVALUATION OF FOOD SENSITIVITY IN CHILDREN WITH ATOPIC DERMATITIS

Atopik Dermatitli Çocuk Hastalarda Besin Duyarlılığının Değerlendirilmesi

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ABSTRACT

Objective: Atopic dermatitis is considered an important risk factor for the development of food allergies. This retrospective study aimed to evaluate food sensitivity in pediatric patients with atopic dermatitis based on skin prick tests.

Material and Methods: The study included children diagnosed with atopic dermatitis who underwent skin prick tests with food allergens at our hospital's Pediatric Allergy Clinic between January 1, 2023 and January 31, 2024. Demographic data, atopic dermatitis onset age, severity, treatments, and co-existing atopic diseases (asthma, allergic rhinitis) were collected from medical records. Skin prick test results were evaluated retrospectively.

Results: The study comprised 229 patients, predominantly male (64.2%) with a median age of 7 months (IQR:5-14). The median age at atopic dermatitis onset was 3 (IQR:2-6) months. Co-existing allergic diseases were present in 12 (5.2%) patients. Based on SCORing Atopic Dermatitis (SCORAD), atopic dermatitis severity was mild in 61.1%, moderate in 29.3%, and severe in 9.6% of patients. Food allergen sensitization was observed in 73 (31.9%) patients, predominantly to hen's egg (28.4%). Multiple food sensitivities occurred in 10% of patients (n=23). Patients with food sensitivity showed earlier atopic dermatitis onset, higher total IgE and eosinophil counts, and more frequent moderate-severe atopic dermatitis ($p<0.05$). Multivariate analysis identified atopic dermatitis onset before 3 months, moderate-severe atopic dermatitis, and eosinophils >500/ mm^3 as risk factors for sensitization.

Conclusion: Approximately one-third of pediatric atopic dermatitis patients exhibited sensitivity to at least one food allergen, most commonly hen's egg. Early atopic dermatitis onset, elevated eosinophils, and moderate-severe atopic dermatitis pose a higher risk for sensitization. Hence, mitigating unnecessary elimination diets and prompt referral of these patients to pediatric allergy clinics is crucial.

Keywords: *Atopic dermatitis, skin prick test, food allergy, food sensitivity, egg allergy*

ÖZ

Amaç: Atopik dermatit, gıda alerjilerinin gelişimi için önemli bir risk faktörü olarak kabul edilmektedir. Bu retrospektif çalışmada, atopik dermatitli pediatrik hastalardaki besin duyarlılığının deri prik testlerine göre değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya, hastanemiz Pediatrik Alerji Kliniğinde 1 Ocak 2023 ve 31 Ocak 2024 tarihleri arasında besin alerjenleriyle deri prik testleri uygulanan atopik dermatit tanılı çocuk hastalar dahil edilmiştir. Demografik veriler, atopik dermatit başlangıç yaşı, şiddeti, tedavileri ve eşlik eden atopik hastalıklar (astım, alerjik rinit) tıbbi kayıtlardan toplanmıştır. Deri prik testlerinin sonuçları retrospektif olarak değerlendirilmiştir.

Bulgular: Çalışmaya %64,2'si erkek ve ortalama yaşları 7 ay (Çeyrekler arası aralık [ÇAA]: 5-14) olan 229 hasta katıldı. Atopik dermatit başlangıç yaş ortancası 3 (ÇAA:2-6) aydı. Hastaların 12'sinde (%5,2) eşlik eden diğer alerjik hastalıklar mevcuttu. SCORAD'a (Atopik dermatit ağırlık ölçeği) göre atopik dermatit şiddeti hastaların %61,1'inde hafif, %29,3'ünde orta ve %9,6'sında şiddetliydi. Hastaların 73'ünde (%31,9), en sık yumurta (%28,4) ile olmak üzere besin alerjen duyarlılığı saptandı. Hastaların %10'unda (n=23) çoklu besin duyarlılığı saptandı. Duyarlılık saptanan hastalarda atopik dermatitin daha erken başladığı, toplam IgE ve eozinofil sayılarının daha yüksek olduğu ve orta-şiddetli atopik dermatitin daha sık olduğu görüldü ($p<0.05$). Çok değişkenli analizde, atopik dermatitin 3 aydan önce başlaması, orta-şiddetli atopik dermatit ve eozinofil sayısının >500/mm^3 olması duyarlılık için risk faktörleri olarak belirlendi.

Sonuç: Pediatrik atopik dermatit hastalarının yaklaşık üçte birinde, en sık yumurta ile olmak üzere, en az bir gıda alerjenine karşı duyarlılık saptanmıştır. Atopik dermatit erken yaşlarda başlaması, yüksek eozinofil sayısı ve atopik dermatitin orta-şiddetli olması, besin alerjen duyarlılığı için daha yüksek risk oluşturur. Bu nedenle, gereksiz eliminasyon diyetlerinin önüne geçebilmek için bu grup hastaların özellikle çocuk alerji kliniklerine yönlendirilmesi çok önemlidir.

Anahtar Kelimeler: *Atopik dermatit, deri prik testi, besin alerjisi, besin duyarlılığı, yumurta alerjisi*

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Received / Geliş Tarihi: 07.04.2024 **Accepted** / Kabul Tarihi: 24.05.2024

KÜ Tıp Fak Derg 2024;26(2):194-200
Doi: 10.24938/kutfd.1466473

INTRODUCTION

Atopic dermatitis (AD) is a common, chronic inflammatory pruritic skin disorder that typically develops during infancy or childhood but can affect individuals of all ages (1). With its increasing prevalence; AD has emerged as a significant global health concern, affecting approximately 10-30% of the pediatric population (2,3). It usually manifests between 3-6 months of age (4,5).

AD is diagnosed primarily through clinical presentation, as reliable biomarkers are currently unavailable. The Hanifin and Rajka diagnostic criteria for AD are commonly used for diagnosis (4,6). To identify triggering allergens in AD, various methods such as skin prick tests (SPT), specific IgE tests, food provocation tests, and elimination diets are used (4).

A well-established relationship exists between AD, food sensitization (FS), and food allergy (FA), particularly in childhood (7). According to the dual allergen hypothesis, epithelial barrier dysfunction in AD significantly increases the risk of developing epicutaneous FS, FA, and other allergic disorders (8,9). Birth cohorts have shown higher rates of FS in patients with AD compared to those without AD, with FA detected in approximately 33% of patients with moderate to severe AD (9).

Allergen sensitivity in patients with AD may vary with age (3,10). Cow's milk, hen's egg, peanuts, and soy are commonly reported as the most prevalent food allergens in infants, while wheat, fish, treenuts, and shellfish are more common in older children (2,11). While FS severity correlates with the severity of AD, recent studies have also reported that sensitization to any FA exacerbates the severity of AD (11-13). Therefore, determining allergen sensitivity is crucial for both effectively managing patients with AD and avoiding unnecessary elimination diets.

This study aimed to evaluate FS in pediatric patients with AD based on skin prick tests.

MATERIALS AND METHODS

Study population

Children diagnosed with AD who underwent SPT with food allergens at the pediatric allergy outpatient clinic of our hospital between January 1, 2023, and January 31, 2024, were screened. Patients with positive SPT results (mean wheal diameter >3 mm) and possessing complete data were included in the study. Ethical approval of the study was taken from the ethics committee of the Ankara Research and Training Hospital (Decision number: E- 24- 41).

Study procedures

Patient data, including demographic and clinical characteristics (age of onset, AD severity, medical treatments), presence of other allergic comorbidities (asthma, allergic rhinitis, allergic conjunctivitis), SPT wheal diameter, eosinophil count and percentage, and total IgE levels at presentation, were recorded. Total IgE was measured by Elisa method and blood eosinophils were measured as part of the complete blood count, and all samples were analyzed at the central laboratory of our hospital.

Diagnosis of atopic dermatitis

The Hanifin Rajka criteria were used for AD diagnosis (6).

Severity of atopic dermatitis

AD severity was assessed using the SCORing Atopic Dermatitis (SCORAD) index (<25: mild, 25-49: moderate, >49: severe) (6). SCORAD index measurements were performed by pediatric allergy physicians (authors of the study).

Skin prick test (SPT)

Allergen sensitization was determined with SPT. Skin prick test was performed for patients with recurrent and persistent atopic dermatitis. SPTs (Solutions: Lopharma, Italy) were performed one week after discontinuing antihistamine therapy using a standard food allergen panel which includes cow's milk, hen's egg, wheat, soy, hazelnut, walnut, fish, negative control (0.9% saline), and positive control (1.7 mg/mL histamine dihydrochloride). Also if parents have suspicions about any foods for trigger or worsen atopic dermatitis; we performed SPT with that food. SPT was performed on the volar surface of the forearm. After 15 minutes, the maximum horizontal and vertical wheel diameter was measured. If the indurations' mean diameter was greater than at least 3 mm from the negative control, it was considered positive.

Multiple food sensitivity was defined as if the patients were sensitized with >1 food**.**

Statistical analysis

SPSS version 22.0 (IBM Corp, Armonk, NY) was used for data analysis. Continuous variables are presented as median and interquartile range (IQR, 25^{th}-75^{th} percentiles). Chi-squared (χ^2) and Fisher's exact test were used for comparisons of qualitative variables between the food sensitized and not sensitized groups. Mann-Whitney U and Wilcoxon rank sum test were used for comparisons of quantitative variables. Predictive factors were analyzed with univariate and multivariate logistic regression analysis. The multivariate logistic regression analysis included variables with $p<0.2$ in the univariate analysis and factors thought to be predictive for food allergen sensitisation. Odds ratio (OR) and 95% confidence interval (CI) of the results were reported. P value <0.05 was considered significant.

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RESULTS

The study comprised 229 patients, predominantly male (64.2%) with a median age of 7 months (IQR: 5-14, min 1–max 156 months). The median age at AD onset was 3 (2-6) months. Co-existing atopic diseases were observed in 12 (5.2%) patients, with 8 patients (3.5%) diagnosed with asthma, and 4 patients (1.7%) with AR. Additionally, 27 patients (11.8%) reported a family history of allergic disease. Characteristics of the patients are shown in Table 1.

Severity of AD

Based on SCORAD, AD severity was mild in 61.1% (n=140), moderate in 29.3% (n=67), and severe in 9.6% (n=22) of patients. In patients exhibiting moderate to severe AD, the age of onset and diagnosis tends to be lower, while eosinophil counts, rates of cesarean delivery, and occurrences of atopic sensitization were higher (p; 0.021, <0.001, <0.001, 0.002, <0.001, respectively). Comparisons of patients according to SCORAD index are shown in Table 2.

Skin prick test results

FS was detected in 73 patients (31.9%), with the most prevalent sensitization being to hen's egg (28.4%). Other allergen sensitivities were observed in 5.7% of patients to milk, 2.2% to peanuts, 4.8% to nuts, and 2.2% to other allergens such as banana, sesame, soy and lentil. Multiple food sensitivities were present in 10% of the patients (n:23). (Figure 1 and 2).

The distribution of food sensitizations among patients according to age is presented in Table 3.

In patients with FS, the median age at onset of AD is younger, with higher median total IgE and eosinophil counts, and a more frequent occurrence of moderate and severe SCORAD severity (p; 0.002, 0.039, <0.001, <0.001, <0.001, respectively) (Table 4).

Predicting factors for sensitization with food allergen

According to multivariate analysis, the onset of AD before 3 months of age, the presence of moderate-to-severe AD, and eosinophil count >500/mm^3 were identified as predictive factors for food sensitization in patients with AD (Table 5).

Table 1: Demografic characteristics of patients (n: 229).

Age [months], median (IQR)		7 (5-14)
Gender [male], n (%)		147 (64.2)
Characteristics of birth	**C/S n (%)**	135 (59)
	Preterm n (%)	16 (6.9)
	Weight [grams] median (IQR)	3200 (2920-3500)
Age at onset of AD [months], median (IQR)		3 (2-6)
Total IgE (kU/L) median (IQR)		22 (8.8-70)
Eosinophil /mm^3, median (IQR)		420 (220-697)
Other Allergic disease; n (%)		12 (5.2)
Asthma		8 (3.5)
Allergic rhinitis		4 (1.7)
Family history of atopic disease, n (%)		27 (11.8)

IQR: Inter quartile range, C/S: Cesarean sectio, AD: Atopic dermatitis, IgE: Immunglobulin E

Table 2: Comparisons of patients with mild and moderate/severe atopic dermatitis (according to SCORAD index)

Parameters	**Mild** (n:140)	**Moderate/Severe** (n:89)	**p**
Age at onset of AD [months], median (IQR)	3.5 (2-7)	3 (1-4.75)	0.021
Age at diagnosis of AD [months], median (IQR)	8.5 (5.5-17)	6 (4.5-8)	0.000
Sensitised with food allergen, n (%)	29 (20.7)	44 (49.4)	0.000
Total IgE (kU/L), median (IQR)	25.8 (8-71.9)	21.4 (9.2-69)	0.72
Eosinophil, median (IQR)			
/mm^3	305 (197-500)	590 (415-830)	0.000
%	3.3 (2.1-5)	5.7 (3.8-8.1)	0.000
Male Gender, n (%)	82 (58.5)	53 (59.5)	0.883
Cesarean birth, n (%)	104 (37)	43 (56)	0.002

AD: Atopic dermatitis, IQR: Inter quartile range, IgE: Immunglobulin E

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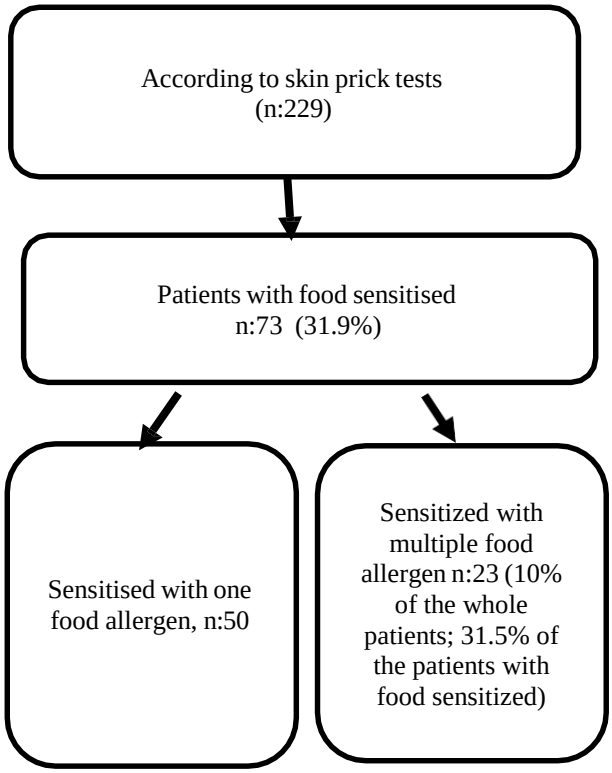

Figure 1: Food allergen sensitisation according to skin prick tests

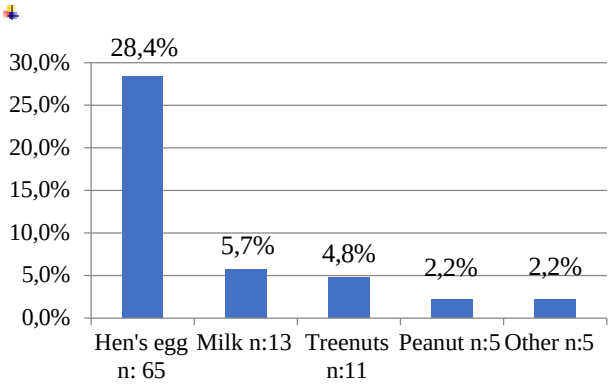

Figure 2: Distribution of sensitized food allergens in pediatric patients with atopic dermatitis

Table 3: Distribution of patients with food sensitization according to age

Age (months)		Sensitized	Not sensitized
0-3	(n:124)	50 (40.3%)	74 (59.7%)
4-6	(n:53)	20 (37.7%)	33 (62.3%)
7-11	(n:23)	1 (4.3%)	22 (95.7%)
12-24	(n:18)	1 (5.5%)	17 (94.5%)
>24	(n:11)	0 (0)	11 (100%)

The comparisons between patients sensitized and those not sensitized to a food allergen

Table 4: Comparisions of patients with and without sensitised with food allergen

Parameters	**Sensitised**(n:73)	**Not Sensitised**-(n:156)	**p**
Gender [male], n (%)	54 (73.9)	93 (59.6)	0.050
Birth with C/S, n (%)	48 (65.7)	87 (55.7)	0.198
Preterm birth, n (%)	4 (5.4)	12 (7.6)	0.767
Age at onset of AD, [months], median (IQR)	3 (1.5-4)	3.5 (2-8)	<0.002
AD at diagnosis of AD, [months], median (IQR)	5 (4-7)	8.5 (6-17)	0.000
SCORAD (Moderate/Severe), n (%)	44 (60.2)	45 (28.8)	0.000
Eosinophil, median (IQR)			
➢ **/mm^3**	570 (375-935)	320 (200-570)	0.000
➢ **%**	5.9 (3.8-8.1)	3.4 (2.1-5.4)	0.000
Total IgE (kU/L, median (IQR)	28.5 (13.6-76)	21 (7.1-68)	0.039

C/S: Cesarean sectio, AD: Atopic dermatitis, IQR: Inter quartile range, IgE: Immunglobulin E

Table 5: Predictive factors for sensitisation with food allergen in patients with atopic dermatitis

	Univariant			**Multivariant**		
	0R	95% CI	p	0R	95% CI	p
Age onset <3 months	2.3	1.27-4.05	0.006	1.95	0.99-3.8	0.049
Eo>500/mm^3	3.98	2.15-7.36	0.000	2.34	1.18-4.64	0.015
IgE>100 kU/L	1.5	0.71-3.15	0.278	-	-	-
Moderate/Severe SCORAD	3.5	1.99-3.45	0.000	2.93	1.49-5.7	0.02
Male	1.87	1.01-3.45	0.046	1.73	0.85-3.53	0.127

Eo: Eosinophil, IgE: Immunglobulin E, OR: Odds ratio, CI: Confidence interval

DISCUSSION

In this study, food allergen sensitivity in patients with AD was evaluated based on SPT results. It was found that 31.9 % of pediatric patients with AD exhibited sensitivity to at least one food allergen, with hen's egg being the most commonly detected allergen. In patients with AD, age of onset younger than 3 months, eosinophil count exceeding 500/mm^3, and the presence

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of moderate to severe AD lesions have been identified as predictive factors for the development of allergen sensitivity.

Several studies have reported that FS frequently coexists with AD. Additionally, AD is considered to be one of the crucial risk factors for FS and IgE-mediated FA (7). The incidence of FS in patients with AD may change according to some factors such as the age of the patients, the severity of AD, and the country where the study was conducted. In a systematic review of 66 studies, FS was found to be 6 times more frequent in children with AD than in children without AD at the age of 3 months (14). Atakul G and colleagues reported that 54% of children had FS according to SPT (13). Smolkin YS et al. reported that 51.9% of patients had hypersensitivity to at least 1 allergen (10). Emeksiz ZŞ et al. reported that 21% of patients with AD had FS according to SPT with food allergens (15). In our study, we found that 31.9% of patients with atopic dermatitis were sensitive to at least one food allergen, and that sensitivity decreased with age.

Hen's egg, milk, wheat, peanut, hazelnut, fish and soy are responsible for approximately 90% of food sensitivities in AD patients (16). However, the most common triggering foods may change with the age of the patients and the countries where the studies were conducted (3,10). When we look at the differences according to age; while the most common food allergens in infants are cow's milk, hen's egg, peanut and soy; it has been reported that wheat, fish, hazelnuts and shellfish are the most common in older children (3). Looking at the differences by country; in a study conducted in the United Kingdom, it was reported that the most common allergen according to the SPT was hen's egg (2.94%), followed by peanut (1.75%) and cow's milk (0.74%) (17). In the Health Nut study from Australia, infants with AD have 6 times more frequent egg allergy and have 11 times more frequent peanut allergy by 12 months than infants without AD at 12 months of age (16,18). Another wider study from Japan shows the relation between AD and FA (the BAMSE cohort), reporting that 27% of the patients with AD had food sensitization according to SPT (21% of them with egg; 15% of them with peanut; 8% of them with milk; and 2% of them with cod) at 2 years of age (19). In an African study, it was reported that 54% of the children with AD had a concomitant egg sensitization and 25% of them had egg allergy (20).

And when we look at the studies from Türkiye (our country); Atakul G et al reported that the most common food allergens were egg white (39%), egg yolk (31%), cow's milk (3%) (13); Kulhaş-Çelik İ et al. reported that egg white sensitivity was the most common detected sensitivity in 85.8% of the children with AD; also they reported that milk was detected in 36.8%, wheat in 3.9%, and walnut in 1.5% of the patients (21). Emeksiz et al. also reported egg sensitivity (78.2%) as the most common food allergen in children with atopic dermatitis; and which was followed by milk sensitivity (52%) and hazelnut sensitivity (39%) (15). Also they reported no peanut sensitivity in patients with AD (15). Similarly, in our study, we detected that hen's egg was the most common (28.4%) allergen and which was followed by milk, nuts, peanuts and other food (banana, sesame, soy, lentil) at 5.7%, 4.8%, 2.2%, 2.2%, respectively.

The severity of AD also affects the prevalence of FS in children with AD. Previous studies reported no or lower level ofsensitization in mild forms, whereas there was higher level of sensitization in moderate-severe forms (22-25). Furthermore, multiple research provide evidence that the prevalence of FA in the general population is believed to be around 0.1-6%. However, more severe forms of AD are more commonly diagnosed in individuals with FA, with rates ranging from 33% to 39% (with uncommon publications reporting even higher rates of up to 80%) (7). Such variations might be attributed to different study designs and populations with different disease severity. There have been several studies showing that FA is strongly associated with a more severe, early onset, and persistent phenotype of AD (16,18,26,27). In our study; according to SCORAD assessment, 140 (61.1%) cases were classified as mild, 67 (29.3%) as moderate, and 22 (9.6%) as severe. In those with moderate to severe severity, the age atonset and diagnosis of AD was lower; eosinophil counts, the frequency of cesarean delivery, and the frequency of atopic sensitization were higher in patients with FS.

According to several studies, the prevalence of FA rates is higher in patients with AD compared to the general population; but not all patients with AD have food allergen sensitivity (17). Patients with both AD and FA were previously reported that more frequently associated with early-onset, severe, or persistent AD (17). Also, Werfel T et al. reported that food sensitizations were proportionally higher in infants with moderate/severe AD, and with increased levels of serum total IgE; and they explained that with atopic conditions of the patients (28). Similarly, in our study, patients with food sensitized had a younger median age at the onset of AD; total IgE and eosinophil count medians were higher, and moderate-severe SCORAD severity was more frequent.

Guidelines do not recommend to perform SPTs in all patients with AD. On the other hand, empirical diets are not recommended too. Because empirical diets with the exclusion of milk, egg, nuts, bananas, strawberries, chocolate, additives, etc may lead to deficiencies in nutrition (9). So, the European Academy of Allergy and

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Clinical Immunology (EAACI) position paper on eczematous reactions to food in AD recommends further investigations if there were AD and a history of an immediate reaction with any foods; or if there were persistent, moderate-to-severe AD, without a history of immediate-reactions to food; or when patients or parents suspected from any food as a trigger factor for persistent AD (28). Also, The National Institutes of Health recommends Children who are younger than 5 years with moderate to severe AD with persistent disease despite appropriate management and topical treatments and/or history of immediate reaction after ingestion of a specific food, should be evaluated about food allergies for milk, egg, peanut, wheat, and soy (29). Emeksiz Z et al reported that serum total IgE level and SCORAD index in three-month-old and younger babies with AD; In addition, they stated that the eosinophil percentage is a useful and easily accessible parameter in predicting the presence of food sensitivity in children between the ages of 3-6 months (15). In our study, multivariate analysis identified AD onset before 3 months, moderate-severe AD, and eosinophils >500/mm^3 as risk factors for sensitization.

There were some limitations in our study; the main limitation is the retrospective manner of our study. Secondly, we evaluated only the sensitization of patients; so our results do not reflect FA; so new studies on FA are needed in this area.

In conclusion; food allergen sensitivity was detected in 31.9% of patients with AD. We found a high risk of detecting FS, especially in patients with age of onset under 3 months, eosinophil count exceeding 500/mm^3, and those presenting moderate-severe AD lesions. We recommend that children in this group should be referred to pediatric allergist for evaluation and to prevent unnecessary elimination diets.

Conflict of Interest: The authors have no conflicts of interest to declare.

*Researchers Contribution Rate Statement***:** Concept/Design: ŞBY, EV; Analysis/Interpretation: ŞBY, EV; Data Collection: ŞBY, EV; Writer: ŞBY, EV; Critical Review: ŞBY, EV; Approver: ŞBY, EV.

*Support and Acknowledgment***:** No financial support was received from any institution or person.

*Ethics Committee Approval***:** The study protocol was approved by the Ankara Research and Training Hospital (Decision number: E- 24- 41).

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