

# Point Prevalence, Risk Factors and Useful Parameters for Food Allergy in Children with Atopic Dermatitis

## Atopik Dermatitli Çocuklardaki Besin Alerjisini Tahminde Kullanılabilecek Parametreler ve Risk Faktörleri, Nokta Prevalans

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### Öz

Atopik dermatit'li çocuklarda besin alerjisi varlığı ve yaygınlığı konusunda fikir birliğine varılamamıştır. Çalışmamızda, okul öncesi çocuklarda atopik dermatit'e eşlik eden besin alerjisi insidansını araştırmak ve bu ilişkiyi tahmin etmede kullanılabilecek parametreleri belirlemeyi amaçladık. Bu vaka-kontrol çalışması, üniversite hastanemizde 2017-2020 yılları arasında SCORAD indeksi >15 olan, 0-6 yaş arası AD'li toplam 401 çocuğun retrospektif bir incelemesidir. Araştırmaya dahil edilen çocukların sosyodemografik özellikleri ve alerji testleri incelenmiştir. Atopik dermatit'in başlangıç yaşına göre çocuklar iki alt gruba ayrılmıştır. (Alt grup I: <24 ay, Alt grup II: ≥24 ay). Atopik dermatit'li hastaların en az bir yiyeceğe karşı besin alerjisi prevalansı %23.6 (n=95) idi. Cinsiyet, çocuğun yaşı, atopik dermatit başlangıç yaşı ve kan eozinofil sayısındaki (KES) artış bağımsız risk faktörleri olarak saptandı. (p-değerleri sırasıyla; 0.047, 0.004, 0.014 ve 0.012). Tamamlayıcı beslenmeye başlama zamanı, akrabalık derecesi ve serum süt spesifik IgE pozitifliği alt grup I için bağımsız risk faktörleriydi (p-değerleri sırasıyla; 0.045, 0.187, 0.019). Alt grup I'deki besin alerjisini tahmin etmede KES için kesme noktası 525 K/mm<sup>3</sup> ve KES/WBC oranı 0.0522 idi (duyarlılık %73.91; özgüllük %63.64). Araştırmamızda belirlenen risk faktörleri ve in-vitro parametreler klinisyenlere AD'li çocuklarda eşlik eden besin alerjisini tahmin etmede yol gösterici olabilir.

**Anahtar Kelimeler:** Atopik Dermatit, Besin Alerjisi, Kan Eozinofil Sayısı, Okul Öncesi Çocuklar

### Abstract

No consensus has yet been reached on the presence and prevalence of food allergy (FA) in children with atopic dermatitis (AD). To investigate the incidence of FA accompanying AD in preschool children and to determine the parameters that can be used to predict this association. This case-control study is a retrospective analysis of 401 children aged 0-6 years with AD who had a SCORAD index of >15 between 2017-2020 at our university hospital. Children were subgrouped regarding the age of onset of AD (subgroup I: <24 months, subgroup II: ≥ 24 months). The sociodemographic characteristics and allergological test results were studied. Food allergy prevalence of patients with AD to at least one food was 23.6% (n=95). Gender, age of the child, and age of onset of AD increase in BEC were the independent risk factors (p=0.047; 0.004; 0.014 and p=0.012, respectively). Time to start complementary feeding, degree of kinship, and serum specific IgE milk positivity were independent risk factors for study subgroup I (p=0.045, 0.187, 0.019, respectively). In predicting FA in subgroup I, the cut-off point for BEC was 525 K/mm<sup>3</sup>, and the BEC/WBCs ratio was 0.0522 (73.91% sensitivity, 63.64% specificity). The risk factors and in-vitro parameters determined can guide physicians in predicting the concomitant FA in children with AD.

**Keywords:** Atopic Dermatitis, Blood Eosinophil Count, Food Allergy, Preschool Children

### Introduction

Atopic dermatitis (AD) is a chronic, itchy inflammatory skin disease that is common in children. AD may represent the initial stage of the concept defined as "Atopic March", which expresses the natural course of the allergic disease sequence in childhood (1). AD, usually associated with the development of immunoglobulin E (IgE) antibodies to food allergens in the early infantile period, may also be associated with food allergy (FA) symptoms (2).

In AD, a food sensitivity can be seen not only as Ig E-mediated hypersensitivity but also as delayed cell-mediated hypersensitivity. In addition to the similarity of the onset times, FA and AD may also

be linked to a causal relationship (3). Besides, deviation in the immune response takes place in both FA and AD. The genetic component is essential in immune deviation, and it has been suggested that the increase in AD and FA in the last decade may be due to epigenomic changes, mainly driven by environmental exposure (4,5).

Three different reaction types to food in AD were defined (6,7). Firstly, non-eczematous reactions such as urticaria, erythema, and pruritus. These are early or immediate-type reactions, Ig-E mediated, usually occurring within the first hour, and may be accompanied by non-cutaneous respiratory or gastrointestinal symptoms or even anaphylaxis. Secondly, there are isolated eczematous reactions with exacerbation of eczema. These are late or delayed-type reactions and are non-Ig E mediated, usually occurring 2-6 hours or days after suspected food intake. Delayed-type reactions can be T cell-mediated or IgE independent reactions to food (8). The mixed type is a combination of eczematous and non-eczematous reactions. Studies to date have shown that the prevalence of FA in AD may vary depending on the severity of AD, the age group tested, the referenced center (primary and referral

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Başvuru Tarihi / Received: 25.08.2020  
Kabul Tarihi / Accepted : 23.01.2021

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center), race, and geographic region. Many studies from high-income countries have shown that children with moderate and severe AD have a sensitivity of about 60% to common foods and about 30-40% of FA associated with food provocation (9-13).

The aim of this study was to investigate the incidence of FA proven with OFC accompanying AD in preschool children and the parameters that can be used to predict this association.

## Material and Method

Our pediatric department is a tertiary care center serving a population of nearly 6 million people. Pediatric allergy and immunology unit usually receive patients from general pediatricians, dermatologists, and general practitioners due to confirmation of initial diagnosis, allergological evaluation, and to receive specialist advice for children with AD. The study was approved by our University Hospital's Ethical Committee (Project/Decision no: 19/412; Meeting no: 2019/18). A total of 401 children, 0-6 years of age, with a diagnosis of AD were analyzed from the hospital's database in years between 2017-2020, retrospectively. The diagnosis of AD was made according to the criteria of Hanifin and Rajka. All families gave agreement to the consent form of allergological assessment of their children.

The severity of AD was evaluated with the SCORAD (Scoring Atopic Dermatitis) index, and children with SCORAD index >15 were included. The exclusion criteria were children who had the diagnosis of asthma, allergic rhinitis, food-induced enteropathy, enterocolitis and/or proctocolitis, and any allergic eosinophilic gastrointestinal disease other than AD. Moreover, children with a history of acute infection and need for systemic, topical or inhaled corticosteroid, montelukast, immunosuppressive, and/or antibiotic use in the last 3 months were not enrolled in the study.

The sociodemographic parameters and allergy histories of children were recorded. Animal contact status was defined as contact with an animal at least several times within one month. Frequent infection evaluation was made according to the ten stimulating signs for primary immunodeficiency, represented by the Jeffrey Modell Foundation. Any missing information was completed with a phone call to families.

All laboratory findings of AD patients at the time of diagnosis were studied including, Wbc (K/mm<sup>3</sup>), blood eosinophil count (BEC) (K/mm<sup>3</sup>) (performed with Beckman Coulter LH 780), total IgE, milk, casein, egg, and wheat flour specific IgE (kU/L) levels, skin prick test (SPT), and hospital-based open oral food challenge test (OFC) results.

Serum total IgE and food-specific serum IgE levels were measured using the CAP System

fluorescence-enzyme immunoassay (CAP limit of the assay 0.35 KUA/L, Pharmacia Diagnostics, Uppsala Sweden). Food-specific IgE level  $\geq 0.35$  KUA/L were considered positive. Food specific IgE selection was determined according to the patient's history and/or SPT results.

SPT was done with the aeroallergens recommended in Global Allergy and Asthma European Network position paper with the same methodology (14). Concerning the food allergens milk, egg yolk, and white, wheat flour, potatoes, green lentils, red lentils, peanuts, hazelnuts, walnuts, almonds, and soy (Allergopharma, Reinbek, Germany) were used. Modified SPT was performed for milk and egg by using raw egg white, yolk, and 2% drops of daily milk. If the initial SPT results were incompatible with the patient's history and clinical status, SPT was performed with additional food antigens.

Food selection was made for the open OFC test based on a history of hypersensitivity to food and SPT and/or food-specific IgE results. Although the allergometric tests were negative, the OFC test was performed with a suspicious food, if there was a history of hypersensitivity to nourishment. If the patient's history and food-specific IgE and/or SPT results were negative, the OFC test was not performed (Figure 1).

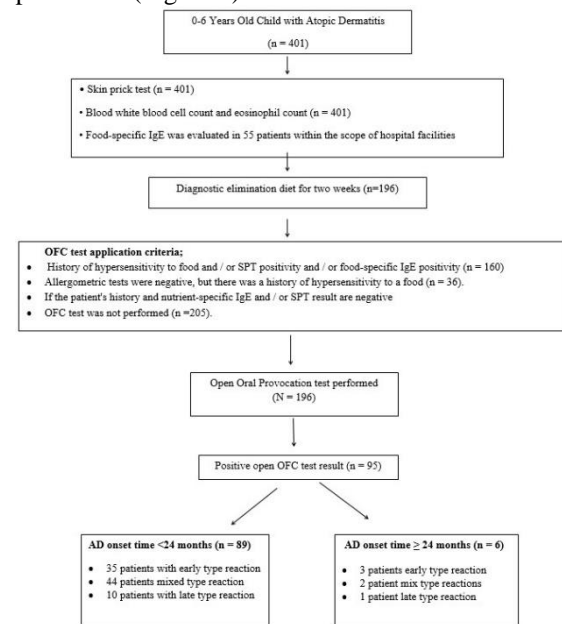


Figure 1. Study flow chart built upon hospital protocol.

All forms of suspected nutrients were removed from the patient's diet at least two weeks before the OFC test. In case of exacerbation of AD during the elimination diet, patients were asked to refer to the hospital. OFC test was performed when the skin lesions were under optimal control, in 7 to 14 days after discontinuation of all medications. If the child is sensitive to more than one food, OFC has performed for each nutrient at least one week apart on different days.

The initial oral provocation doses were determined based on the type of food, the patient's history, and the expected reactions. Provocation doses were gradually increased (max: 6 doses) until they reached the required daily intake for the age. Oral provocation test intervals were 15 min if IgE-mediated food sensitivity was suspected, and 45 min if non-Ig E-mediated food sensitivity was suspected. The criteria used to determine the outcome of food provocation included only signs and symptoms that had just begun objectively (15). Positive OFC results were divided into early, late/delayed and mixed reactions.

The patients were observed for 2-4 hours after a positive OFC and at least 2 hours after a negative test. Families were phoned 48-72 hours after OFC to question child's well-being and late symptoms. The diagnosis of FA was made as an early and/or late reaction to at least one food in the open-controlled OFC test.

The clinical phenotype of the enrolled children was determined according to the age of onset of AD (16), as subgroup I (very early-onset; <24 months) and subgroup II (early-onset; ≥24 months). The quantitative parameters and risk factors that can be used to predict FA that may accompany during the diagnosis of AD were investigated. Secondly, the change of these parameters between subgroups were examined.

Data were analyzed with IBM SPSS V23. The Shapiro Wilk test examined compliance with a normal distribution. Independent samples t-test was used to compare the normal distribution of the data according to additional allergic disease. The double logistic regression analysis method was used to determine independent risk factors affecting the additional allergic disease. Analysis results were presented as percentages for the frequency of categorical data and as mean standard deviation, minimum, and maximum values for quantitative data. Logistic regression analysis results were expressed as OR (95% CI). The significance level was taken as p<0.05. Cut-off values according to FA were examined by ROC analysis, and the results were presented as AUC, Sensitivity, Specificity, PPV, NPV, and Accuracy.

## Results

The mean (±SD) age of 401 Caucasian origin children was 41.27±11.04 months. Of those, 28.9% were female (n=116) and 71% (n=85) were male. The demographic parameters of children are summarized in Table 1. The onset age of symptoms of AD was 14.93±22.79 months, the time length of breastfeeding of AD infants was 11.43±5.35, and the start of complementary foods to infants of AD was 6.78±1.37 months.

**Table 1.** Sociodemographic characteristics of preschool children with atopic dermatitis.

	Patient count (n)	Percentage (%)
<b>Sex</b>		
Female	116	28.9
Male	285	71.1
<b>Birth Time</b>		
Premature	25	6.2
Mature	376	93.7
<b>Kinship</b>		
None	367	91.8
1 <sup>st</sup> Degree	10	2.4
2 <sup>nd</sup> Degree	7	1.7
3 <sup>rd</sup> Degree	8	1.9
Far relative	8	1.9
<b>Breastfeeding</b>		
Yes	397	99.1
No	4	0.9
<b>Vaccination status in preschool children with atopic dermatitis</b>		
Yes	397	99.1
No	4	0.9
<b>The living environment in preschool children with atopic dermatitis</b>		
Village	1	0.3
Town	394	99.5
Village+Town	1	0.3
<b>Domestic animal feeding status after birth</b>		
None	383	96.5
Cat	6	1.4
Dog	5	1.2
Parakeet	7	1.7
<b>Getting over frequent infectious disease status in preschool children with atopic dermatitis according to Jeffrey Modell Foundation</b>		
Yes	31	7.8
No	370	92.2
<b>Hospitalization history in preschool children with atopic dermatitis</b>		
Yes	7	1.8
No	394	98.2
<b>Allergic disease existence in the family</b>		
No	240	60
Atopic dermatitis	28	6.9
Asthma	70	17.4
Allergic rhinitis	38	9.4
Food Allergy	6	1.4
Drug Allergy	2	0.5
Insect bite/venom allergy	1	0.2
Chronic idiopathic urticaria	6	1.4
<b>Autoimmune disease status in the family</b>		
No	382	95.5
Familial Mediterranean fever	1	0.2
Psoriasis	2	0.49
Type 1/Type 2 Diabetes Mellitus	3	0.7
Inflammatory bowel disease	1	0.2
Hashimoto Thyroiditis	3	0.7
Celiac disease	1	0.2
Rheumatoid Arthritis	4	0.99
<b>The living environment in pregnancy</b>		
Village	5	1.3
Town	394	98.2
Village+Town	2	0.5

Animal contact status in pregnancy		
No	386	96.2
Cat	5	1.2
Dog	4	0.9
Parakeet	6	1.4
How long has the mother been in contact with the animal during pregnancy?		
No	386	96.2
1 <sup>st</sup> trimester	7	1.7
2 <sup>nd</sup> trimester	5	1.2
3 <sup>rd</sup> trimester	1	0.2
Throughout pregnancy	2	0.5

The laboratory data of AD children are presented in Supp. Table 1. In 55 patients (13.7%), at least one food-specific IgE value was examined. Serum specific IgE positivity of patients ( $\geq 0.35$  KUA/L) were against to milk in 65.4% (n=36), casein in 36.3% (n=20), egg in 41.8% (n=23) and 3.6% (n=2) in wheat flour.

SPT was positive in 39.9% (n=60) of 401 AD patients, with sensitivity to at least one food in SPT (n=153; 37.4%). SPT showed the highest sensitivity to egg (n=9; 9.7%) (Table 2). OFC test was performed to 196 (48.8%) patients with suspicion of FA. In the hospital-based OFC tests of AD patients (23.6%; n=95); 38 had early, 11 had late and 46 had mixed type reactions against at least one food. 6 patients with positive OFC tests had an AD onset time  $\geq 24$  months; 3 early-type (one in egg white, one in cow's milk and one in multi-food), 2 mixed types (one in egg, one in multi-food) and one late-type (egg white) reaction. The highest positivity in OFC was with egg white in 37 patients, secondly with milk in 28 patients, and at least two foods in 16 patients.

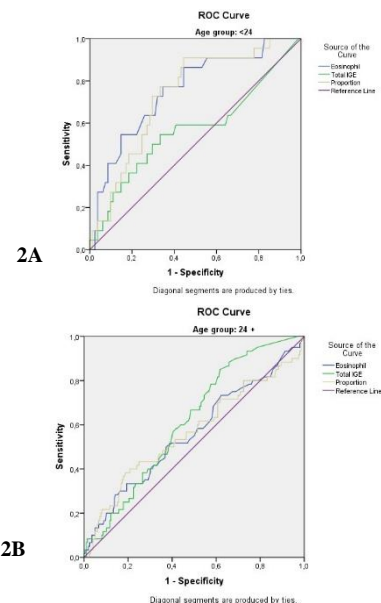
**Table 2.** Skin prick test and food provocation test results of preschool children with atopic dermatitis.

	Patient count (n)	Percent (%)
<b>Skin Prick Test</b>		
Positive	160	39.9
Negative	241	60.1
Total	401	
<b>Skin test Positivity Results</b>		
Milk	17	4.2
Egg yolk	10	2.4
Egg whites	8	1.9
Egg yolk+Egg whites (Egg)	39	9.7
Wheat flour	8	1.9
Soy	3	0.7
Potato	8	1.9
Hazelnut	3	0.7
Multiple nuts	1	0.2
Multiple foods	50	12.4
Domestic inhaled allergens (house dust, mold., animal epithelium, cockroaches)		
Out-of-home inhaler allergens (pollen)	3	0.7
Home/outdoor inhaler allergens+Food allergens	7	1.7
<b>Food provocation results</b>		
Positive	95	23.6
Negative	101	25.2
Total	196	48.8

According to the presence of FA accompanying AD, only serum total IgE mean values were significantly different (p=0.002). The mean value of FA was 144.7, while the mean value was 62 for those without FA (Table 3).

The risk factors associated with AD, which may affect the presence of FA, were examined by dual logistic regression analysis (Table 4). The gender, age of the child, and age of onset of AD were found to be independent risk factors socio demographically (p=0.047, 0.004 and 0.014, respectively). As a laboratory parameter, increased BEC has been identified as an independent risk factor on the presence of FA in AD patients, and increases the risk of the existence of FA by 1001 times (p=0.012).

In subgroup analysis time to start complementary feeding, degree of kinship and serum specific IgE milk positivity were independent risk factors for study subgroup I (n=334), [p=0.045, OR (95% CI)=0.444 (0.201-981); p=0.187, OR (95% CI)=0.187 (0.05-0.693); p=0.019, OR (95% CI)=0.012 (0-0.478), respectively]. In subgroup II (n=67), serum total IgE and specific IgE egg positivity were the independent risk factors [p=0.042, OR (95% CI)=1.005 (1-1.01); p=0.042, OR (95% CI)=0.169 (0.031-0.934), respectively]. The cut-off point for BEC was 525 K/mm<sup>3</sup> in study subgroup II in predicting the presence of concomitant FA. The significant cut-off value for BEC/WBCs ratio was 0.0522 (Figure 2A, Supplemental Table 2). Serum total Ig E level above 26.85 kU/L was significant for FA concomitant with AD in study subgroup II (Figure 2B, Supplemental Table 2).



**Figure 2.** 2A, and 2B. The eosinophil count, Total Ig E value and Eosinophil count / White blood cell count ratio for the presence of concomitant food allergy in preschool children with atopic dermatitis (subgroups I and II).

**Table 3.** Comparison of quantitative data according to the presence of food allergy in preschool children with atopic dermatitis.

	Negative Food Allergy				Positive Food Allergy				P value
	Median	S.Deviation	Minimum	Maximum	Median	S.Deviation	Minimum	Maximum	
WBC (K/mm <sup>3</sup> )	10226.5	7660.2	950.0	120000.0	10137.2	2996.7	4400.0	22100.0	0.900
Eosinophil count (K/mm <sup>3</sup> )	477.1	554.0	20.0	5200.0	568.6	506.1	1.0	2920.0	0.121
Eosinophils count / WBC ratio	0.048	0.045	0.0026	0.368	0.054	0.039	0.0001	0.182	0.176
Total Ig E (kU/L)	62.0	163.7	1.0	1931.0	144.7	351.3	3.8	3010.0	0.002

**Table 4.** Logistic regression of independent risk factors affecting the presence of food allergy in preschool children with atopic dermatitis.

Sociodemographic Characteristics of Preschool Children with Atopic Dermatitis	Multivariate (Enter Metodu)	
	OR (%95 CI)	p-value
Sex (male)	2.112 (1.009-4.419)	0.047
Age (month)	1.0288 (1.009-1.047)	0.004
Age of onset of atopic dermatitis (months)	0.967 (0.942-0.993)	0.014
Birth time	0.558 (0.182-1.706)	0.306
Time to take breast milk of the child	1.018 (0.967-1.072)	0.493
Supplement food starting time of child	0.877 (0.682-1.127)	0.305
Degree of kinship between parents (Mother and Father)	0.698 (0.231-2.104)	0.523
Vaccination Status of Child	2.101 (0.361-12.219)	0.408
Getting over frequent infectious disease status of child	0.47 (0.148-1.493)	0.200
Hospitalization status of the child	0.58 (0.066-5.105)	0.623
Atopic disease existence status of family	0.917 (0.47-1.79)	0.800
Autoimmun disease existence status of family	0.821 (0.234-2.881)	0.758
<b>Laboratory Parameters of pre-school children with atopic dermatitis</b>		
WBC	1 (1-1)	0.685
Eosinophils count	1.001 (1-1.002)	0.012
Total Ig E Level	1.001 (0.999-1.004)	0.267
Specific Ig E Milk	0.58 (0.242-1.386)	0.220
Specific Ig E Casein	1.829 (0.772-4.33)	0.170
Specific Ig E Egg	0.731 (0.259-2.061)	0.554
Specific Ig E Wheat flour	0.319 (0.071-1.431)	0.136
Determining Positivity in the skin prick test	0.504 (0.141-1.805)	0.293

**Supplemental Table 1.** Laboratory values of preschool children with atopic dermatitis.

	Patient count (N)	Median±SD	Minimum	Maximum
WBC (K/mm <sup>3</sup> )	401	10197±6494.5	950	120000.0
Eosinophils (K/mm <sup>3</sup> )	401	507.4±539.7	1.0	5200.0
Total Ig E (KU <sub>A</sub> /L)	401	89.2±244.6	1.0	3010.0

**Supplemental Table 2.** The eosinophil count, Total Ig E value and Eosinophil count / White blood cell count ratio for the presence of concomitant food allergy in preschool children with atopic dermatitis

	Eosinophils count (K/mm <sup>3</sup> )	Total IgE (kU/L)	Eosinophils count/WBC ratio
<b>1<sup>st</sup> study subgroup</b>			
Cut Off	525	13.85	0.0522
AUC (%95 CI)/p	0.754 (0.641-0.868)/<0.001	0.657 (0.419-0.716)/0.334	0.732 (0.622-0.843)/0.001
Sensitivity	73.91 (51.59-89.77)	81.69 (70.73-89.87)	73.91 (51.59-89.77)
Specificity	63.64 (52.69-73.63)	37.16 (30.73-43.94)	65.91 (55.03-75.68)
PPV	34.69 (26.89 – 43.42)	29.74 (26.70-32.97)	36.17 (27.96-45.28)
NPV	90.32 (82.17-94.98)	86.17 (78.73-91.30)	90.62 (82.70-95.13)
Accuracy	65.77 (56.16-74.51)	48.10 (42.21-54.02)	67.57 (58.03-76.15)
Cut Off	355	26.85	0.0397
<b>2<sup>nd</sup> study subgroup</b>			
AUC (%95 CI)/p	0.560 (0.473-0.646)/0.162	0.616 (0.541-0.691)/0.006	0.564 (0.475-0.654)/0.132
Sensitivity	60.56 (48.25-71.97)	64.79 (52.54-75.76)	59.15 (46.84-70.68)
Specificity	50.46 (43.63-57.28)	53.21 (46.35-59.98)	57.34 (50.48-63.99)
PPV	28.48 (24.04-33.40)	31.08 (26.53-36.03)	31.11 (26.08-36.64)
NPV	79.71 (74.10-84.36)	82.27 (76.77-86.69)	81.17 (76.11-85.36)
Accuracy	52.94 (47.01-58.81)	56.06 (50.12-61.86)	57.79 (51.86-63.55)

AUC: Area under the curve, CI: Confident Interval, PPV: Positive Predictive Value, NPV: Negative Predictive Value.

## Discussion

Three significant results have been reached in predicting the presence of FA at the time of AD diagnosis in children. Firstly, gender, age, the age of onset of AD, and BEC were determined as independent risk factors. Secondly, for patients, who started AD very early, time to start complementary feeding, kinship degree, and serum specific IgE milk positivity were independent risk factors, whereas, for patients with early-onset AD, serum total Ig E and specific IgE egg positivity were independent risk factors. Thirdly, in the evaluation of the presence of concomitant FA with quantitative data, a significant cut-off was determined for BEC and a ratio of BEC/WBC for patients with very early AD onset age. Besides, a significant cut-off value for serum total IgE in patients with early-onset AD was identified.

Schloss et al. first reported the patients recovered from AD after the elimination of disturbing foods and demonstrated the relationship between FA and AD clinically (17). Then in many studies, food sensitivity was shown to be critical in the pathogenesis of AD (18). The prevalence of FA in AD varies between 33% and 75% (19,20). This wide prevalence range may be the result of differences in the definition of FA in AD or referral of patients with severe AD to the tertiary centers (6,7). This study was also performed in a tertiary care center, in which patients were directed to allergy and immunology clinics from Pediatrics and Dermatology departments. FA confirmed by OFC was detected in 23.6% of our AD patients simultaneously.

Early-type reaction was found in 19.3%, late-type reaction in 5.6%, and mixed type reaction in 23.4% of our patients, who underwent OFC test. AD was mostly accompanied by mixed food reactions. Werfel T et al. reported isolated eczematous responses in 10-25% and mixed type reactions in 40% of OFC tests in patients with AD (8). In this study, 9.7% of the SPTs showed the highest sensitivity to egg and 12.4% sensitivity to at least two nutrients. Similarly to us, Dharma et al. reported that allergen sensitization patterns in children with AD between 1-3 years of age were most susceptible to food, egg, milk, and peanut, respectively (21). In the OFC tests of our patients, the highest positivity was found against egg white, milk at the second frequency, and at least two foods at the third frequency. Likewise, in the literature, it is emphasized that more than 90% of the food allergies in children with AD are responsible for cow's milk, eggs, peanuts, soy, nuts, and fish.

In this study, only serum total IgE mean values were significantly different in preschool age children with AD, according to the presence of concomitant FA. Serum total Ig E mean value of those with FA was more than twice as high as those without FA. In contrast, Beken et al. did not report any significant

difference in serum total Ig E value between the moderate-severe eczema group and mild-severe eczema among children ages 0-18 (22). We speculate that the difference might be associated with the type of FA reactions of children enrolled in their study.

There are few studies in identifying risk factors, in-vitro tests that can be used to predict the presence of FA in children with AD. Mailhol et al. identified age, AD onset age, and severity of AD as risk factors for FA that may accompany AD in children aged 0-18 years (23). In addition to these parameters, we had also identified gender, age, and age of onset of AD, and BEC as independent risk factors for FA concurrent with AD. Accordingly, the increase in BEC in pre-school children with AD increases the risk of accompanying FA by 1001-fold. Noh et al. reported an FA rate of 70.8% in the AD group with high BEC in children with a mean age of 14-15, who had eczematous AD. The majority of these cases were late-type eczematous FA (24).

The Filaggrin (FLG) mutation as a genetic susceptibility may have a significant role in the pathogenesis of AD. Patients with FLG mutations tend to have early-onset, severe, and persistent AD and are more likely to have asthma and allergic sensitivities (25,26). FLG mutation was determined as an important risk factor for IgE-mediated peanut allergy and blamed epithelial barrier dysfunction in the pathogenesis (27). Similarly, we found that the increased degree of kinship in infants, whose atopic symptoms started very early, increases the risk of FA.

Spergel et al. aimed to determine serum specific Ig E cut off value of 6 nutrients (milk, egg, peanut, soybean, wheat flour, and seafood) in predicting FA in 3-18 months children with mild to severe AD. They concluded with the useless of using food-specific IgE to predict the development of FA clinically (28). However, we found only serum milk specific IgE and total IgE as an independent risk factor for the development of FA for patients, who had very early-onset AD.

High blood eosinophil counts were reported by Noh et al. as a predictor of anticipating FA in children with AD with a mean age of  $14.3 \pm 14.7$  years. They recommended only elimination diet in patients with eczematoid AD with high eosinophilia [ $>5\%$ ,  $\text{mean} \pm \text{SD} = 8.9 \pm 5.0\%$ ,  $\text{TEC} = 10.9 + (7.15 \times \text{EOS}\%)$ ] (24). Although we determined a significant cut-off value of BEC and BEC/WBCs ratio in predicting FA in children, who had very early-onset AD, this was not the case for children, who had early-onset AD.

To date, elevated serum total IgE levels have not seen as a non-specific marker affecting the interpretation of food-specific IgE in patients with allergic disorders. Therefore, it is reasonable not to recommend measuring total IgE levels in the evaluation and treatment of FA (29). However,

Federly et al. reported that there was a significant and parallel relationship between serum total IgE and food-specific IgE levels, in particular with egg, milk, peanut, and soy (30). In a way of supporting them, we found a significant cut off value for serum total IgE value in predicting FA in children with early-onset AD with a sensitivity and specificity of 65% and 53%, respectively. The correct use of serum total IgE in FA prediction in children with AD deserves further studies.

The limitations of this study were its retrospective design and the lack of food-specific IgE parameters in our patient group due to the limited laboratory facilities. Concomitant FA reactions in our children with AD differed according to the OFC test results, and the number of patients for these three types of food reactions was relatively low. Therefore, studies with a higher number of patients are needed for all three types of nutritional reactions in AD.

Consequently, approximately one-third of children with AD have food allergies. We suggest that the parameters that will help to predict the presence of FA in AD patients will not only determine the accompanying FA but will also prevent unnecessary food elimination in these children, which is highly essential in their age of growth.

#### Acknowledgment

My special thanks to Naci Murat (Assoc. Prof.) for assistance in performing the statistical analysis of the research data. I am also grateful to Ozlem Ezgingil (Nurse), who served with love for our patients.

**Ethics Committee Approval:** The study was approved by University of Health Sciences, Gulhane Research and Training University Hospital's Ethical Committee (Project/Decision no: 19/412; Meeting no: 2019/18).

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