The Presence of Atopic March in Patients Diagnosed with Atopic Dermatitis
Atopik Dermatit Tanılı Hastalarda Atoptik Yürüyüşün Varlığı

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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
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 admission 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 wheat 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 fariniae, 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 pteronyssinus, Dermatophagoides fariniae); 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 (\( p = 0.04; r = 1.00 \)).

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 (\( p = 0.01 \)). The demographic characteristics and laboratory findings of the patients are summarized in Table I.

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 with allergic rhinitis at the age of 5. However, there is no significant relationship between the presence of food allergy and the development of asthma (\( p = 0.90 \)) or allergic rhinitis (\( p = 0.25 \)). 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...
In Table IV, the total IgE level of the patients, absolute eosinophil count, scorad score, 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 = 0.61). 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 = 0.04). We found that 5-year-old IgA levels of patients diagnosed with AD in the first 6 months were lower (p = 0.04). Aeroallergen sensitivity more frequently in patients diagnosed with AD in the first 6 months (p = 0.02). However, we could not show its relationship with the presence of allergic diseases at the age of 5 (p = 0.15).

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).

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We did not find a relationship between the presence of atopy and scorad severity (p = 0.31) 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 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 (/µL)        | 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 (/µL)              | 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
The presence of atopic march

The presence of atopic march

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

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

| Table V: Risk Factors For Developing Asthma And Allergic Rhinitis |
| --- | --- | --- | --- |
| | Asthma | P | AR | P |
| AD Diagnosis Age (Months) | 0.93 | 0.720 | 1.20 | 0.200 |
| | (0.63-1.37) | | (0.90-1.60) | |
| Scorad score | 1.00 | 0.990 | 1.04 | 0.390 |
| | (0.88-1.12) | | (0.94-1.14) | |
| Total IgE in application (IU/ml) | 0.99 | 0.900 | 1.01 | 0.100 |
| | (0.97-1.02) | | (0.99-1.04) | |
| AECc in application (/uL) | 0.99 | 0.740 | 1.00 | 0.480 |
| | (0.99-1.00) | | (0.99-1.00) | |
| Total IgE at age 3 (IU/ml) | 1.01 | 0.280 | 0.99 | 0.380 |
| | (0.99-1.02) | | (0.97-1.00) | |
| Total IgE at age 5 (IU/ml) | 0.99 | 0.590 | 1.00 | 0.900 |
| | (0.98-1.00) | | (0.99-1.00) | |
| IgA at age 5 (mg/dl) | 1.08 | 0.010 | 1 | 0.880 |
| | (1.01-1.16) | | (0.97-1.02) | |
| Gender | 5.73 | 0.120 | 0.81 | 0.820 |
| | (0.63-52.06) | | (0.13-5.07) | |
| Presence of atopy in parents | 1.64 | 0.490 | 2.71 | 0.220 |
| | (0.39-6.84) | | (0.54-13.51) | |
| Food sensitivity at application | 0.89 | 0.890 | 0.54 | 0.510 |
| | (0.15-5.04) | | (0.08-3.37) | |
| Aeroallergen sensitivity at age 5 | 0.95 | 0.950 | 0.163 | 0.060 |
| | (0.20-4.43) | | (0.02-1.09) | |

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

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