Risk factors of severe atopic dermatitis in childhood: single-center experience

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SUMMARY: Akan A, Azkur D, Civelek E, Erkoçoğlu M, Yılmaz-Öztorun Z, Kaya A, Özcan C, Vezir E, Toyran M, Dibek-Mısırlıoğlu E, Kocabaş CN. Risk factors of severe atopic dermatitis in childhood: single-center experience. Turk J Pediatr 2014; 56: 121-126.

The aim of this study was to evaluate the risk factors of disease severity to facilitate better management of children with severe atopic dermatitis (AD). All the patients were diagnosed using Hanifin-Rajka criteria. After medical and family histories were obtained and a detailed physical examination was performed, disease severity was determined with the objective SCORing Atopic Dermatitis (SCORAD) index. Skin prick tests were performed, and percent of peripheral blood eosinophils, total serum IgE and specific IgE were measured. The median age of the 501 patients was 15 months (interquartile range [IQR]: 6-40 months), and 62.9% (315) were male. Sensitization to at least one allergen and foods was observed in 40.3% (202) and 30.9% (155) of all patients, respectively. Of the study group, 17.6% (88) had severe disease. When logistic regression analyses were performed, with adjustments, the risk factors for severe AD were determined to be eosinophilia (odds ratio [OR] 1.137, 95% confidence interval [CI] 1.062-1.217; p=0.003) and food allergen sensitization (OR: 1.937, 95%CI: 1.217-3.084; p=0.005). The patients with severe AD had sensitization to common allergens, food allergens and eosinophilia more frequently than those with mild-moderate disease (p=0.001, p=0.001 and p=0.005, respectively). Eosinophilia may predict severe disease and allergic sensitization. Further large-scale follow-up studies are needed to improve the reliability and relevance of this relation.

Key words: severe atopic dermatitis, child, objective SCORAD, risk factors.

The prevalence of atopic dermatitis (AD) is increasing. In industrialized countries, it affects 15-30% of children[1]. It commonly presents during early infancy, but may persist or begin later in childhood or even in adulthood[2]. AD is characterized by itchy dry skin, eczematous flares, and age-specific distribution, with or without allergic sensitization[1,2].

The severity of eczema varies among children with AD. There are several scoring systems in clinical use to identify the severity of eczema. Objective SCORAD (SCORing Atopic Dermatitis) is the scoring system of choice, particularly in recent clinical studies about AD[3,4]. The patients with moderate-severe disease need further investigation and immediate evaluation for triggering factors in order to treat the eczema and improve quality of life. There are studies relating eczema severity with density of *Staphylococcus aureus* colonization on the skin, with biological markers as interleukin-18, serum CCR4 ligands, total serum immunoglobulin E (tIgE), and transepidermal water loss[5-8]. However, most of these parameters are not appropriate for use in daily clinical practice.

In this study, we aimed to make a contribution to identify the clinical characteristics of children with AD and to investigate the risk factors of severe disease in childhood AD using the objective SCORAD index.

Material and Methods

Patients with Clinical and Laboratory Investigations

Five hundred and one children who were diagnosed as AD in the Pediatric Allergy Division of our tertiary hospital from January 2010 to June 2012 were included in the study. They were not using any treatment at the time of enrollment and almost all had skin lesions. The medical and family histories were taken from their caregivers. Family history of atopy was defined as having at least one parent with physician-diagnosed asthma and/or allergic rhinitis. The patients were also questioned about prenatal and current tobacco exposure. All of the patients were evaluated by the same group of pediatric allergists (AA, DA, EC). All patients fulfilled the criteria of Hanifin and Rajka[9]. Disease severity was determined according to the objective SCORAD index[10]. Skin prick tests (SPT) and laboratory investigations were performed. Patients with positive results in SPT and/or specific IgE tests were accepted as "sensitized".

The study was approved by the Ethical Review Board of our hospital. Informed consent was received from the caregivers and the patients.

Skin Prick Test

Skin prick test (SPT) was performed on the volar aspect of the forearm for foods (cow's milk, hen's egg white, wheat, peanut, soy, and fish) and common aeroallergens (Dermatophagoides, cockroach, animal danders, fungi, and mixed grass pollens). All SPTs were performed using commercial extracts (Laboratoire Stallergenes, France). Temoline was used as negative and histamine (10 mg/ml) as positive control. Reaction was evaluated after 15-20 minutes. The test was considered positive if the wheal diameter was at least 3 mm greater than that of the negative control[11].

Laboratory Investigations

The percent of peripheral blood eosinophils was determined by complete blood count. tIgE was measured in all patients with nephelometric method (Siemens Healthcare Diagnostics Products; Marburg, Germany).

Specific serum IgE levels were measured with fluorescence enzyme immunoassay (FEIA) as proposed by the manufacturer (UniCAP, Phadia; Uppsala, Sweden). Specific IgE tests were defined as positive if the results were above the detection limit (≥0.35 kU/L).

Severity Assessment of Eczema

The severity of AD was determined according to the objective SCORAD index[10], which consists of A and B scores. The A score is the definition and grading of intensity items. Six items are selected: erythema, edema/papules, oozing/crusts, excoriations, lichenification, and dryness. Each item may be graded from 0 to 3 (0=absent, 1=mild, 2=moderate, 3=severe), and thus, the A score ranges from 0-18. The B score grades the extent of eczema and is indicated as percent of the patient's total body surface. It ranges from 0-100. The total final score is calculated as A/5+7B/2. The patients with a total score under 15 were classified as mild, 15-40 as moderate, and over 40 as severe AD [10].

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 15.0 (SPSS Inc.; Chicago, IL, USA) software was used for the statistical analysis of the obtained data. The definitions were provided as number and percentage for discrete variables and mean and standard deviation or as median and interquartile range (IQR) for continuous variables. Chi-square test was used for discrete variables of two unrelated groups, and Mann-Whitney U test for constant variables not distributed normally. Spearman's rank correlation coefficients were assessed as measures of correlation between variables of interest. To analyze the risk factors of severe AD, logistic regression analyses were performed. The variables with p values less than 0.25 in univariate analyses were evaluated with multivariate analyses. Statistical significance was defined as $p<0.05$.

Results

Characteristics of the General Study Population

The study group consisted of 501 children with AD, whose median age was 15 months (IQR: 6-40 months), and of whom 62.9% (315) were male. The median age of disease onset was 4 months (IQR: 2-12). Ninety-seven percent of the patients were exclusively breastfed, while 27.9% had cow's milk in the first year of life. Mothers of 12% of patients smoked during

pregnancy, and parents of 51.9% of patients smoked at home. Twenty-two percent (110) of the patients had a family history of atopy.

The median total objective SCORAD score of the study population was 25.8 (IQR: 15.7-35.5). According to classification of severity, 23.4% (117) of the patients had mild, 59.1% (296) moderate and 17.6% (88) severe AD; 17.8% (89) of the patients had coexistent allergic diseases like asthma and/or allergic rhinitis.

Among all patients, 40.3% (202) had IgE-mediated allergic sensitization to at least one allergen. Regarding patterns of allergic sensitization, 30.9% (155) of the study group had sensitization to foods, 14.4% (72) to aeroallergens and 5% (25) to both foods and aeroallergens. Median percent of blood eosinophils was 3.5 (IQR: 2.0-5.5). Forty percent of patients had blood eosinophils ≥4%.

Characteristics of the Patients with and without Allergic Sensitization

When the patients were divided into two groups according to presence of IgE-mediated allergic sensitization, there was no difference between the groups in age, gender, age of disease onset, and family history of atopy ($p>0.05$). The patients with sensitization had coexistent allergic diseases more frequently than those who were not sensitized (49% and 39%, respectively; $p=0.001$). The prevalence of current tobacco exposure was significantly higher in the sensitized group than in patients without sensitization (57.2% and 48.1%, respectively; $p=0.047$). Regarding disease severity, the sensitized patients had a higher objective SCORAD score than patients without sensitization (29 and 23.5, respectively; $p<0.001$). Severe AD was significantly more frequent in the sensitized group than in patients without sensitization (49% and 39%, respectively; $p=0.004$). Total peripheral blood eosinophil percent was significantly higher in the sensitized group than in patients who were not sensitized (4% and 3%, respectively; $p<0.001$). In the sensitized group, tIgE was significantly higher than in the group without sensitization (45 IU/ml and 21 IU/ml, respectively; $p<0.001$).

Characteristics of the Groups of Disease Severity

The study group was evaluated as mild-moderate and severe AD. The patients with severe AD had IgE-mediated allergen sensitization more frequently than those with mild-moderate disease ($p=0.001$) (Table I). As the allergens were assessed separately as foods and aeroallergens, the patients with severe AD had food allergen sensitization more frequently than those with mild-moderate disease ($p=0.001$). Total peripheral blood eosinophil percent was significantly higher in the severe AD group when compared with the mild-moderate AD group ($p<0.001$). Total peripheral blood eosinophil percent was significantly correlated with objective SCORAD score ($r=0.209$, $p<0.001$). tIgE did not differ between the groups according to disease severity ($p=0.542$), and there was no correlation between IgE and objective SCORAD score ($r=0.012$, $p=0.797$).

Eosinophilia (odds ratio [OR]: 1.137, 95% confidence interval [CI]: 1.062-1.217; $p=0.003$) and food allergen sensitization (OR: 1.937, 95%CI: 1.217-3.084; $p=0.005$) were found to be risk factors for severe AD when logistic regression analyses were performed, with adjustment for age, tIgE, presence of allergic sensitization, family history of atopy, and coexistent allergic disease (Table II).

Discussion

In the present study, the clinical and laboratory characteristics of 501 children with AD were evaluated, and the risk factors of severe AD were defined. The frequency of food sensitization and the percent of peripheral blood eosinophils were significantly higher in the patients with severe AD. Eosinophilia and food allergen sensitization were risk factors for severe AD.

Children with AD may have varying severity of eczema. In our study, one-fifth of the children had severe AD according to objective SCORAD. The severity distribution of our study population was similar to that of the study conducted by Ricci et al.[12], who used the SCORAD index to determine eczema severity.

In AD, 60-80% of patients have IgE-mediated sensitization. Food allergy plays an important immunopathogenic role in 30-50% of young children with AD[1]. Of our study population, 40.3% revealed IgE-mediated sensitization and 30.9% had sensitization to foods. In a study from East Germany, 41.9% of the

Table I. The Comparison of the Clinical and Laboratory Characteristics of Patients According to Disease Severity

	Mild-Moderate AD (n=413)	Severe AD (n=88)	p
Gender (male)	61.7 (255)	68.2 (60)	0.256
Age (month)	16 (7-41)	11 (6-37)	0.117
Age of disease onset (month)	4 (2-12)	3 (1-10)	0.056
Breastfed patients	98.3 (401)	96.6(85)	0.305
Cow's milk in the first year of life	30.6 (114)	32.1 (26)	0.798
Family history of atopy	21.0 (86)	27.3 (24)	0.196
Prenatal tobacco exposure	12.8 (51)	10.3 (9)	0.536
Current tobacco exposure	53.2 (219)	46.6 (41)	0.263
Percent of eosinophils (%)	***3.2 (2.0-5.2)***	***4.6 (3.0-7.4)***	***<0.001***
Eosinophil percent >4%	***35.3 (143)***	***59.8 (52)***	***<0.001***
Patients with allergic sensitization	***37.2 (153)***	***55.7 (49)***	***0.001***
With food sensitization	***27.7 (114)***	***46.6 (41)***	***0.001***
With aeroallergen sensitization	13.9 (57)	19.3 (17)	0.192
IgE (IU/ml)	28.7 (16.4-93.9)	31.3 (13.5-170.5)	0.544
Coexistent allergic diseases (asthma, allergic rhinitis)	16.7 (69)	22.7 (20)	0.180
History of wheezing (at least one episode)	31.2 (129)	36.4 (32)	0.350

Data shown as percent (absolute numbers) and median (interquartile range); statistically significant data shown in bold and italic.

study population was reported to have allergic sensitization, which was similar to our results[13]. In the study by Ricci et al.[12], in which the study population consisted of children with AD aged 6-36 months, the frequency of sensitization to foods and inhalant allergens was reported as 37.1% and 25.9%, respectively, in accordance with our results. Park et al.[14] reported a relation between allergic AD and higher SCORAD score for young children. In two other studies, food allergen sensitization was found to be more prevalent in patients with moderate-severe disease compared to those with mild disease[15,16]. In our study, the patients sensitized to food allergens had severe AD more frequently compared with those without sensitization. These data indicate that children with AD with allergic sensitization should be followed more closely, as they may have more severe disease.

Some studies investigating the relation between laboratory parameters and disease severity have been conducted[5,17,18]. Eosinophilia in patients with AD is usually assigned as a nonspecific finding[1]. In our study group, patients with severe AD had a higher percent of eosinophils than those with mild-moderate disease. Additionally, objective SCORAD scores and percent of peripheral blood eosinophils of the sensitized patients were significantly higher than of those not sensitized. Accordingly, in a study in which both children and adults were enrolled, eosinophilia was found to be a predictor of food allergy in patients with AD[19]. Recent studies in both adults[20,21] and children[14,19] have indicated the more prominent role of eosinophils in sensitized patients than in those not sensitized. There are also studies underlining the relation of eosinophil count, eosinophil-associated cytokines and disease severity[17,22]. Regarding these results, it seems that eosinophils indicate both severe disease and allergic sensitization.

Recent studies including children with eczema demonstrated a correlation between severity of AD and tIgE[23,24]. Both of these studies included children who were older than those of our study population. In our study, there was no difference in tIgE between severe AD and mild-moderate AD groups. There was also no correlation between objective SCORAD score and tIgE. This result may be attributed to the younger age of our patients. Park et al.[14] also found no correlation between SCORAD score and serum IgE in the sensitized group of patients with AD. Their study population was younger than two years of age, similar to our study population. In our study, both in the sensitized and not-sensitized groups,

Table II. Risk Factors for Severe Atopic Dermatitis

	Univariate analyses			Multivariate analyses		
Variables	OR	95%CI	p value	OR	95%CI	p value
Age of disease onset	0.995	0.984-1.006	0.347			
Age	0.996	0.990-1.003	0.234			
Male gender	1.328	0.813-2.169	0.257			
Percent of eosinophils	1.179	1.102-1.262	<0.001	1.157	1.079-1.240	<0.001
IgE	1.001	1.000-1.002	0.193			
Allergic sensitization	2.119	1.330-3.375	0.002			
Food sensitization	2.273	1.419-3.641	0.001	1.908	1.163-3.130	0.011
Breastfeeding	0.495	0.125-1.951	0.315			
Cow's milk in the first year of life	1.070	0.639-1.792	0.798			
Family history of atopy	1.413	0.835-2.390	0.198			
Prenatal tobacco exposure	0.790	0.373-1.671	0.537			
Current tobacco exposure	0.769	0.485-1.219	0.264			
Coexistent allergic diseases	1.466	0.836-2.571	0.182			

The variables used for multivariate analyses are shown in italic.
OR: Odds ratio. CI: Confidence interval.

there was no correlation between tIgE and objective SCORAD score. This result may be related with the immature development of the cytokine system in younger children, as was indicated in the study of Park et al.[14]. It has been demonstrated in recent studies that tIgE increases with age[25,26].

Moreover, by epidemiological studies, the factors predicting the development and severity of AD and additional allergic diseases were explored[12,27]. Ben-Gashir et al.[28] especially investigated epidemiological features that may affect the development and course of AD, based on the report of the patients. They found disease onset during the first year of life, area of residence, asthma, and allergic rhinitis to be risk factors of severe AD. In our study population, age of onset was not a risk factor for severe AD. Only 17.8% of patients in our study had coexisting allergic diseases. The mean age in Ben-Gashir's study[28] was 8 years of age, older than our study population. The higher rate of coexistent allergic diseases than in our study group may be due to the older age of their study population.

The advantages of our study are the large number of patients, its single-center design and the fact that the patients were evaluated by the same pediatric allergists. There are also limitations: Our study is a cross-sectional study, and as a result, the defined risk factors are only at a degree of associations. To define the risk factors of severe AD reliably for children, multicenter prospective studies conducted with birth cohorts are needed.

In conclusion, there was a relation between allergic sensitization, eosinophil count and disease severity in young children with AD. The presence of allergic sensitization and eosinophil count may be used to assess disease severity in children with AD. Further, disease severity and elevated percent of peripheral blood eosinophils may help the physician to indicate the possibility of allergic sensitization and investigate the patient with specific tests for allergic sensitization. Peripheral eosinophil percent can be obtained easily in clinical settings and has potential utility in clinical practice. However, further large-scale follow-up studies are needed to improve the reliability and relevance of these tools.

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