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The effect of age at the time of diagnosis in atopic dermatitis on development of additional allergic disease

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Summary

Aim: The aim of this study is to determine the effect of age at the time of diagnosis on development of additional allergic diseases and aeroallergen sensitivity in pediatric patients with a diagnosis of AD.

Material and Method: The study includes 114 pediatric patients who were diagnosed as atopic dermatitis according to Hanifin and Rajka criteria. After all patients were divided into two groups according to age at the time of diagnosis as less than 24 months and more than 24 months, total serum IgE, inhalant specific IgE, ECP levels were measured and skin prick tests were performed. The additional allergic diseases developed during the follow-up were recorded.

Results: 90 patients (%78.9) were under 24 months of age, 24 (%21.1) patients were over 24 months of age, when the patients were grouped according to age at the time of diagnosis. In our study group, mean age at the time of diagnosis was 14.0 ± 21.4 months, the duration for development of an additional allergic disease was 23.8 ± 22.3 months and mean follow-up period was 58.7 ± 41.2 months (min.8 months - max.180 months ; median 50.5 months). In the group who were under 24 months of age at the time of diagnosis, a significant difference was determined for development of asthma in the future ($p=0.042$).

Conclusions: To prevent the allergic process in cases in whom atopic dermatitis findings start at an early age, the families should be warned about the allergic diseases associated with the respiratory system and should protect their children from inhalant allergens. (*Turk Arch Ped* 2011; 46: 299-303)

Key words: Dermatitis, atopic, age of diagnosis, allergy, atopic march

Introduction

Atopic dermatitis (AD) is a frequently recurring, chronic and pruritic inflammatory skin disease (1). In recent years, a 2-3 fold increase in the frequency of AD has been reported and the increase is continuing (2,3). Atopic dermatitis affects 2-20% of children according to the results of an international study on asthma and allergy (4). Although the primary cause leading to the disease is not known definitely, it is thought that genetic, immunologic, environmental and infectious factors are involved in the pathogenesis of the disease.

Atopic march is used as a term expressing the natural course of atopic findings. According to this, while AD findings which start during the first year of life regress in a few years, the bronchi become the target organ for allergic stimuli and asthma occurs. While asthma findings decrease between the ages of 6 and 8, the frequency of allergic rhinitis increases after these

ages (5). In the consensus report of PRACRALL, asthma was reported to develop in later years in 50% of children who had AD findings during the first two years of life (6). The severity of atopic dermatitis increases the risk of asthma and allergy with early sensitization against food. It is assumed that asthma may develop in a large portion of children who have a familial history of atopy and AD during early infancy and who develop sensitivity against food and aeroallergens (7,8). The skin is a strong region for Th2 dependent sensitization against protein antigens. In animal studies, IgE levels were found to be increased 100-1000 fold with antigens given through the skin compared to allergens received through the nose (9). Many researches on atopic dermatitis suggest that allergic sensitization develops secondary to disruption of skin barrier (10). There are studies suggesting that especially filaggrin mutations cause allergic sensitization and thus development of asthma by disrupting barrier function of the skin (11).

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The objective of this study was to investigate the effect of the age at the time of diagnosis in children with a diagnosis of AD on development of additional allergic diseases.

Material and Method

The study was performed prospectively in Uludağ University Medical Faculty, Department of Pediatrics, Pediatric Allergy outpatient clinic between September 2010 and January 2011. 114 children who were diagnosed as atopic dermatitis according to Hanifin and Rajka criteria and who accepted to participate in the study by signing the informed consent form were included in the study. Uludağ University local ethics committee approval was given for this study (2.9.2010/2010-8/12). The patients who were included in the study had to fulfill the diagnostic criteria of atopic dermatitis in Hanifin-Rajka classification and had to have no additional systemic disease.

The severity of the patient group was evaluated using SCORAD index (12). According to this index, A, B and C criteria were used to determine disease activity. In the category of A, the distribution area of inflammatory lesions (1-100) was calculated by nine rule. In the category of B (0-18), the mean grades of severity of a total of 6 properties including erythema, edema/papulation, exudation/crusting, peeling, lichenification and dryness were calculated on a scale of 0-3 (0=none, 1= mild, 2= moderate, 3=severe). In the category of C (1-30), the answers to questions "what was the severity of pruritus during the last 3 nights or days? How do sleeplessness and the general state of the skin affect daily life?" which are objective findings were evaluated between 1 and 10. $A/5+7B/2+C$ formula was applied to all data obtained and SCORAD index for each patient was calculated.

On the clinical interviews with the patients, histories were taken. age, gender, the age at the time of diagnosis, familial atopy, the time between the diagnosis of AD and development of additional disease were interrogated. In all patients, IgE and Eozynophyle Cationic Protein (ECP) levels (Immulate® 2000, Siemens, USA) and inhalant allergen specific IgE levels (ImmunoCAP 250, Phadia, Sweden) were measured. All skin tests (ALK-Abello, Prick-test diagnostic, Madrid) were performed as negative and positive controls using histamine and mite. mould, grass and tree pollen as standart inhalant allergens. Values >3 mm 15-20 minutes after the application were considered to be positive.

The statistical evaluation of the results was done in Uludağ University Department of Biostatistics using 'SPSS for Windows Version 13.0' statistical package program. Mann Whitney U test was used for comparison of two independent groups. Pearson qui-square and Fisher qui-square tests were used for comparison of categorical variables. Standard deviation was given with mean values. A p value ≤ 0.05 was considered to be significant.

Results

When the age distribution of 114 children included in the study was evaluated, the mean age of 47 female (41.2%) and

67 male (58.8%) patients was found to be 71.4 ± 46.5 months (median 58.5). The mean age of our study group was found to be 14.0 ± 21.4 months. The mean time passed for development of an additional allergic disease was found to be 23.8 ± 22.3 months and mean follow up time was found to be 58.7 ± 41.2 months (the shortest 8 months and the longest 180 months; median 50.5 months). The severity of AD was considered to be severe in 12 patients (10.5%) with a SCORAD index above 50, moderate in 21 patients (18.4%) with a SCORAD index between 25 and 50 and mild in 81 patients (71.1%) with a SCORAD index below 25 (Table 1).

Mean age at the time of diagnosis was found to be 14.0 ± 21.4 months. Mean total IgE value was found to be 321.5 ± 513.1 kUA/L and mean ECP value was found to be 44.8 ± 42.1 ng/ml. When the subjects were examined in terms of familial atopy, 61 subjects (53.5%) were found to have familial history of atopy.

When all patients were evaluated in terms of development of an additional allergic disease, 63 subjects (55.2%) were found have developed an additional allergic disease and 51 (44.7%) subjects were not found to have developed an additional allergic disease. Among the subjects who developed an additional disease, 23 (20.2%) were found to have asthma, 18 (15.8%) were found to have rhinitis and 22 (19.3%) were found to have asthma and rhinitis together.

When the patients were grouped as below and above 24 months in terms of the age at the time of diagnosis, 90 patients (78.9%) were found to be diagnosed at an age younger than 24 months and 24 patients (21.1%) were found to be diagnosed at an age older than 24 months. In the group who were diagnosed at an age younger than 24 months, no additional allergic disease developed in 40 patients (44.4%), asthma was found in 22 patients (24.4%), rhinitis was found in 10 patients (11.1%) and asthma and rhinitis were found together in 18 patients (20%). In the group who were diagnosed at an age older than 24 months, no additional allergic disease developed in 11 patients (45.8%), asthma was found in one patient (4.2%), rhinitis was found in 8 patients

Table 1. Properties of 114 patients (patient group) with atopic dermatitis

		% rate	
Age (months)	Mean \pm SD	71.4 \pm 48.5	
	Median	58.5	
Gender	Female	47	41.2
	Male	67	58.8
SCORAD index	Severe	12	10.5
	Moderate	21	18.4
	Mild	81	71.1

(33.3%) and asthma and rhinitis were found together in 4 patients (16.7%). In the group who were diagnosed at an age younger than 24 months, a significant difference was found in terms of asthma development in the future (p=0.042). No significant difference was found in terms of development of rhinitis (p>0,05) (Table 2).

When the relation between SCORAD index which shows the severity of the disease and the risk of development of an additional allergic disease was examined, no additional allergic disease was found to have developed in 30 patients, asthma was found in 19 patients, rhinitis was found in 15 patients, asthma and rhinitis were found together in 17 patients in the group with mild disease. No additional allergic disease was found to have developed in 12 patients, asthma was found in 3 patients, rhinitis was found in 2 patients and asthma and rhinitis were found together in 4 patients in the group with moderate disease. No additional allergic disease was found to have developed in 9 patients, asthma was found in 1 patient, rhinitis was found in 1 patient and asthma and

rhinitis were found together in 1 patient in the group with severe disease (Table 3). No significant difference was found between the patients with mild disease and the patients with moderate disease and between the patients with moderate disease and the patients with severe disease in terms of development of an additional allergic disease (P=0.095 and p=0.46, respectively). The rate of development of additional allergic diseases was found to be significantly higher in patients with mild disease compared to the patients with severe disease (p=0.012).

When the relation of disease severity and the age at the time of diagnosis was evaluated, 64 patients had mild disease, 16 patients had moderate disease and 10 patients had severe disease in the group who were diagnosed at an age younger than 24 months, while 17 patients had mild disease, 5 patients had moderate disease and 2 patients had severe disease in the group who were diagnosed at an age older than 24 months (Table 4). No significant difference was found between the patients who were diagnosed at an age younger than 24 months and the patients who were diagnosed at an age older than 24 months and between the patients who had mild-moderate, mild-severe and moderate-severe disease (p=0.77, p=1.00, p=1.00, respectively).

Aeroallergen sensitivity was found in 53 of the subjects (46.4%) in our patient group. Mite sensitivity was found in 31 subjects (27.1%), pollen sensitivity was found in 18 subjects (15.8%) and mould sensitivity was found in 4 subjects (3.5%).

Discussion

Atopic dermatitis is a chronic inflammatory disease which displays its first signs during childhood. Although atopic dermatitis is observed in boys and girls with an equal rate independent of the gender, the frequency of AD was found to

Table 2. The relation between the age at the time of diagnosis and development of an additional allergic disease

Additional allergic disease	The age at the time of diagnosis		Total	p
	<24 months Total n=90 n (%)	>24 months Total n=24 n (%)		
None	40 (78.4%)	11 (21.6%)	51	>0.05
Asthma	22 (95.7%)	1 (4.3%)	23	0.042
Rhinitis	10 (55.6%)	8 (44.4%)	18	>0.05
Asthma+rhinitis	18 (81.8%)	4 (18.2%)	22	>0.05

Table 3. The relation between SCORAD index and development of an additional allergic disease

SCORAD index		Additional allergic disease				Total	p
		None	Asthma	Rhinitis	Asthma and rhinitis		
Severe	n	9	1	1	1	12	>0.05
	%	75	8.3	8.3	8.3	100	
Moderate	n	12	3	2	4	21	>0.05
	%	57.1	14.3	9.5	19	100	
Mild	n	30	19	15	17	81	0.012
	%	37	23.5	18.5	21	100	

Table 4. The relation between the age at the time of diagnosis of atopic dermatitis and the severity of the disease

SCORAD index	Age at the time of diagnosis		Total	p
	<24 months n (%)	>24 months n (%)		
Mild	64 (79)	17 (21)	81	>0.05
Moderate	16 (76.2)	5 (23.8)	21	
Severe	10 (83.3)	2 (16.7)	12	

be slightly higher in male patients in some studies performed in China and Switzerland (13,14). When the gender distribution was evaluated in our study, 67 male patients (58.8%) and 47 female patients (41.2%) were found in the group with AD and the male/female ratio was found to be 1.42.

The diagnosis of atopic dermatitis is made based on history and clinical properties. Hanifin and Rajka criteria have been widely used since 1980 for the diagnosis (15). SCORAD index which is used to evaluate the severity of atopic dermatitis is used mostly in clinical investigations (12). Since the severity of disease at the beginning of the disease is one of the factors responsible of poor prognosis, we classified the patients with AD using SCORAD index in our study. The severity of AD was considered to be severe in 12 patients (10.5%) with a SCORAD index above 50, moderate in 21 patients (18.4%) with a SCORAD index between 25 and 50 and mild in 81 patients (71.1%) with a SCORAD index below 25. Severe forms of atopic dermatitis are observed rarely. In a study performed to examine the prevalence of AD in children of school-age in Japan, mild disease was found in 74% of the patients, moderate disease was found in 24% of the patients and severe disease was found in 0.3% of the patients in the group with a diagnosis of AD (16). In our study, most of our patients had mild disease which was compatible with the literature.

In more than half of the patients with atopic dermatitis the disease starts before one year of age and the complaints start before the age of 5 in 85% of the patients (17). Mean age at the time of diagnosis was 14 ± 21.4 months in our study which was compatible with the literature. Increase in production of IgE is one of the important findings of AD. It has not been shown clearly if there is a certain consistency between high IgE and lesions. Laske and Niggemann (18) investigated the relation between the severity of eczema and IgE level and found a significant relation in their study. In our study, total IgE level was found to be 321.5 ± 513.1 kUA/L and in a large portion of our patients with a diagnosis of AD, IgE level was found to be high. Serum ECP level is one of the variables demonstrating the severity of the disease. Although there are studies showing that ECP level reflects the severity of AD, Selnes and Dotterud found no relation between serum ECP level and AD or other allergic diseases (19). While serum ECP level was found to be high (44.8 ± 42.1 ng/mL) in the subjects in our study group, it can be suggested that ECP level may change during suppression and exacerbation of AD.

Atopic dermatitis is a disease which tends to show hereditary transition. Studies performed found a strong relation between eczema and familial atopy (20). In a study including 531 children with AD performed in our country, the rate of familial atopy was reported to be 56.5% (21). In our study, familial atopy was found in approximately half of our subjects (53.5%).

Allergic diseases occur in a chronological process which is defined as allergic march. Rhodes et al. (22) followed up 100 children who were born to atopic families. AD developed

with a rate of 20% in the first year of life in these children and the rate of allergic rhinitis was reported to be 3%. At the end of the 22 years of follow up, the frequency of AD decreased to 5%, while the frequency of allergic rhinitis increased to 15%. In another study, the possibility of development of asthma in the future was calculated to be 70% in the presence of severe AD symptoms (8). In a study where 169 infants with AD were followed up for 4 years, 45% of the subjects showed asthma-like symptoms and 35% were diagnosed as asthma by a physician (23). When our patients in our study were examined in terms of development of additional allergic disease, it was found that 63 (55.2%) of 114 subjects developed additional allergic disease 23 of whom (20.2%) had asthma, 18 of whom (15.8%) had rhinitis and 22 of whom (19.3%) had asthma and rhinitis together and 51 subjects (44.7) did not develop any additional allergic disease. Development of asthma and rhinitis in our study group was found to be compatible with the literature data.

Kjellmann et al (24) reported that asthma developed with a rate of 58% in the following years in patients in whom AD started before the age of 2 and the rate of development of asthma was 7% in patients in whom AD started after the age of 2 (24). In our study, we found that asthma developed in 40 (35%) of our patients with an age younger than 24 months at the time of diagnosis and in 5 (4.3%) of our patients with an age older than 24 months at the time of diagnosis ($p=0.042$). The rate of development of asthma as an additional allergic disease was found to be higher in subjects in whom AD started early. We think that families should be informed about exposure to environmental allergens and allergic diseases related to the respiratory system and patients should be closely monitored in cases where atopic dermatitis findings start before the age of 2.

It has been reported that food allergens in patients younger than 2 years old, food allergens and aeroallergens in patients at the age of 2-5 years and aeroallergens in patients older than 5 years of age have a significant role in AD (25). Aeroallergens which frequently affect atopic individuals include mite, pollens, mould spores, pet dander and cockroach. Among these aeroallergens, mite activate proteinase activated receptor-2 (PAR-2) and disrupt barrier function. As a result of this, entering of allergens and microorganisms is facilitated (26). In a study where 57 infants with AD were followed up for 12 months, the frequency of wheezing was found to be 11% in subjects who lived in houses where mite control measures were taken and 37% in subjects who lived in houses where mite control measures were not taken (27). In studies performed, mite sensitivity was found with a higher rate in children with atopic dermatitis (28). Similar to the data in the literature mite allergy was found to be high (27.1%) in 31 subjects in our study. It may be suggested that this arises from the fact that our region has a high level of humidity and constitutes an appropriate environment for mite.

Although no significant difference was found between the age at the time of diagnosis and the severity of disease, the

rate of development of an additional allergic disease was found to be higher in patients with mild disease compared to patients with severe disease ($p=0.012$). This may arise from the fact that the number of our patients with severe disease was low or from the presence of gene polymorphism of glutathione-S-transferase which functions in the antioxidant pathways or mutations in the filaggrin gene which has an important role in the skin's barrier function (29,30).

Conclusively, allergic process starts with AD and may continue with the pictures of bronchial asthma and allergic rhinitis when sensitivity to respiratory allergens is added. In our study, the rate of development of asthma was found to be statistically higher in children who were diagnosed as AD at a younger age than 24 months. In subjects with signs of atopic dermatitis occurring at an early period, warning of physicians and families about allergic diseases related to the respiratory system will be beneficial to prevent the allergic process.

Conflict of interest: None declared.

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