The Presence of Atopic March in Patients Diagnosed with Atopic Dermatitis

Atopik Dermatit Tanılı Hastalarda Atopik Yürüyüşün Varlığı

Ozge ATAY, Suna ASILSOY, Gizem ATAKUL, Serdar AL, Ozge KANGALLI BOYACIOGLU, Neviz UZUNER, Ozkan KARAMAN

Department of Pediatric Immunology And Allergy, Dokuz Eylül University, Faculty of Medicine, İzmir, Turkey

ABSTRACT

Objective: Atopic march is a model that explains the progression of allergic diseases from atopic dermatitis (AD) to allergic asthma and rhinitis. In our study, while evaluating the presence of allergen sensitivity and allergic diseases in patients who were diagnosed with AD and followed up until the age of at least 5 years, we wanted to investigate how much the definition of classical atopic gait responded to expectations.

Material and Methods: We retrospectively reviewed the file records of patients diagnosed with atopic dermatitis, whose ages were 2 years and under at the time of application and followed up regularly until at least 5 years of age. We recorded the clinical and laboratory findings. We noted the allergic disease status and allergen sensitivity of the patients when they were 5 years old.

Results: Forty-one patients with a diagnosis of AD who met the criteria were identified. During the application, we found food sensitivity in 28 (68.3%) patients. When 41 patients reached the age of 5, 13 (31.7%) were diagnosed with asthma and 12 (29.2%) were diagnosed with allergic rhinitis.

Conclusion: We found the frequency of asthma and allergic rhinitis higher in patients with AD than in the normal population. However, we could not show a relationship between food sensitivity and the development of asthma and/or allergic rhinitis. Effective skin care in AD can be protective for developing of allergic diseases. In order for clinicians to understand the heterogeneity of atopic disease models in children and to eliminate this variability, infants with AD should be followed up in later life.

Key Words: Allergic rhinitis, Allergy, Asthma, Atopic dermatitis, Food allergy

0000-0002-7673-3601: ATAY O
0000-0002-4235-0995: ASILSOY S
0000-0002-3508-1360: ATAKUL G
0000-0002-4846-6761: AL S
0000-0003-3393-489X: KANGALLI BOYACIOGLU O
0000-0001-8862-7825: UZUNER N
0000-0002-5675-3808: KARMAN O

Conflict of Interest / *Çıkar Çatışması*: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. Ethics committee approval was received for this study from the Local Ethics Committee of Dokuz Eylül University, School of Medicine (approval number: 2021/03-34).

Contribution of the Authors / Yazarların katkısı*: *ATAY O: Constructing the hypothesis or idea of research and/or article, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***ASILSOY S:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***ATAKUL G:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study. ***AL S:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***KANGALLI BOYACIOGLU O:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results. ***UZUNER N:*** Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Reviewing the article before submission scientifically besides spelling and grammar. ***KARMAN O:*** Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study,Reviewing the article before submission scientifically besides spelling and grammar.

How to cite / *Atıf yazım şekli* : Atay O, Asilsoy S, Atakul G, Al S, Kangallı Boyacioglu O, Uzuner N, et al. The Presence of Atopic March in Patients Diagnosed with Atopic Dermatitis. Turkish J Pediatr Dis 2022;16:389-394.

Correspondence Address / Yazışma Adresi:

Ozge ATAY
Department of Pediatric Immunology and Allergy,
Dokuz Eylül University, Faculty of Medicine, İzmir, Turkey
E-posta: dr_ozge@hotmail.com

Received / Geliş tarihi : 10.10.2021
Accepted / Kabul tarihi : 16.12.2021
Online published : 24.02.2022
Elektronik yayın tarihi
DOI: 10.12956/tchd.993670

ÖZ

Amaç: Atopik yürüyüş, alerjik hastalıkların atopik dermatitten (AD) alerjik astım ve rinite ilerlemesini açıklayan bir modeldir. Çalışmamızda AD tanısı konan ve en az 5 yaşına kadar takip edilen hastalarda alerjen duyarlılığı ve alerjik hastalık varlığını değerlendirirken, klasik atopik yürüyüş tanımının beklentilere ne kadar cevap verdiğini araştırmak amaçlanmıştır.

Gereç ve Yöntemler: Başvuru sırasında yaşları 2 yaş ve altında olan, AD tanılı, ve en az 5 yaşına kadar düzenli olarak takip edilen hastaların dosya kayıtları geriye dönük olarak incelendi. Klinik ve laboratuvar bulguları kaydedildi. Hastaların 5 yaşında iken alerjik hastalık varlığı ve alerjen duyarlılık durumları not edildi.

Bulgular: Kriterleri karşılayan AD tanılı 41 hasta belirlendi. Başvuru sırasında 28 (%68.3) hastada besin duyarlılığı saptandı. Hastaların 5 yaşına geldiğinde 13 (%31.7)'ünde astım, 12 (%29.2)' sinde alerjik rinit tanısı saptandı.

Sonuç: AD'li hastalarda astım ve alerjik rinit sıklığı normal popülasyon verilerine göre daha yüksek bulundu. Ancak gıda duyarlılığı ile astım ve/veya alerjik rinit gelişimi arasında bir ilişki gösterilemedi. AD'de etkili cilt bakımının, alerjik hastalıkların gelişmesine karşı koruyucu olabileceği düşünüldü. Klinisyenlerin çocuklarda atopik hastalık modellerinin heterojenliğini anlamaları ve bu değişkenliği ortadan kaldırabilmeleri için AD'li bebeklerin sonraki yaşamlarında takip edilmeleri faydalı olacaktır.

Anahtar Sözcükler: Alerjik rinit, Alerji, Astım, Atopik dermatit, Besin alerjisi

INTRODUCTION

Atopic dermatitis (AD) is a chronic, itchy, recurrent inflammatory skin disease that affects 2-20% of the general population (1). Studies show that having AD is associated with the later development of other atopic diseases known as "atopic march" (2,3). Today, food allergy and AD are the early steps of atopic march, while allergic rhinitis and asthma are the late steps. It is believed that the concept of atopic march helps to recognize allergic patients that may develop in the future and to provide their treatment or prevention. However, instead of focusing on the classical atopic march, studies have stated that it would be beneficial to develop this concept today (4,5). In our study, while evaluating allergen sensitivity and the presence of allergic diseases in patients diagnosed with AD and followed up up to the age of at least 5 years, we also wanted to investigate how well the classical atopic march responds to the expectations for predicting allergic diseases.

MATERIALS and METHODS

Based on the Hanifin-Rajka Criteria, we analyzed the file records of patients who were diagnosed with atopic dermatitis and 2 years of age or younger at the time of admission, followed up regularly until at least 5 years of age, and without any additional chronic disease (6). We recorded the following parameters and identified the groups.

We retrospectively reviewed the file records of patients diagnosed with atopic dermatitis whose, ages were 2 years and under at the time of application and followed up regularly until at least 5 years of age.

We recorded the application dates of the patients. We divided it into 2 groups according to the age of diagnosis of AD, diagnosed in the first 6 months and diagnosed over 6 months. We recorded total IgE and blood eosinophil levels in peripheral blood at admission, 3 years old and 5 years old. According to previous studies, we considered 470 eosinophils / μL and higher values for eosinophilia and 45 IU/ml and higher concentrations at Total IgE level as high (7).We recorded the results of the skin prick test (SPT) at the time of admission and at the age of five. SPT results were considered positive if a wheal size was >3 mm compared with the negative control. In the application; grasses/cereals, trees I-II mixture, mushrooms I-II mixture, Dermatophagoides pteronyssinus, Dermatophagoides farinae, cat-dog epithelium, cow's milk, chicken egg white-yolk, wheat flour commercial extracts (Allergovit, Allergopharma, Germany) were used. Age of five and over, pollens (Grasses (herbs), Artemisia vulgaris (wormwood), Alnus glutinosa (alder), Populus alba (poplar tree), Betula alba (birch), Fagus silvatica (beech), Parietaria officinalis (sticky grass), Olea europaea (olive tree)]; mites (Dermatophagoides pteronysinus, Dermatophagoides farinae); animal epithelium [Felis domesticus (cat), Canis familiaris (dog), Blatella germanica (cockroach)]; Commercial extracts of fungi (Alternaria alternata, Cladosporium herbarum, Aspergillus fumigatus) (Alk-Abello®, Hørsholm, Denmark) were used. We noted specific IgE levels on house dust mite, cat and dog hair, grasses / cereals pollen, cow's milk, chicken egg whites and yolks, and wheat allergens operated by the ImmunoCAP (Phadia AB®, Uppsala, Sweden) method. We accepted 0.35 kU/L and above as positive for allergen-specific IgE value. We considered the patient atopic in case of positivity to at least one allergen according to SPT and/or allergen specific IgE results at the time of application.We recorded the SCORAD scores of patients with mild atopic dermatitis below 20 points, moderate between 20 and 40 points, and severe atopic dermatitis above 40 (8). We considered the detection of more than 2 positivity in SPT and/or allergen specific IgE values as multiple sensitivity to allergens. According to the IgA levels of Turkish children, we classified the IgA levels of our patients as low, normal and high at the time of admission and between the ages of 5-6 (9).Although the use of skin moisturizing creams or emollients was recommended to all patients, topical corticosteroids and topical Calcineurin Inhibitors were used for.

Ethics committee approval was received for this study from the Local Ethics Committee of Dokuz Eylül University, School of Medicine (approval number: 2021/03-34).

Statistical analysis

Kolmogorov Smirnov normality test was performed to select the statistical methods to be used. If any group did not meet the normality assumption, nonparametric test methods were chosen. The chi-square and Fisher's exact tests were used to analyze the relations between categorical variables or differences between groups. Logistic regression analysis was performed to determine the risk factors thought to affect the development of asthma and allergic rhinitis, and correlation analysis was performed to determine related factors. Statistical analysis of the study was performed using IBM SPSS Statistics for Windows, Version 25 and the statistical significance limit was determined as $p \leq 0.05$.

RESULTS

We identified 645 patients, but we included 41 patients with a diagnosis of AD who met our criteria. The median age of diagnosis of AD was 7 (min-max: 2-11) months. When the patients were classified according to AD diagnosis age, 19 (46.3%) were in the range of 0-6 months and 22 (53.7%) were older than 6 months. We found a relationship between the increase in the age of diagnosis of AD and the development of asthma at the age of 5 years ($p = 0.040$; $r = 1.00$).

Twenty (48.8%) of the 21 patients who went to daycare were between the ages of 2-5. It was observed that AD often improved in the first 24 months in patients who went to daycare ($p = 0.010$). The demographic characteristics and laboratory findings of the patients are summarized in Table I.

Table I: Demographic Characteristics and Laboratory Findings of the Cases.

Category	n (%)
Gender	
Female	10 (24.4)
Male	31 (75.6)
Presence of atopy in parents	
Yes	22 (53.7)
No	19 (46.3)
Bronchiolitis attack in the first 3 years	
Yes	30 (73.2)
No	11 (26.8)
Bronchiolitis attack in the last 12 months	
<3	26 (63.4)
≥3	15 (36.6)
Scorad score	
Mild	15 (36.6)
Moderate/Severe	26 (%63.4)
AD recovery age	
<24 months	20 (48.8)
>24 months	21 (51.2)

AD: *Atopic dermatitis*

Table II: Allergen Sensitivity Of Patients At Age 5 According To Skin Prick Tests.

Allergen sensitivity	n (%)
Egg	2 (4.9)
Egg+ grasses / grains	1 (2.4)
Egg+Fungi	4 (9.8)
Cow milk+Cat epithelium / hair	1 (2.4)
Wheat+Mites	1 (2.4)
Grasses / grains	4 (9.8)
Mites	2 (4.9)
Cat epithelium / hair	2 (4.9)
Fungi	1 (2.4)
Grasses / grains+Mites	1 (2.4)

Table III: Presence of an allergic disease at age 5 in patients.

Allergic disease	n (%)
No	21 (51.2)
Food allergy	9 (21.9)
Asthma	7 (17.1)
Allergic Rhinitis	6 (14.6)
Urticaria	1 (2.4)
Atopic dermatitis	0 (0)
Asthma + Allergic Rhinitis	6 (14.6)

During the application, we found food sensitivity in 31 (75.6%) patients according to allergen-specific IgE results and 28 (68.3%) patients according to SPT. 19 (46.3%) of the patients had egg sensitivity, 6 (14.6%) had cow milk sensitivity, and 3 (7.3%) had both cow milk and egg sensitivity. We did not detect aeroallergen sensitivity in any of our patients. However, when the patients reached the age of 5, according to SPT, aeroallergen sensitivity developed in 17 (41.4%). When they were 5 years old, 2 (4.9%) patients were sensitive to only food, 10 (24.4%) patients to only aeroallergens, 7 (17.1%) patients to both food and aeroallergens. However, all patients could consume the foods they were sensitive to without any problems. We found that the most common aeroallergen sensitivity in grasses/grains 6 (14.6%). When 41 patients reached the age of 5, 13 (31.7%) were diagnosed with asthma and 12 (29.2%) were diagnosed with allergic rhinitis. Of the 31 patients who were found to have food sensitivity at the time of application, 10 (32%) were diagnosed with asthma and 8 (25%) were diagnosed allergic rhinitis at the age of 5. However, there is no significant relationship between the presence of food allergy and the development of asthma ($p = 0.900$) or allergic rhinitis ($p = 0.250$). The allergen sensitive of the patients at the age of 5 is shown in Table II, and the development of allergic diseases in Table III.

The median Scorad score of the patients was 22 (min-max: 12-48). According to this scoring system, 15 (36.6%) of the

Table IV: Patients' total ige level, absolute eosinophil count, scorad score, age at admission and differences between gender.

Category	Female Median (Min-Max)	Male Median (Min-Max)	p	Total Median (Min-Max)
AD Diagnosis Age (Months)	4.5 (2-9)	7 (2-11)	0.180	7 (2-11)
Application Age (Months)	9 (2-23)	9 (3-21)	0.980	9 (2-23)
Scorad score	22.5 (15-38)	21 (12-48)	0.960	22 (12-48)
AEC in application (/uL)	200 (10-800)	400 (100-2200)	0.030	400 (10-2200)
Total IgE in application (IU/ml)	28.5 (10.6-158)	25.8 (1.1-322)	0.840	25.8 (1.1-322)
Total IgE at age 3 (IU/ml)	71.5 (20.7-303)	57.5 (9.8-568)	0.440	60.5 (9.8-568)
Total IgE at age 5 (IU/ml)	92.8 (17.1-350)	75 (14.6-818)	0.770	84 (14.6-818)
AEC at age 5 (/uL)	200 (0-400)	300 (100-900)	0.009	300 (0-900)
IgA at age 5 (mg/dl)	78.5 (41-100)	89 (48-317)	0.010	87 (41-317)

AD: *Atopic dermatitis,* ***AEC:*** *Absolute eosinophil count*

patients were in the mild, 22 (53.7%) were in the moderate and 4 (9.8%) were in the severe.

Total IgE level was 45 IU/ml and above in 17 patients (41.5%) at admission and in 27 patients (65.9%) aged 5 years. Total IgE level evaluated at admission, it was higher in patients with food sensitivity (p = 0.040). Additionally, the Total IgE level at the time of admission was higher in patients with AD recovery age greater than 24 months (p = 0.030). Total IgE levels of 5-year-old patients with positive SPT were also significantly higher (p = 0.003).

While eosinophilia was detected in 16 (39%) patients at the time of admission, it was found in 11 (26.8%) patients when they were 5 years old. In patients with eosinophilia at the time of admission, had more allergic diseases at the age of 5 years (p = 0.040). Also, we observed eosinophilia more frequently in male patients when they were 5 years old (p = 0.020). At the time of diagnosis, we found a positive correlation between high eosinophil count and Scorad scores (p = 0.030; r = 0.36).

Of the 21 (51.2) patients whose IgA levels were found to be low for age at the time of admission, only 8 (19.5%) of them were still low in the 5 years old. However, in all patients over 5 years of age, IgA level was above 40 mg/dl. The incidence of asthma was higher in patients with still low IgA levels at the age of 5 years (p = 0.030).

There were 32 (78%) patients who regularly used moisturizers during the active dermatitis period. Between the patients who used skin moisturizer and those who did not, we found a significant difference between the development of asthma (p <0.001).

In Table IV, the total IgE level of the patients, absolute eosinophil count, scorad score, distribution of age at presentation and diagnosis of AD and the difference between genders are shown.

We found that 30 (73.2%) of all patients had bronchiolitis attacks in the first 3 years of their lives. 24 of these 30 patients had food sensitive. However, we did not find a significant relationship between the presence of food allergy and having a bronchiolitis attack (p = 0.610). Of the 15 patients who had 3 or more episodes of bronchiolitis in the last 12 months, 8 were receiving regular low-dose inhaled corticosteroids, 4 were receiving montelukast, and 3 were receiving intermittent low-dose inhaled corticosteroid therapy.

The distribution of patients by the age of AD recovery; 20 (48.8%) in the first 2 years, 11 (26.8) in 25-48 months, 9 (22%) in 49-60 months, 1 (2.4%) above 60 months. The rate of bronchiolitis attack was higher in the group who received a diagnosis of AD over the age of 6 months. (p = 0.040). We found that 5-year-old IgA levels of patients diagnosed with AD in the first 6 months were lower (p = 0.040). Aeroallergen sensitivity more frequently in patients diagnosed with AD in the first 6 months (p = 0.020). However, we could not show its relationship with the presence of allergic diseases at the age of 5 (p = 0.150).

We did not find a relationship between the presence of atopy and scorad severity (p = 0.310) at the time of admission. However, we found that the Total IgE levels of patients who were atopic at admission were significantly higher at the time of admission (p = 0.005), 3 years old (p = 0.006), and 5 years old (p = 0.007).

Factors affecting the patients' risk of developing asthma and allergic rhinitis at 5 years of age were analyzed using univariate

Table V: Risk Factors For Developing Asthma And Allergic Rhinitis

	Asthma		AR	
	OR (CI 95%)	p	OR (CI 95%)	p
AD Diagnosis Age (Months)	0.93 (0.63-1.37)	0.720	1.20 (0.90-1.60)	0.200
Scorad score	1.00 (0.88-1.12)	0.990	1.04 (0.94-1.14)	0.390
Total IgE in application (IU/ml)	0.99 (0.97-1.02)	0.900	1.01 (0.99-1.04)	0.100
AEC^{c} in application (/uL)	0.99 (0.99-1.00)	0.740	1.00 (0.99-1.00)	0.480
Total IgE at age 3 (IU/ml)	1.01 (0.99-1.02)	0.280	0.99 (0.97-1.00)	0.380
Total IgE at age 5 (IU/ml)	0.99 (0.98-1.00)	0.590	1.00 (0.99-1.00)	0.900
IgA at age 5 (mg/dl)	1.08 (1.01-1.16)	0.010	1 (0,97-1,02)	0.880
Gender	5.73 (0.63-52.06)	0.120	0.81 (0.13-5.07)	0.820
Presence of atopy in parents	1.64 (0.39-6.84)	0.490	2.71 (0.54-13.51)	0.220
Food sensitivity at application	0.89 (0.15-5.04)	0.890	0.54 (0.08-3.37)	0.510
Aeroallergen sensitivity at age 5	0.95 (0.20-4.43)	0.950	0.163 (0.02-1.09)	0.060

AR: *Allergic Rhinitis,* ***AD:*** *Atopic dermatitis,* ***AEC:*** *Absolute eosinophil count*

logistic regression analysis. The age of onset of AD, gender, presence of food allergy and presence of atopy in the family were evaluated, but no significant risk factor was found on its own. The data are shown in Table V.

DISCUSSION

Atopic dermatitis most often begins between three and six months, and 60% of patients are diagnosed by the age of one (1). Nineteen (% 46.3) of our patients were diagnosed with AD in the first 6 months and all of them were diagnosed before the age of 2. Additionally, AD improved in about half of our patients in the first 2 years of age and almost all by the age of 5.

Food allergy (most commonly cow's milk and eggs) is present in 30% of patients with atopic dermatitis (10). In the Danish Allergy Research Cohort (DARC) study in which children from three months to six years of age were followed, food sensitivity was observed in 52% of 122 patients with AD, and food allergy confirmed by food provocation test was found in only 15% (11). In our study, we found food sensitivity in 28 (68.3%) of the patients, the most common being egg. There were 7 (17%) patients whose diagnosis was confirmed by food provocation test.

Especially, 35% of patients with early onset, severe and persistent AD have accompanying food allergy (1). Tsakok et al. (12), in the meta-analysis, the frequency of food sensitivity was found six times higher in those who had AD at the age of three months compared to those who had not. In our study, we found food sensitivity in 17 (41.4%) of 19 patients diagnosed with AD in the first 6 months. We did not find a relationship between the Scorad scores and food sensitivity of our patients.

In the TUCSON cohort, the development of AD in the first year of life has been shown to be a risk factor for persistent wheezing (1). Additionally, studies have shown that correcting the skin barrier can prevent subsequent atopic disorders (10). The rate of bronchiolitis attack was higher in our patients who were diagnosed with AD after the 6th month. We thought that the delay in diagnosis and treatment of AD might be effective in this situation.

In a study evaluating children diagnosed with AD in the first three months of life, it was reported that 69% were sensitized to aeroallergens until the age of five (13). In a different study in which 2270 children diagnosed with AD were evaluated, it was shown that 66% of the children developed asthma and/or allergic rhinitis at the age of three and these diseases were associated with poor AD control (14). In studies conducted with normal population; the frequency of asthma is 4-17.8% and the frequency of allergic rhinitis is 6.3-17.6% (15). When our patients are over the age of 5; aeroallergen sensitivity was developed in 17 (41.4%), asthma in 10 (31.7%) and allergic rhinitis (AR) in 12 (29.2%) patients. We did not find any correlation between food sensitivity and the development of asthma and / or AR at the age of 5 years. Therefore, we think that atopic dermatitis has

a more important risk in terms of respiratory allergic diseases than food sensitivity.

In studies, early-onset AD, male gender, presence of eosinophilia, food and aeroallergen sensitivity have been shown as risk factors for the development of asthma (4,16-19). In our study, we could not find a significant risk factor for the development of asthma or allergic rhinitis. This situation reminds us of the fact that asthma is a complex disease that occurs under the influence of genetic, environmental and epigenetic factors.

Mechanically, the questions of whether skin barrier defects will encourage allergen entry and whether this will contribute to allergic diseases afterward have been questioned in studies (5). However, the effect of early control of AD on atopic march is still unclear (20). We saw less asthma development in patients who regularly used moisturizers. We thought this might be related to the contribution of moisturizers to the skin barrier.

In a study conducted in our region; Asthma, past wheezing, atopic dermatitis, food allergy, and atopic sensitization were found to be higher in individuals with Ig A deficiency compared to studies conducted in a normal population (15). Similarly, we found that the frequency of asthma was higher in patients with still low IgA levels when they were 5 years old.

As a result, compared to the studies conducted in the normal population, we found the frequency of asthma and allergic rhinitis more in patients with AD. However, we could not show the relationship between food sensitivity and the development of asthma and/or allergic rhinitis. It should be kept in mind that the treatment of AD, especially the measures to protect the integrity of the skin, can help prevent the development of asthma. In order for clinicians to understand the heterogeneity of atopic disease models in children and to eliminate this variability, patients should be followed up in later life. This is also critical for the prognosis of allergic diseases.

The small sample size of the study, the absence of a control group, and the retrospective design of the study are the limitations of our study.

REFERENCES

1. Aksu K, Arga M, Asilsoy S Avcil S, Çetinkaya F, Civelek E, et al. Diagnosis and management of atopic dermatitis: national guideline 2018. Asthma Allergy Immunol 2018;16:1-130.
2. Uysal P, Uzuner N. How is atopic dermatitis diagnosed in children? İzmir Dr. Behçet Uz Çocuk Hastanesi Dergisi 2013;3:1-11.
3. Bawany F, Beck LA, Järvinen KM. Halting the march: primary prevention of atopic dermatitis and food allergies. J Allergy Clin Immunol Pract 2020;8: 860-75.
4. Aw M, Penn J, Gauvreau GM, Lima H, Sehmi R. Atopic March: Collegium Internationale Allergologicum Update 2020. Int Arch Allergy Immunol 2020;181:1-10.
5. Busse WW. The atopic march: fact or folklore? Ann Allergy Asthma Immunol 2018;120:116-8.
6. Rudzki E, Samochocki Z, Rebandel P, Saciuk E, Gałecki W, Raczka A, et al. Frequency and significance of the major and minor features of Hanifin and Rajka among patients with atopic dermatitis. Dermatology 1994; 189:41-6.
7. Just J, Deslandes-Boutmy E, Amat F, Desseaux K, Nemni A, Bourrat E, et al. Natural history of allergic sensitization in infants with early-onset atopic dermatitis: results from ORCA Study. Pediatr Allergy Immunol 2014; 25:668-63.
8. Bieber T, D'Erme AM, Akdis C, Traidl-Hoffmann C, Lauener R, Schäppi G, et al. Clinical phenotypes and endophenotypes of atopic dermatitis: Where are we, and where should we go? J Allergy Clin Immunol 2017; 139: 58-64.
9. Tezcan I, Berkel Al, Ersoy F, Sanal O. Sağlıklı Türk çocukları ve erişkinlerde turbidometrik yöntemle bakılan serum immunoglobulin düzeyleri. Çocuk Sağlığı ve Hastalıkları Dergisi 1996; 39;649-56.
10. Bantz SK, Zhu Z, Zheng T. The Atopic March: Progression from atopic dermatitis to allergic rhinitis and asthma. J Clin Cell Immunol 2014;5: 202.
11. Eller E, Kjaer HF, Høst A, Andersen KE, Bindslev-Jensen C. Food allergy and food sensitization in early childhood: results from the DARC cohort. Allergy 2009; 64: 1023-9.
12. Tsakok T, Marrs T, Mohsin M, Baron S, du Toit G, Till S, et al. Does atopic dermatitis cause food allergy? A systematic review. J Allergy Clin Immunol 2016; 137: 1071-8.
13. Klinnert MD, Nelson HS, Price MR, Adinoff AD, Leung DY, Mrazek DA. Onset and persistence of childhood asthma: predictors from infancy. Pediatrics 2001; 108: E69.
14. Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. J Allergy Clin Immunol 2013; 132: 1132-8.
15. Ağralı N, Köse SŞ, Asilsoy S, Anal Ö. Frequency of Atopic Diseases in Immunoglobulin A Deficiency. Journal of Dr. Behcet Uz Children's Hospital 2020;10:15-21.
16. Lowe AJ, Carlin JB, Bennett CM, Hosking CS, Abramson MJ, Hill DJ, et al. Do boys do the atopic march while girls dawdle? J Allergy Clin Immunol 2008; 121: 1190-5.
17. von Kobyletzki LB, Bornehag CG, Hasselgren M, Larsson M, Lindström CB, Svensson Å. Eczema in early childhood is strongly associated with the development of asthma and rhinitis in a prospective cohort. BMC Dermatol 2012; 12: 11.
18. Ćosićkić A. Development of respiratory allergies, asthma and allergıc rhinits in children with atopic dermatitis. Acta Clin Croat 2017; 56: 308-17.
19. Dharmage SC, Lowe AJ, Matheson MC, Burgess JA, Allen KJ, Abramson MJ. Atopic dermatitis and the atopic march revisited. Allergy 2014; 69: 17-27.
20. Maciag MC, Phipatanakul W. Preventing the development of asthma stopping the allergic march. Curr Opin Allergy Clin Immunol 2019;19:161.