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Atopic march in children with early-onset atopic dermatitis: A retrospective study

Marche atopique chez les enfants atteints de dermatite atopique précoce: une étude rétrospective

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ABSTRACT

Background. – Atopic march is a term that describes the progression of atopic disorders, from atopic dermatitis in young infants and toddlers to allergic rhinitis and asthma in later childhood. The aim of this study was to elucidate the course of allergic diseases between 3–7 years of age in patients with atopic dermatitis in the first 2 years of life.

Methods. – A total of 211 children have been analyzed in this retrospective study. The atopic dermatitis group consisted of 119 children diagnosed with atopic dermatitis between the ages of 0–2 in 2013 and the control group consisted of 92 children aged 0–3 months who had a hearing test for screening in the same year. The diagnoses of wheezing, atopic dermatitis, and allergic rhinitis in both groups below 2 years old and between 3–7 years old were examined from the hospital database and government e-health service.

Results. – The frequency of at least one wheezing attack (28.6% vs. 29.3%), at least three wheezing attacks (15.1% vs. 9.8%) and allergic rhinitis (22.7% vs. 22.8%) were not significantly different between atopic dermatitis and control groups in children between 3 and 7 years old. However, in the atopic dermatitis group, the frequency of at least one wheezing attack (42.6% vs. 19.4%, $P=0.006$), at least three wheezing attacks (25.6% vs. 8.3%, $P=0.011$), and allergic rhinitis (38.3% vs. 12.5%, $P=0.001$) were significantly higher in children with food sensitization than individuals without food sensitization.

Conclusion. – This study showed that the later allergic respiratory diseases in children with early-onset atopic dermatitis were associated with food sensitization regardless of early wheezing, and the persistence of atopic dermatitis was associated with multiple food sensitizations.

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R É S U M É

Contexte. – La marche atopique est un terme qui décrit la progression des troubles atopiques, depuis les tout-petits jusqu'à la rhinite allergique et l'asthme plus tard dans l'enfance. Le but de cette étude était d'élucider l'âge de 3 à 7 ans chez les patients atteints de dermatite atopique au cours des 2 premières années de vie.

Méthodes. – Au total, 211 enfants ont été analysés dans cette étude rétrospective. Le groupe dermatite atopique était composé de 119 enfants diagnostiqués avec une dermatite atopique âgés de 0 à 2 ans en 2013 et le groupe témoin était composé de 92 enfants âgés de 0 à 3 mois qui avaient passé un test auditif de dépistage la même année. Les diagnostics de respiration sifflante, de dermatite atopique et de rhinite allergique dans les deux groupes de moins de 2 ans et de 3 à 7 ans ont été examinés à partir de la base de données hospitalière et du service de santé en ligne du gouvernement.

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Résultats. – La fréquence d' au moins une crise sifflante (28,6 % vs 29,3 %), au moins trois crises sifflantes (15,1 % vs 9,8 %) et la rhinite allergique (22,7 % vs 22,8 %) n'étaient pas significativement différentes entre les dermatites atopiques et des groupes témoins chez les enfants entre 3 et 7 ans. Cependant, dans le groupe dermatite atopique, la fréquence d' au moins une crise de respiration sifflante (42,6 % vs 19,4 %, $p=0,006$), d' au moins trois crises de respiration sifflante (25,6 % vs 8,3 %, $p=0,011$) et de rhinite allergique (38,3 % contre 12,5 %, $p=0,001$) étaient significativement plus élevés chez les enfants avec une sensibilisation alimentaire que chez les individus sans sensibilisation alimentaire.

Conclusion. – Cette étude a montré que les maladies respiratoires allergiques tardives chez les enfants atteints de dermatite atopique précoce étaient associées à une sensibilisation alimentaire indépendamment d'une respiration sifflante précoce, et la persistance de la dermatite atopique était associée à de multiples sensibilisations alimentaires.

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1. Introduction

Atopic Dermatitis (AD) is a chronic inflammatory skin disease manifested by skin barrier dysfunction, frequent skin infections, and impaired quality of life. Depending on epidemiological studies, 60–80% of AD is seen in the first 2 years of life [1]. Atopic march is defined as the progression of atopic disorders, from atopic dermatitis in young infants and toddlers to allergic rhinitis and asthma in later childhood. The clinical signs of atopic dermatitis precede the development of allergic rhinitis and asthma, suggesting that atopic dermatitis marks the beginning of the atopic march [2]. In several prospective birth cohorts, it was shown that there was an association between early-onset atopic dermatitis and the development of allergic rhinitis and asthma at school age [3,4].

Atopy is defined as a personal and/or familial propensity to produce IgE antibodies and sensitization in response to allergen exposures. The major food allergens in pediatric patients with atopic dermatitis include egg whites, cow's milk, soy, wheat, and peanuts [5]. Patients with atopic dermatitis with specific IgE antibodies to common allergens (extrinsic atopic dermatitis) are at higher risk of allergic rhinitis and asthma than patients with atopic dermatitis without IgE sensitization (intrinsic atopic dermatitis) in atopic march [6]. The aim of this study was to elucidate the course of allergic diseases between 3–7 years of age in patients with atopic dermatitis in the first 2 years of life.

2. Methods

This single-center retrospective study has been conducted in Diyarbakır Children's Hospital, the largest children's hospital in Diyarbakır, Turkey. A total of 211 children have been analyzed in this retrospective study. The atopic dermatitis group consisted of 119 children diagnosed with atopic dermatitis by a pediatric allergist using Hanifin and Rajka (1980) criteria between the ages of 0–2 in 2013 and the control group consisted of 92 healthy children aged 0–3 months who had a hearing test for screening in the same year. The children's laboratory results were retrospectively analyzed from the hospital electronic database. The diagnoses of wheezing, atopic dermatitis, and allergic rhinitis in both groups below 2 years old and between 3–7 years old were examined from the hospital database and government e-health (e-pulse) service. E-pulse service is a personal health records system that allows users to access all health information and history, regardless of the institution and city. This study was approved by the ethics committee of the Diyarbakır Gazi Yaşargil Training and Research Hospital.

The diagnosis of wheezing has been conducted in patients who applied to the emergency department with respiratory distress and were received nebulized albuterol treatment. The wheezing below 2 years old was defined as early wheezing, the wheezing between 3 and 7 years old was defined as later wheezing. The patient has been

enrolled if the diagnosis of atopic dermatitis has been performed by a pediatric allergist or dermatologist and the diagnosis of allergic rhinitis has been performed by a pediatric allergist or otolaryngologist. Persistent atopic dermatitis has been diagnosed in patients with continue to have atopic dermatitis between 3 and 7 years old.

Laboratory data included specific IgE for food (egg white, cow's milk, wheat flour, hazelnut, and peanut), blood eosinophil count, and total immunoglobulin E (IgE) in the AD group. The control group had only blood cell counts in the records, so only eosinophil counts were examined in this group. The food sensitization diagnosis was made if food-specific IgE levels were >0.35 kU/L.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) program. Values were either provided as numbers and percentages or as mean $\pm$ standard deviation, where applicable. Comparisons of the frequency of all variables between groups were analyzed using the Chi² test, Fisher's exact test, and Student's *t*-test. A *P*-value of ≤ 0.05 was considered indicative of statistical significance.

3. Results

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) program. Values were either provided as numbers and percentages or as mean $\pm$ standard deviation, where applicable. Comparisons of the frequency of all variables between groups were analyzed using the Chi² test, Fisher's exact test, and Student's *t*-test. A *P*-value of ≤ 0.05 was considered indicative of statistical significance.

3.1. Comparison between the AD and control groups

The medical records of 119 patients with AD (AD group) and 92 healthy infants in the control group were analyzed. In the AD group, the mean age was 12.1 ± 7.3 months, and 72 (60.5%) were boys. The mean serum total IgE level was 157.9 ± 232.5 kU/L in the AD group. The mean blood eosinophil count was significantly higher in the AD group than in the control group ($738/\text{mm}^3$ vs. $364/\text{mm}^3$, $P < 0.001$).

The frequency of at least three wheezing attacks was significantly higher in the AD group than in the control group in children under 2 years old. (17.6% vs. 4.3%, $P = 0.002$). The frequency of persistent atopic dermatitis was significantly higher in the AD group than in the control group (21.8% vs. 5.4%, $P = 0.001$). The characteristics of AD and control groups are shown in Table 1.

3.2. Food sensitization in the AD group

Sensitization to food allergens have been observed in 39.5% ($n = 47$) of children. The most common was egg white, with 37.0% ($n = 44$ of 119) subjects. Also 12.7% ($n = 15$ of 118) of children had

Table 1
The characteristics of AD and control groups.

Characteristics	AD group <i>n</i> = 119 (%)	Control group <i>n</i> = 92 (%)	<i>P</i>
Gender (male)	72 (60.5%)	51 (55.4%)	0.274
Mean blood eosinophil count $\pm$ SD (mm ³)	738.1 $\pm$ 663.3	364.1 $\pm$ 400.7	<0.001
At least one wheezing below 2 years	52 (43.7%)	44 (47.8%)	0.323
At least three wheezing below 2 years	21 (17.6%)	4 (4.3%)	0.002
At least one wheezing between 3–7 years	34 (28.6%)	27 (29.3%)	0.511
At least three wheezing between 3–7 years	18 (15.1%)	9 (9.8%)	0.173
Allergic rhinitis between 3–7 years	27 (22.7%)	21 (22.8%)	0.555
Atopic dermatitis between 3–7 years	26 (21.8%)	5 (5.4%)	0.001

sensitization to cow's milk, 13.5% (*n* = 12 of 89) to wheat flour, 17.2% (*n* = 11 of 64) to hazelnut and 7.9% (*n* = 6 of 76) to peanut.

3.3. Comparison of children with and without food sensitization

The mean serum total IgE level was significantly higher in children with food sensitization compared to others (227 kU/L vs. 109 kU/L, *P* = 0.013). Moreover, the mean blood eosinophil count was higher in children with food sensitization, but there was no statistically significance (853/mm³ vs. 662/mm³, *P* = 0.134).

The frequency of at least one wheezing attack (42.6% vs. 19.4%, *P* = 0.006), at least three wheezing attacks (25.6% vs. 8.3%, *P* = 0.011), and allergic rhinitis (38.3% vs. 12.5%, *P* = 0.001) were significantly higher in children with food sensitization between 3 and 7 years old. However, the frequency of persistent atopic dermatitis was not significantly different between with and without food sensitization (19.1% vs. 23.6%, *P* = 0.367). The details food sensitization was shown in Table 2.

3.4. Egg white and cow's milk sensitization

The frequency of at least one wheezing attack (80.0% vs. 37.9%, *P* = 0.002) and at least three wheezing attacks (40.0% vs. 14.6%, *P* = 0.027) was significantly higher in children with cow's milk sensitization than in children without cow's milk sensitization under 2 years of age. The frequency of at least one wheezing attack (43.2% vs. 20.0%, *P* = 0.007) and at least three wheezing attacks (27.3% vs. 8.0%, *P* = 0.006) was significantly higher in children with egg white sensitization than in children without egg white sensitization between 3 and 7 years old.

3.5. Comparison of children with multiple food sensitizations and with single food sensitization

The mean serum total IgE level was significantly higher in children with multiple food sensitization (318 kU/L vs. 145 kU/L, *P* = 0.019). Moreover, the mean blood eosinophil count was higher in children with multiple food sensitization but there was no statistically significance (977/mm³ vs. 754/mm³, *P* = 0.369).

The frequency of at least one wheezing attack (61.9% vs. 30.8%, *P* = 0.033) and at least three wheezing attacks (33.3% vs. 7.7%, *P* = 0.032) was significantly higher in children with multiple food sensitization under 2 years old. Also, the frequency of persistent atopic dermatitis was significantly higher in children with multiple food sensitizations than in children with single food sensitization (33.3% vs. 7.7%, *P* = 0.032) (Table 3).

3.6. Comparison of children with and without persistent atopic dermatitis

The frequency of at least one wheezing attack (50.0% vs. 17.6%, *P* = 0.008) and allergic rhinitis (38.5% vs. 18.3%, *P* = 0.032) was significantly higher in children with persistent atopic dermatitis between 3 and 7 years old. The frequency of at least three wheezing attacks

was higher in children with persistent atopic dermatitis, but this was not statistically significant (26.9% vs. 11.8%, *P* = 0.061). The characteristics of children with and without persistent atopic dermatitis were shown in Table 4.

3.7. Comparison of children with and without wheezing under 2 years old

The frequency of at least one (36.5% vs. 22.4%, *P* = 0.068), and three later wheezing attacks (17.3% vs. 13.4%, *P* = 0.370), allergic rhinitis (25.0% vs. 20.1%, *P* = 0.377) and persistent atopic dermatitis (25.0% vs. 19.4%, *P* = 0.304) were not significantly different between children with and without wheezing under 2 years old.

4. Discussion

In this study we have found that 21.8% of patients with atopic dermatitis in the first 2 years of age continued to have atopic dermatitis between 3 and 7 years old. In a birth cohort study, 15.5% of patients with atopic dermatitis continued to have atopic dermatitis until the age of 11 [7]. Regarding these data, one can say that approximately one-sixth of children with atopic dermatitis at an early age continue to have atopic dermatitis in later childhood.

Previous studies have reported that one-third of children with atopic dermatitis have food sensitization under the age of 2, and egg white, cow's milk, wheat, and peanuts were the most common food types contributing to sensitization [5,8]. In this study, 39.5% of the patients with atopic dermatitis had food sensitization and the most common was egg white (37%) in patients under 2 years old. Unlike other studies, hazelnut sensitization was also common (17%) in patients with atopic dermatitis under the age of 2.

In the birth cohort of the Tucson Children's Respiratory Study, atopic dermatitis under 2 years was found to be associated with persistent wheezing at age 6 [4]. However, in a multicenter birth cohort study, it was found that in the first 2 years, atopic dermatitis alone was not a risk factor for later wheezing but sensitization and early wheezing were risk factors for later wheezing at age 7 [9]. Similarly, in our study, there was no significant difference between the AD and the control group in terms of later wheezing and allergic rhinitis, however, in the AD group, the frequency of later wheezing and allergic rhinitis were significantly higher in patients with food sensitization. These findings support the idea that an AD phenotype with high serum IgE levels and sensitivity to food allergens, which was noted in previous studies, maybe the initial step of atopic march [10,11].

Lowe A.J. et al. found that infants with allergic atopic dermatitis (atopic dermatitis + sensitization) had a greater risk at 7 years of age of having asthma and allergic rhinitis than infants with non-allergic atopic dermatitis, even after early wheezing had been excluded [12]. Lowe L. et al. identified that atopy, regardless of wheezing in the first 3 years of life was associated with lung dysfunction [13]. Similarly, there was no significant difference between early wheezing and later wheezing and allergic rhinitis in the AD group in our

Table 2

The characteristics of children with food sensitizations and without food sensitization in the AD group.

Characteristics	Children with food sensitization <i>n</i> = 47 (%)	Children without food sensitization <i>n</i> = 72 (%)	<i>P</i>
Gender (male)	33 (70.2%)	39 (54.2%)	0.059
Mean serum total IgE level $\pm$ SD (kU/L)	227.4 $\pm$ 238.0	109.1 $\pm$ 217.5	0.013
Mean blood eosinophil count $\pm$ SD (mm ³)	853.3 $\pm$ 749.5	661.9 $\pm$ 593.1	0.134
At least one wheezing below 2 years	21 (44.7%)	31 (43.1%)	0.505
At least three wheezing below 2 years	9 (19.1%)	12 (16.6%)	0.455
At least one wheezing between 3-7 years	20 (42.6%)	14 (19.4%)	0.006
At least three wheezing between 3-7 years	12 (25.6%)	6 (8.3%)	0.011
Allergic rhinitis between 3-7 years	18 (38.3%)	9 (12.5%)	0.001
Atopic dermatitis between 3-7 years	9 (19.1%)	17 (23.6%)	0.367

Table 3

The characteristics of children with multiple food sensitizations and with single food sensitization in the AD group.

Characteristics	Children with multiple food sensitization <i>n</i> = 21 (%)	Children with single food sensitization <i>n</i> = 26 (%)	<i>P</i>
Gender (male)	17 (81.0%)	16 (61.5%)	0.130
Mean serum total IgE level $\pm$ SD (kU/L)	318.4 $\pm$ 273.1	145.1 $\pm$ 168.4	0.019
Mean blood eosinophil count $\pm$ SD (mm ³)	977.5 $\pm$ 1029.4	754.0 $\pm$ 409.7	0.369
At least one wheezing below 2 years	13 (61.9%)	8 (30.8%)	0.033
At least three wheezing below 2 years	7 (33.3%)	2 (7.7%)	0.032
At least one wheezing between 3-7 years	11 (52.4%)	9 (34.6%)	0.177
At least three wheezing between 3-7 years	6 (28.6%)	6 (23.1%)	0.461
Allergic rhinitis between 3-7 years	9 (42.9%)	9 (34.6%)	0.391
Atopic dermatitis between 3-7 years	7 (33.3%)	2 (7.7%)	0.032

Table 4

The characteristics of children with and without persistent atopic dermatitis in the AD group.

Characteristics	Children with persistent atopic dermatitis <i>n</i> = 26 (%)	Children without persistent atopic dermatitis <i>n</i> = 93 (%)	<i>P</i>
Gender (male)	15 (57.7%)	57 (61.3%)	0.455
Mean serum total IgE level $\pm$ SD (kU/L)	199.2 $\pm$ 227.8	145.1 $\pm$ 234.0	0.333
Mean blood eosinophil count $\pm$ SD (mm ³)	735.6 $\pm$ 684.7	738.7 $\pm$ 661.1	0.983
At least one wheezing below 2 years	13 (50.0%)	39 (41.9%)	0.304
At least three wheezing below 2 years	6 (23.1%)	15 (26.1%)	0.289
At least one wheezing between 3-7 years	13 (50.0%)	21 (17.6%)	0.008
At least three wheezing between 3-7 years	7 (26.9%)	11 (11.8%)	0.061
Allergic rhinitis between 3-7 years	10 (38.5%)	17 (18.3%)	0.032

study. On the contrary, the frequency of later wheezing and allergic rhinitis was higher in patients with food sensitization.

Wand et al. showed that early-onset and early resolving atopic dermatitis did not increase the risk of allergic rhinitis and asthma development, while early-onset persistent atopic dermatitis increased the risk of allergic rhinitis development [14]. In our study, we have found that the frequency of later wheezing and allergic rhinitis was higher in children with persistent atopic dermatitis.

Chiu et al. reported that at 6 months of age; only sensitization to egg white (not milk or wheat) showed a statistically significant risk association with atopic diseases including eczema, rhinitis, and asthma at age 4 in a birth cohort study [15]. Ricci et al. have shown that egg sensitization was significantly associated with the development of asthma [16]. In our study, while the frequency of later wheezing was high in children with egg white sensitization, the frequency of early wheezing was high in children with cow's milk sensitization.

Hill et al. found that patients with multiple food allergies were at increased risk of developing asthma and allergic rhinitis as compared to patients with a single food allergy in a retrospective birth cohort study of nearly 30000 children [17]. However, in our study, we did not find a significant difference between multiple and single food sensitizations regard to later wheezing and allergic rhinitis, but the frequency of early wheezing and persistent atopic dermatitis were significantly higher in children with multiple food sensitization.

Limitations of this study are that it was retrospective, failed to classify the severity of atopic dermatitis, diagnosed food sensitization with specific IgE only, not performing the skin prick test, and small sample size. As noted in a review of atopic march by Bawany et al. many publications rely on diagnoses obtained through a history of symptoms or parent report, rather than diagnosis by physicians [18]. The strengths of this study are that diagnoses by a doctor rather than by parents' statements and by the e-pulse service, the patients' application to any hospital in the country can be monitored.

This retrospective study showed that early-onset atopic dermatitis did not increase the risk of later wheezing and allergic rhinitis. However, sensitization to food in children with early-onset atopic dermatitis increased the risk of later wheezing and allergic rhinitis. It was egg white sensitization that caused this increased risk. The multiple food sensitizations in children with early-onset atopic dermatitis increased the risk of early wheezing and persistence of atopic dermatitis but did not increase the risk of later wheezing and allergic rhinitis. Also, the persistence of atopic dermatitis increased the risk of later wheezing and allergic rhinitis.

In conclusion, this study showed that the later allergic respiratory diseases in children with early-onset atopic dermatitis were associated with food sensitization regardless of early wheezing, and the persistence of atopic dermatitis was associated with multiple food sensitizations. Also, the recurrent wheezing in the first 2 years

old was associated with atopic dermatitis and multiple food sensitizations. The larger prospective studies are needed to confirm these findings.

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Disclosure of interest

The author declare that they have no competing interest.

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