

Characteristics and Prognosis of Childhood Atopic Dermatitis: A Multicenter Study in Turkey

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Key Words

Atopic dermatitis · Atopic march · Allergy

Abstract

Background: Childhood atopic dermatitis (AD) is classically accepted as initial finding of atopic march; however, non-atopic cases do not follow this course. The aim of this study was to determine the characteristics and prognosis of AD in childhood in Turkey. **Methods:** The study included 531 children with AD that presented to pediatric allergy departments in 11 different regions of Turkey. Age at diagnosis, total serum and inhalant-specific immunoglobulin E (IgE) levels and allergen skin prick test results were recorded retrospectively. Clinical characteristics like additional allergic diseases at presentation or during follow-up were recorded as well as duration of follow-up. **Results:** Mean age at diagnosis was 37.8 ± 36.2 months. Mean IgE level was $318.3 \pm$

677.8 IU/ml (median 100 IU/ml). Skin prick tests yielded positive results in 47% of children. At presentation, 31.6% of children reported additional allergic disease, while 11.7% developed allergic disease during follow-up. Among all, 46.6% had additional allergic disease at any point. IgE levels were significantly higher in children with additional allergic diseases ($p = 0.001$). Allergen skin prick test positivity and family history of allergic diseases increased the risk of additional allergic diseases significantly (OR = 3.90, 95% CI = 2.3–6.6 and OR = 1.89, 95% CI = 1.3–2.8, respectively). **Conclusions:** Allergic sensitization is not present in all cases of AD. Coexistence of additional allergic diseases is not as high as expected but more common in children who have been demonstrated to have atopic sensitization with high IgE levels and allergen skin prick test positivity.

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Introduction

Atopic dermatitis (AD) is defined as inflammatory, chronic skin disease characterized by intense pruritus, dry skin and typically distributed eczematous skin lesions [1, 2]. It has a chronically relapsing course that usually begins in early childhood and is expected to regress by 5 years age but may continue into adulthood [1, 2]. Development of AD is determined by genetic, immunological, environmental factors and skin barrier function defects [3]. Most AD cases were proposed to be atopic with high serum immunoglobulin E (IgE) levels and positive skin prick test [2]. However, it is reported that there is a group of AD patients that have clinically relevant findings but are not sensitized to allergens termed as intrinsic or nonatopic AD [2].

Previously, it has been proposed that 30–60% of children with AD will develop respiratory diseases like asthma and allergic rhinitis in the context of the ‘atopic march’ [2]. Atopic sensitization that is described as genetic predisposition to produce specific IgE against antigens is required for the development of these disorders [4]. The atopic march has been described as IgE-related AD that starts in infancy and progresses with respiratory allergies in later life, pointing out a developmental progression of allergic diseases [5, 6]. However, considering intrinsic AD cases and recent epidemiological data, the context of the atopic march is weakened and a common etiopathogenetic mechanism for AD and allergic respiratory diseases is supported [7]. Moreover, many current data have supported that children with AD have a lower incidence of other allergic diseases like asthma and rhinitis than expected [8]. Thus, the atopic march may not be a classical feature of AD.

The aim of this study was to evaluate clinical characteristics of the AD cases in Turkey and to delineate distribution of allergic sensitization in these cases as well as the association with other allergic respiratory diseases.

Materials and Methods

Study Population

This retrospective study included 531 children (290 male, 241 female) with AD that were followed up in pediatric allergy departments in different regions of Turkey. Diagnosis of AD depended on clinical findings of intense pruritus, dry skin and typically distributed eczematous skin lesions [1, 2].

Study Design

From different areas of Turkey, 11 pediatric allergy centers participated in this retrospective study. Demographic characteristics including age, gender and familial history of atopy were recorded. Additional information about age at diagnosis, pres-

Table 1. Sociodemographic characteristics of the children included in the study

	n	%
Age		
Mean $\pm$ SD	59.9 $\pm$ 40.5	
Median	48.0	
Gender		
Male	290	54.6
Female	241	45.4
Family history of atopy		
Present	300	56.5
Absent	231	43.5

ence of additional allergic diseases at presentation, duration of follow-up and development of any other allergic diseases during follow-up was recorded. Total serum and common environmental allergen-specific IgE levels were measured in 423 and 256 children, respectively. Serum IgE levels above 230 IU/ml were categorized as high for male and values above 170 IU/ml were categorized as high for females [9]. Skin prick tests performed according to European Academy of Allergology and Clinical Immunology guidelines were present in 265 children [10]. All skin prick tests were performed using commercial extracts, and negative control and histamine as positive control were added to the panel. After 15–20 min of exposure (after prick), positive results were defined as wheal >3 mm. Standard panel of inhalant allergens included mainly dermatophagoides, fungi, grass and tree pollens.

Disease severity was assessed retrospectively according to Investigators’ Global Assessment. It is a 6-point scale where 0 indicates absence of inflammatory findings of AD and 5 indicates severe erythema, infiltration and excoriation [11, 12].

Statistical Analysis

Statistical analyses were performed by the SPSS 11.0 (SPSS Inc., Chicago, Ill., USA) computer program. Comparison of IgE levels between patients with and without additional diseases was carried out by the Mann-Whitney U test because the values of IgE did not show normal distribution. Frequency of allergen skin prick test positivity, high IgE levels and family history of atopy between children with and without additional allergic diseases was performed with χ^2 test, and risk estimate with odds ratio (OR) was calculated.

Results

Sociodemographic Characteristics

Mean age of the 531 children (290 male, 241 female) included in the study was found to be 59.9 ± 40.5 months (table 1). Mean age at AD diagnosis was 37.8 ± 36.2 months (median 24 months) and the mean duration of follow-up was 13.0 ± 17.9 months (range 0–120 months;

Table 2. Presence or development of additional allergic diseases in children with AD

	Additional disease (+)		Additional disease (-)	
	n	%	n	%
At presentation (n = 531)	168	31.6	363	68.4
During follow up (n = 394)	46	11.7	348	88.3
Among children ≥ 5 years of age at the end of follow-up (n = 217)	117	53.9	100	46.1

Table 3. Serum IgE levels and allergen SPT results in children with different AD severity scores

IGA	Serum IgE		p ¹	Allergen SPT				p ²
	mean ± SD	median		positive		negative		
				n	%	n	%	
0	407.2 ± 601.8	118.5	0.08	5	26.3	14	73.7	0.11
1	255.4 ± 344.4	122.0		26	51.0	25	49.0	
2	278.6 ± 664.1	63.0		45	44.1	57	55.9	
3	342.4 ± 856.4	101.0		40	58	29	42.0	
4	496.9 ± 675.1	161.0		6	31.6	13	68.4	
5	399.7 ± 558.6	106.0		1	50.0	1	50.0	

IGA = Investigators' Global Assessment.

¹ Kruskal-Wallis analysis.

² χ^2 test.

median 6 months). Family history of atopy was present in 300 children (56.5%; table 1).

An additional disease was reported in 31.6% of children at first presentation. Similarly, in 394 children that were on follow-up, an additional allergic disease subsequently developed in 11.7%. Among all children, 217 were at or above 60 months of age at the end of follow-up and 53.9% had an additional allergic disease (table 2).

Serum IgE Levels and Skin Prick Test Results

Mean total IgE level in the whole group was 318.3 $\pm$ 677.8 IU/ml (median 100.0 IU/ml, range 0–3,170 IU/ml). Total IgE level measurement was found in 423 patients and 34.3% of these had high values. Specific IgE to inhalant antigens was positive in 128 (50%) children. Skin prick tests yielded positive results in 118 (47%) children. Mean levels of total IgE were significantly different between children with positive and negative skin prick tests

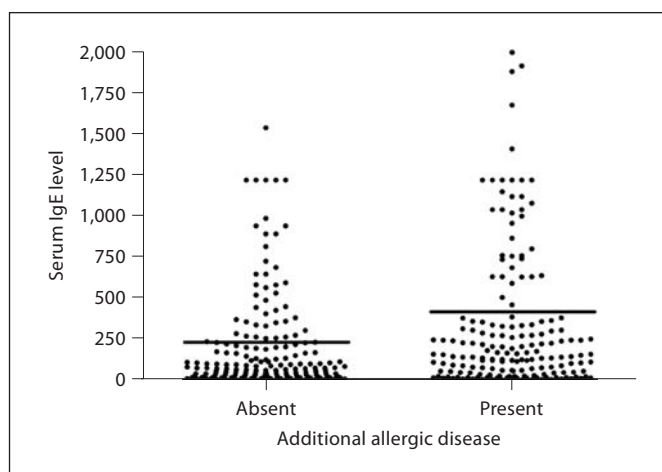


Fig. 1. Comparison of total serum IgE levels among patients with and without an additional allergic disease.

(488.3 $\pm$ 913.2 vs. 282.7 $\pm$ 674.6, $p < 0.001$). Frequencies of having high IgE levels were compared between children with positive and negative SPT results; there was a significant difference and IgE levels were high in 60% of children with positive SPT while they were high in 40% of children with negative SPT ($p = 0.002$).

Association of AD Severity with Serum IgE Levels and Skin Prick Test Results

Serum IgE levels were not found to change significantly among children with different AD severity scores ($p = 0.08$). Similarly, skin prick test results did not differ significantly among children with different AD severity scores ($p = 0.11$; table 3).

Association of Additional Allergic Diseases with Family History, Total Serum and Specific IgE Levels, and Skin Prick Test Results

Among children enrolled in the study, 37.9% had an additional allergic disease at presentation or developed one during follow-up.

Total serum IgE levels were significantly higher in children with additional allergic diseases (421.6 $\pm$ 805.3 vs. 224.7 $\pm$ 423.9, $p = 0.00$; fig. 1). When risk of presence or development of an additional allergic disease was investigated, family history of atopy, high IgE level, positive specific IgE and positive skin prick test were found to be significant risk factors.

High serum IgE levels and positive specific IgE levels increased the risk of additional allergic diseases 2.2 times

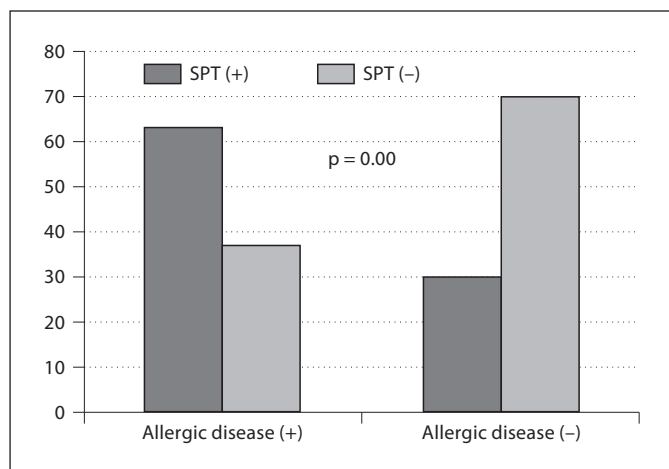


Fig. 2. Frequency of skin prick test (SPT) positivity in children with and without additional allergic diseases.

(OR = 2.2 for both, 95% CI = 1.4–3.4 for IgE and 1.4–3.7 for specific IgE). Similarly, skin prick test positivity was associated with a 3.9-fold increase in the risk of additional allergic diseases. Family history increased the risk of an additional allergic disease (OR = 1.89, 95% CI = 2.3–6.6; table 4; fig. 2).

When logistic regression analysis was performed for the influence of these parameters on the risk of additional allergic diseases, it was found that IgE and specific IgE lost significance ($p = 0.43$ and 0.11 , respectively), but family history and skin prick test remained significant risk factors ($p = 0.01$ and 0.003 , respectively).

Discussion

Coexistence of other allergic diseases with AD has been previously demonstrated in an epidemiological survey-based study from our area, and it was reported that AD increased the risk of asthma 2.5 times [13]. However, AD may or may not be associated with high IgE levels and allergic sensitization [2]. The frequency of the nonallergic or intrinsic dermatitis is around 5.4% in adults but is expected to be much higher in young children [2, 3, 14]. It is considered to comprise two thirds of all AD cases when population-based studies are considered instead of the hospital-based ones [15]. Similarly, a previous study demonstrated that there was a significant number of children with non-IgE-mediated eczema, asthma and rhinitis during childhood besides atopic children [4]. Further epide-

Table 4. Risk associated with high IgE levels, skin prick test and family history of atopy in children with and without additional allergic disease

	Additional disease (+)		Additional disease (-)		OR
	n	%	n	%	
Family history of atopy					
(+)	102	50.7	81	35.2	1.89 (1.3–2.8)
(-)	99	49.3	149	64.8	
IgE					
High	76	57.1	47	25.8	2.16 (1.4–3.4)
Normal	101	42.9	135	74.2	
Specific IgE					
(+)	69	61.1	59	41.3	2.2 (1.3–3.7)
(-)	44	38.9	84	58.7	
Allergen SPT					
(+)	82	62.6	36	30	3.9 (2.3–6.6)
(-)	49	37.4	84	70	

Figures in parentheses are 95% CI. SPT = Skin prick test.

miological studies have shown that association between AD and atopy was weak with odds ratios ranging between 1.17 in developing and 2.69 in industrialized countries and the population attributable fraction less than 15% in developing countries and 2.8% when all centers included were considered [16]. These results point out that IgE sensitization is not a prerequisite for development of AD but the role of IgE in development of AD cannot be excluded [17]. The results of our study are in concordance with these findings because only 34.3% of the children included in the study had high IgE levels for their age.

The atopic march has been described as IgE-related AD that starts in infancy and progresses with respiratory allergies in later life pointing out a developmental progression of allergic diseases [5, 6]. On the other hand, the context of atopic march has been challenged by the presence of eczema cases that have clinically similar findings with atopic patients but are non-atopic [2]. In a previous study, it has been reported that 25% of late-onset and 59% of early-onset atopic children with eczema developed asthma while none of the non-atopic ones did [14]. There is some evidence to increased risk of allergic respiratory diseases in extrinsic AD cases [15]. Moreover, in a recent study, it has been demonstrated that severity of AD and high IgE levels in the first year of life are predictors of development of allergic asthma [18]. In contrast, a previous epidemiological study has reported that risk of child-

hood asthma did not differ between children with AD with and without sensitization [19]. On the other hand, in our study, 37.9% of the children with AD had an additional allergic disease and IgE levels were significantly higher in children who developed an additional allergic disease when compared to the ones who did not. This finding is important to support that not all children with AD follow the conventional course of atopic march to develop additional allergic diseases and that children with higher IgE levels indicating allergic sensitization are more prone to develop additional allergic diseases. Therefore, cases with AD need to be followed up for development of additional allergic diseases considering the atopic status. Moreover, skin prick test positivity increased the risk for additional allergic diseases even when adjusted for familial history of allergic diseases. These findings also support that intrinsic AD cases do not tend to develop additional allergic diseases and do not follow the conventional atopic march. This finding is in concordance with the German 'Multicenter Allergy Study Group' results, which have demonstrated that in children with AD who develop asthma at school age, wheezing starts before or with onset of AD described as a distinct phenotype rather than atopic march [8].

Development of AD is determined by genetic, immunological, environmental factors and skin barrier function defects [3, 20]. Genetic basis of AD has been suggested from family and twin studies; however, a specific gene locus has not been identified yet [2]. Epidermal barrier defect has been attributed to filaggrin protein mutations which lead to defects in keratin cytoskeleton aggregation defects [2, 20]. There is a generalized defect of epidermal function in AD involving both lesional and intact skin [2]. This defect is characterized by decreased ceramide and sphingosine amount in stratum corneum, impaired lipid metabolism and increased chymotryptic enzyme levels, and it is not only associated with AD but also with other allergic diseases like rhinitis and this might be attributable to increased penetrance of antigens through the skin of these individuals [2, 7]. Therefore, filaggrin mutations have been found to be associated with not only AD but also with rhinitis [7]. This again weakens the idea of 'atopic march' but supports the idea of common etiopathogenetic mechanisms for AD and allergic respiratory diseases. In the immunopathologic aspect, it has been detected that there is increased expression of cutaneous lymphocyte antigen expression on T lymphocytes and this leads to homing of lymphocytes to skin in the presence of T-cell attractant chemokine [2]. These T cells favor a Th2 type immunological reaction initially, which is shifted to Th1

type in the chronic phase [2, 3]. This alteration in immunological regulation is responsible more of the extrinsic AD and is the main mechanism of development of other allergic diseases in AD cases [3]. However, consideration of the fact that immunological alteration is only one aspect of the pathogenetic mechanism of AD necessitates evaluation of AD in a spectrum adjacent to other allergic diseases not among the same group as all other allergic diseases. This idea is especially prominent for intrinsic AD cases. The results of our study emphasize that not all cases with AD cases co-occur with allergic diseases. Therefore, as suggested in a previous review, it would be wise to think that asthma and AD tend to co-occur in same patients because they share some of the causative factors, especially the immunological aspect [16].

Severity of AD is suggested to affect natural history of allergic sensitization and therefore atopic march [6]. Moreover, children with severe AD were reported to have higher rates of allergic sensitization, and early disease severity has been reported to be associated with specific IgE responses [6, 18]. However, AD severity assessed by IGA scale in our study failed to demonstrate a significant difference in IgE levels, rates of skin prick test positivity or frequency of co-existing allergic diseases.

One of the limitations of this study include the cross-sectional design which has precluded us from detection of future allergic diseases considering that 11% of children have atopy detected after age of 10 years [5]. This was tried to be overcome by repeating the analysis for additional allergic disease among the children who had reached five years of age during follow up. Children that had reached the age of 5 years at the end of follow-up constituted 40.9% of the study sample. Retrospective design forms the second limitation of the study. Therefore, only cases diagnosed by a pediatric allergist were included in the study and clear definitions were used to overcome this limitation. Moreover, description of clinical severity by different physicians in different centers might have caused some variation in recording. This was minimized by the use of Investigators' Global Assessment which is a validated clinical severity assessment tool [11, 12].

In conclusion, nearly half of the children with AD in Turkey are intrinsic and development of additional allergic diseases is significantly lower in these children. This finding supports the idea that there may be a common atopic etiopathogenetic background for AD and other allergic diseases instead of an atopic march that progresses from one to the other disease. This common background seems to be absent in intrinsic AD cases, so these do not tend to develop additional allergic diseases.

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