The clinical and laboratory findings of infants with atopic dermatitis during diagnosis and follow-up

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SUMMARY

Introduction: The aim of this study is to investigate the relationship between the clinical and laboratory findings of children aged 0-2 years with atopic dermatitis at the time of admission and prognosis during follow-up. **Materials and methods:** The study was conducted in İzmir Health Sciences University Tepecik Training and Research Hospital. The clinical and laboratory data of patients between January 2014 and December 2019 were scanned from the patient records and the hospital data system. **Results:** 102 patients with a median age of 8(9)(min 2- max 24)months were included in the study. The median age of onset of the symptoms was 3(5)(min 1-max 21) months. The patients most frequently (85.2%) presented with eczema and lesions were most common (60.7%) in the extremities. Most of the patients (56.9%) had mild dermatitis. In the 6th month, 26.5% who continued follow-up, had clinical improvement. Food allergy was present in 33.3% of the patients. The most common food allergen was egg (52.9%). Food allergy was associated with the severity of atopic dermatitis (p=0.033), and the symptoms started earlier (p=0.002). There is no relationship between the severity of atopic dermatitis and gender, family history, presence of additional atopic disease, response to treatment, total IgE and eosinophil count (p>0.05); however, it was determined that the symptoms started earlier in patients with moderate/severe atopic dermatitis (p = 0.002). **Conclusion:** Food allergy is more common in the early-onset and moderate/severe atopic dermatitis. Accurate diagnosis of food allergy is necessary to increase the success of treatment and to prevent unnecessary diets.

Keywords: Atopic dermatitis, food allergy, infant, prognosis

İmpact Statement: Food allergy should be investigated at patients with early -onset and moderate/severe atopic dermatitis.

Introduction

Atopic dermatitis (AD) is a chronic, recurrent, inflammatory skin disease that affects 2-20% of the population. Among children, nearly 50% begins in the first year of life and the frequency of the disease decreases by older age(1). More than half of the patients develop asthma and allergic rhinitis later in their life.

Atopic dermatitis etiology is complex; genetic, environmental factors, skin barrier dysfunction, and immune dysregulation take place. Both IgE mediated and non-IgE mediated food allergy can be related to AD. It is reported that most patients with severe disease have food allergy in epidemiologic studies(2). Immune alteration due to changes in epigenome driven by environmental exposure plays a role both in AD and food allergy(3). Prenatal (mother's nutrition, obesity, microbial exposure, etc), perinatal (type of delivery, antibiotics, season of birth), and postnatal early exposure to food allergens influence the development of AD and food allergy. Diagnosis of AD is made by typical morphological distribution of the lesions and history. The Hanifin-Rajka (H-R) criteria is the most common used diagnostic criteria accepted to be the gold standard for diagnosis. Papules, papulovesicules and, eczematous plaques typically affect the face, and extensor surface of extremities in infants. The diaper area is usually spared(4).

Further investigations for food allergy should be done in the following situations according to The European Academy of Allergy and Clinical Immunology (EAACI) position paper on late eczematous

reactions; a) History of an immediate reaction against foods; b) Persistent, moderate-to-severe AD, no history of immediate-reactions to food, no suspected eczematous reactions to food; c) Food is suspected by patients or parents as a trigger factor of persistent AD (without obvious immediate reactions)(5).Identification of the causative allergen is important to improve symptoms of AD. Cow's milk, egg, wheat and soy are the most common allergens during childhood.

Clinic and severity of AD are highly variable. It is valuable for treatment selection and monitoring the response. SCORing AD (SCORAD) index and the Eczema Area and Severity Index (EASI) are validated scoring systems, that evaluate both clinical signs and area of involvement(6,7).

Atopic dermatitis is a chronic relapsing disease. Some of the patients go into remission in late childhood, however, in some cases the disease persists into adulthood. A recent review reported 80% of the patients' AD did not persist by 8 years old age and children younger than 2 years had less persistent disease(8).

In this study, we aim to evaluate the clinical and laboratory findings of children aged 0-2 years who were diagnosed with atopic dermatitis, and to investigate the existence of a relationship between the findings at admission and follow-up findings.

Material and methods

The study was performed at Pediatric Allergy Department of Saglik Bilimleri University Izmir Tepecik Training and Research Hospital and was approved by Saglik Bilimleri University Izmir Tepecik Training and Research Hospital ethics committee (Date: 23.03.2022 No:2020/1-6).

Patients and study design

The hospital records of the patients with atopic dermatitis from 2016 to 2020 were analyzed retrospectively. The patients diagnosed with atopic dermatitis according to Hanifin-Rajka criteria and who were under two years old at the time of admission, without any other chronic disease were enrolled to the study. The patients with another dermatologic disease and, whose follow-up results

could not be reached were excluded from the study. Clinical and demographic characteristics (gender, age at onset of symptoms, age at diagnosis, history of family atopy, symptoms, duration, distribution and severity of lesions, comorbid allergic diseases, treatments, treatment responses) and laboratory data (complete blood count, immunoglobulin levels, skin prick test results, specific IgE levels, oral food challenge results) were recorded from the patient file and hospital registry system.

Laboratory Tests

Results of laboratory parameters were evaluated according to the patient's age and defined as low, normal, or high. The number of eosinophils was >500 /mm^3 or >4% considered eosinophilia. Total serum IgE level >165 UI/ml was defined as elevated IgE.

Skin Prick Tests

Skin prick testing was performed using the prick to prick method with cow's milk, egg white, egg yolk, wheat, soy, peanut and, other suspicious foods. Saline and histamine solutions were used as the negative and positive controls, respectively. The results were evaluated after 15 min. A wheal with a diameter 3 mm greater than the negative control was taken as a positive result. Children with at least one positive skin test were considered as sensitized.

Specific IgE levels

Specific IgE (spIgE) levels were measured by the enzyme-linked immunosorbent assay (ELISA) method for the single allergen (milk, egg white, egg yolk, wheat) and/or multi allergen panel (Food panel 1 contains wheat, codfish, soybean, milk, peanut, egg white spIgE and Food panel 2 contains almond, hazelnut, peanut, or coconut). Test results above 0.35 kIU/L were considered positive(9).

Elimination diet and oral food challenge tests

For the infants who suspected food allergy (and their mothers for breastfed infants), the elimination diet with suspected food was performed for 2-4 weeks and clinical findings of patients were observed. After the elimination diet, for IgE mediated food allergy, oral food challenge was applied in the

hospital. Increasing doses of the offending food at 20 minutes interval were given with a starting dose of %0.1 of the total dose according to PRACTALL guidelines (10). For patients with non-IgE mediated food allergy, the food challenge was applied at home. For completely breastfed infants under six months old, elimination diet and oral food challenges were performed by changes in mothers' diet.

Statistical analysis

Statistical analyses were performed using the SPSS program version 24 ("IBM SPSS 24 (IBM, Armonk, NY, ABD)"). Shapiro–Wilk and Kolmogorov–Smirnov tests were used for the conformity of the data to normal distribution. The results were expressed as frequency (percentage) for categorical data and mean ± standard deviation (SD) for numerical data with normal distribution or median (minimum-maximum and interquartile range-IQR) for numerical data without normal distribution. Independent sample t-test was used to compare continuous variables in two groups with normal distribution; Mann–Whitney U tests were used to compare variables that did not have normal distribution. The *p* values <0.05 were considered statistically significant.

Results

A total number of 102 patients were enrolled in the study. The median age of the patients was 8.0 (9.0) (min. 1, max. 24 months) and 63 (61.8%) of them were male. The median onset age of the symptoms was months 3.0 (5.0) (min. 2, max. 21 months). Thiry-two (31.4%) of the patients had a family history of atopy and 17 (16.7%) of them had a co-morbid allergic disease (14 wheezy child, 1 proctocolitis, 1 allergic rhinitis and, 1 eosinophilic esophagitis). Most of the patients (56.8%) had mild dermatitis. Eczema was the most seen symptom at 87 (85.2%) of the patients at the first evaluation. The other symptoms were skin dryness at 68 (67.3%) and pruritus in 52(50.9%) of the patients. Lesions were seen at extremities mostly. The characteristics of the patients were shown in Table 1.

When laboratory examinations of patients were evaluated, 47 patients (46.1%) had anemia and 20 patients (19%) had eosinophilia. Total serum IgE level was high in 49 (48%) patients. Serum IgA levels were low at 13 patients, IgG levels were low at 13 patients, and IgM levels were low at 7 patients. None of these patients were diagnosed with immune deficiency at follow-up. Fifty-two (51%) of the patients had skin test positivity with at least one of the tested allergens. The most common sensitivity was against egg white (%45.1). At least one food sensitization was detected in 41(58.6%) of 69 patients whose sIgE was measured. Complete blood count, skin prick test, and sIgE levels of the patients were shown in Table 2.

Oral food challenge was applied to 63(61.7%) of the patients; (10.8%)11 at home, 52(51%) at the hospital. Based on laboratory tests and oral food challenge results, 46 food allergy was diagnosed in 34 (33.3%) of the patients. Among food allergic patients 19 (52.9%) had an egg allergy, 12 (35.2%) had both milk and egg allergies, 2 (5.8%) had cow's milk allergy. None of the patients had peanut, wheat, or soybean allergy. A patient who had a history of urticaria with potato had positive food challenge with potato.

Moisturizers were recommended for all patients and local steroid treatment was given to 65(63.7%) patients. None of the patients received systemic treatment. Diet was given to 34 (33.3%) food allergic patients. While treatment response was complete at 39 (38.2%) patients, it was partial at 63 (61.8%) patients. The characteristics of the treatment were shown in Table 3.

When compared the characteristics of patients with and without food allergies, in food allergic patients, atopic dermatitis was more severe ($p=0.033$), and the symptoms had begun earlier ($p=0.002$). There was no difference for gender, history of family and individual atopy and treatment responses, eosinophil counts and sIgE levels between allergic and nonallergic patients ($p>0.05$). The results were shown in Table 4.

Patients were grouped according to the severity of atopic dermatitis (as mild and moderate/severe) and compared for demographic data and clinical findings. There was no statistically significant

difference between the groups in terms of gender, family history, presence of additional atopic disease, allergic food and treatment response ($p>0.05$). In the moderate/severe AD group, the onset age of symptoms was younger, and the difference was statistically significant ($p=0.002$). The results were shown in Table 5.

Clinical and laboratory findings in the 6^{th}, 12^{th}, 24^{th}, and 36^{th} months were examined to evaluate the changes in the follow-up. It was found that most patients without food allergies did not come for outpatient follow-ups. Among the patients who continued to follow up, AD severity decreased in 51 patients. (27 patients in the 6th month, 17 patients in the first year, 6 patients in the second year, 1 patient in the third year). Among 14 patients with cow's milk allergy who continued to follow up, 12 (85.7%) of them recovered in the follow-up period (10 patients in the 6th month, 1 patient in the first year, 1 patient at the second year). Among 22 patients with egg allergy, 15 (68.1%) of them recovered in the follow up period (12 patients in the 6th month, 1 patient in the first year, 1 patient in the second year and 1 patient in the third year. Also, among the patients who continued to follow up new food sensitization occurred in 11 patients. (9 patients in the 6th month, 1 patient in the first year, 1 patient at the second year). The changes in laboratory and clinical findings during follow-up period were shown in Table 6.

Discussion

In our study, it was found that mild AD was the most seen pattern in our patients. AD was accompanied by food allergy in 1/3 of the patients, and egg allergy was the most common food allergen. Also, atopic dermatitis had started earlier and was more severe in patients with food allergies. During follow-up, half of the patients had both food allergies and atopic dermatitis findings regressed in the first 6 months, while almost all had recovered at the age of three.

The median age at onset of symptoms was less than 6 months in our study, which is consistent with the literature. Kay et al., reported that 60% of 1104 patients developed the disease younger than 1

year and ¾ of them were younger than 6 months(11). It was seen that the patients' admissions were 4 months after the onset of the symptoms on average. It was thought that this period between the onset of the disease and the admission of the patients to our outpatient clinic was related to the fact that the patients had to apply to the pediatrician first, the first examination and treatments were started, and the time taken to make an appointment.

Family history of atopy was found in 1/3 of our patients and nearly half of them with maternal history. In a cohort of 4089 children from Stockholm, AD was detected in 39% of those with AD in one parent, in 50% of those with AD in both parents, and 27% of those without atopic history (12). In a prospective study from Sweden, the incidence rate of AD in any parent of the patients was 58%, and atopy in any parent was 69% (13). Laske et al. reported a positive family history for atopic diseases was 60% (14). As it is known that genetic predisposition plays role in the development of allergic diseases, consistent with literature we found the presence of atopy in the family was common in patients with AD.

Weidinger et al. reported EASI and SCORAD as the most performed tests in 32 international AD centers with accurate AD severity (15). It was observed that more than half of the patients in our study had mild AD and almost none of the patients had severe AD. Laske et al., reported that mild and severe disease were detected in 60% and 54% of boys, 40% and 46% of girls, respectively (14). Roehr et al. who used a modified scoring system from Hanifin and Rajka, reported that 62% of the patients had mild, 27% had moderate, and 10% had severe disease (16). Although almost all our patients had mild and moderate atopic dermatitis, which is consistent with the literature, it was noteworthy that the rate of severe disease was much lower than in the literature. In our center, which is a 3rd level hospital, the reason for the low number of patients was that the time between the onset of the complaints of the patients and the admission was long (almost 4 months), and the complaints had partially regressed with the treatments applied during this time.

In our study, more than half of our patients had positive skin prick test and sIgE levels for food. Similar to our results, in a 7-year cohort study conducted in Sweden, 61% of patients younger than 36 months were found to be positive for specific IgE (fx5 food group) (13).

Double-blind placebo-controlled food challenges (DBPCFCs) are the gold standard tests for diagnosing food allergy. Because our children were under two years old, we used open oral food challenges (OFC). We found that approximately 1/3 of the patients with positive skin test did not have a food allergy and the results of the skin test were compatible with the sensitivity. In a study involving 88 patients with AD in children aged 3 months to 7 years in Greece, food sensitivity was found in 39 patients, and 23 of these patients were diagnosed with food allergy (17). It is known that although the negative predictive value of skin prick test and sIgE is high as 90-95%, its positive predictive value is low (50%) (18). Rowlands et al. performed 91 food challenge tests to 19 children with severe AD refractory to multiple therapies. They found a rare relation between foods and eczema and emphasized that diagnosis of food allergy inducing eczema cannot be said without food challenge testing (19). Compatible with the literature, our results are important to show that skin test or sIgE positivity for food is not sufficient for the diagnosis of food allergy and a food challenge test is required.

In our study 1/3 of all AD patients had a diagnosis of food allergy. In a study conducted in South Korea in 2013, the frequency of food allergy in infants with AD was reported to be 37.1% in 0-5 month-old infants and 38.5% in 6-11 month infants (20). Mavroudi et al. reported that in children aged three months to seven years, food allergy was found in 26% of AD patients(17). The presence of food allergy in our patients with AD was found to be compatible with studies conducted in other countries. In our study, more than half of the patients with food allergy were found to be allergic to egg white and yolk. This was followed by milk allergy in 1/3 of the patients and more than half of the patients had both milk and egg allergies. None of our patients had sensitization to soy, peanut, or wheat. Mavroudi et al. reported milk (80%) had the most common sensitization rate in their study, followed by the egg (55%), wheat (20%), cod, and soy (2.5%) (17). Various food sensitizations from

various countries were reported according to complementary feeding sources and habit (21,22). In our country egg and milk are the most common used foods during infancy, so we saw more sensitization with these foods.

When the clinical findings of patients with and without food allergy were evaluated, we found that AD started earlier and more severe in patients with food allergy. In a study by Şengül et al. it was reported that the SCORAD index and total IgE levels were higher in children with food sensitivity younger than three months of age (23). In a study conducted in Thessaloniki, it was reported that 47% of patients with mild-to-moderate AD and 39% of patients with severe AD had a food allergy (17). A population-based study evaluating 619 children aged 3 months, reported that patients with SCORAD index greater than 20, had more association between food sensitization and AD (OR, 25.60; 95% CI, 9.03-72.57; p <0 .001) (24).

In our study, it was found that the clinical findings started earlier in the group with severe AD. In an international study conducted 12 countries, (n=2048, age range 11.5 – 25.5 months, mean 17.6 months), a statistically significant relationship was found between early-onset AD and the severity of clinical severity ($p<0.001$) (25). Cansever et al. also reported that early age of onset was one of the risk factors for the severity of AD (26).

In the treatment of AD, multifaceted, stepwise approach consisting daily shower, moisturizers, avoidance of triggers as irritants and food allergens (for allergic patients) is advised in the literature. Moisturizers were started for all our patients, more than half of them with topical steroids, and all those with food allergies were on a diet. It was observed that all the patients responded to the treatment, but in most the response was partial. In AD patients younger than 12 months of age, significant regression was reported in the lesions of patients who used both moisturizing and topical steroids in the sixth week of treatment (24). In a study conducted with 110 children, it was reported that symptoms regressed in all patients treated with diet (23).

Due to the multifactorial nature of the disease, it was thought that all our patients did not respond fully to the treatment.

Our study reveals the data of our region. The most important limitation of this study is its' retrospective design. The lack of a standard follow-up form and the deficiencies in the data led to the low number of patients included in the study. We could not get data especially about prognosis and new atopic disease development.

Conclusions

The presence of skin test and/or sIgE positivity in AD patients does not mean food allergy, and the diagnosis should be made by elimination diet and oral food challenge test. It should not be forgotten that food allergy is more common especially in the early-onset and severe patient group. Accurate diagnosis of food allergy is necessary to increase the success of treatment and to prevent unnecessary diets. The regression of clinical findings in most patients within the first year is also an important finding in terms of prognosis.

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Table 1. Characteristics of the patients

Gender F/M	39/63
Age median(IQR)(min -max)(months)	8.0 (9.0) (2-24)
Symptom onset age median(IQR)(min -max)	3.0 (5.0)(1-21)
Family history of atopy n (%) Mother history of atopy Father history of atopy Sibling history of atopy	32(31.4) 18(17.6) 10(9.8) 12(11.8)
Symptoms n (%) Eczema Skin dryness Pruritis Mucus stool Urticaria Bloody stool	 87(85.2) 68(67.3) 52(50.9) 3(2.9) 2(1.9) 2(1.9)
Lesion area n (%) Extremities Trunk Cheek Scalp	 62(60.7) 41(40.2) 31(30.3) 11(10.7)
Severity of AD n (%) Mild Moderate Severe	 58(56.9) 42(41.2) 2(1.9)
Comorbid atopic disease n (%)	17(16.7)

Table 2. Laboratory findings of the patients

Laboratory parameters	
Hemoglobin (gr/dL)(mean ±SD)	11.3±0.8
White blood cell /mm^3(mean ±SD)	7655±662
Platelet count x10^3/mm^3(mean ±SD)	384±123
Absolute neutrophil count/mm^3(mean ±SD)	8590±739
Absolute lymphocyte count/mm^3(mean ±SD)	5130±428
Eosinophil count /mm^3(mean ±SD)	62±73
Eosinophil (%)	5.1±4.2
IgA (mg/dL) (mean ±SD)	30.7±30.8
IgM (mg/dL)(mean ±SD)	68.6±130.0
IgG (mg/dL)(mean ±SD)	402.7±280.2
Total IgE (IU/mL) (mean ±SD)	109.8±183.7
Skin Prick Test positivity n (%) Negative Egg White Egg Yolk Milk Wheat Soy Peanut	 50(49.0) 46(45.1) 36(35.3) 16(15.7) 5(4.2) 1(0.8) 3(2.5)
Spesific IgE positivity n (%) Egg White Egg Yolk Milk Wheat Soy	 29(28.4) 19(18.6) 12(11.7) 4(3.9) 1(0.9)

Table 3. The treatments and treatment response of the patients

Treatment		n(%)
Diet	No	68(66.6)
	Both mother and child	32(31.3)
	Only child	2(1.9)
Local corticosteroid	No	37(36.2)
	Low potency	63(61.7)
	Mediate/High potency	2(1.9)
Moisturizer	No	0(0.00)
	Yes	102(100.0)
Response to treatment	Complete	39(38.2)
	Partial	63(61.8)

Table 4. The comparison of the characteristics of the patients with food allergy and without food allergy

		Patients without food allergy n=68	Patients with food allergy n=34	p
Gender n (%)	Female	25(36.7)	14(41.1)	0.666
	Male	43(63.2)	20(58.8)	
Family history of atopy n (%)	No	44(64.7)	26(76.5)	0.327
	Yes	24(35.3)	8(25.5)	
Comorbid atopic disease n (%)	No	57(83.8)	28(82.3)	0.851
	Yes	11(16.2)	6(17.7)	
Severity of AD n (%)	Mild	43(63.2)	15(44.1)	0.033
	Moderate	25(36.8)	17(50.0)	
	Severe	0(0)	2(5.9)	
Response to treatment n (%)	Partial	43(63.2)	20(58.8)	0.666
	Complete	25(36.8)	14(41.2)	
Age at onset of AD (median-IQR)		5.2(4.7)	2.6 (2.2)	0.011

Table 5. The comparison of the characteristics of the patients according to severity of atopic dermatitis

		Mild AD n=58	Moderate/severe AD n=44	P
Gender n (%)	Female	22(37.9)	17(38.2)	0.942
	Male	36(62.0)	27(61.8)	
Family history of atopy n (%)	No	41(70.6)	29(65.9)	0.606
	Yes	17(29.3)	15(34.1)	
Comorbid atopic disease n (%)	No	47(81.0)	38(86.4)	0.474
	Yes	11(18.9)	6(13.6)	
Allergic food n (%)	Cow's milk	1(1.7)	1(2.3)	0.615
	Egg	10 (17.2)	9(21.4)	
	Cow's milk and egg	4 (6.8)	6(14.2)	
Treatment response n (%)	Partial	36(62.0)	27(61.4)	0.942
	Complete	22(37.9)	17(38.6)	
Age at onset of AD (median-IQR)		5.2 (4.2)	3.2 (2.0)	0.017

Table 6. The changes of the patient's laboratory and clinic findings during follow- up

	6^{th} month n=53	12^{th} month n=22	24^{th} month n=10	36^{th} month n=3

Regression of food allergy* n (%)	22(61.1)	2(5.5)	2(5.5)	1(3.7)
Decreased severity of atopic dermatitis n (%)	27(50.9)	17(32.1)	6(11.3)	1(1.9)
Development of new sensitization n (%)	9 (16.9)	1(1.8)	1 (1.8)	0

*A total of 36 food allergies in 25 patients