

## Characteristics of Atopic Dermatitis in a Post-childhood Atopic March Group

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**Background:** Little knowledge is available on the characteristic differences between patients with atopic dermatitis (AD) with and without atopic march after childhood.

**Objective:** To observe and compare the phenotypes of patients with AD in regards to atopic march tendency at a single point.

**Methods:** We enrolled patients with AD aged between 10 and 30 years. The patients were divided into the atopic march and non-atopic march groups on the basis of an investigator-designed survey questionnaire, and their serum-specific immunoglobulin E (IgE) levels or results of the skin prick test were compared.

**Results:** In a total of 182 patients enrolled in the study, 93 patients with atopic march and 89 patients with non-atopic march were observed. When their serum-specific IgE levels or results of the skin prick test were compared between the two groups, there was no significant difference, except for a in the atopic march group. Analysis of AD severity, family history of allergic diseases, and total IgE levels between the two groups showed no statistically significant differences.

**Conclusion:** Our findings suggest that although no apparent phenotype characteristics could differentiate the presence of atopic march, the history of the patient's allergic diseases should be revalidated, and clinicians should watch out for future developments of atopic march when a patient shows a high-class sensitization rate to dust mite. (**Korean J Dermatol 2017;55(2):110~115**)

**Key Words:** Atopic dermatitis, Atopic march, Allergic march, Dust mite

### INTRODUCTION

Atopic march is a natural history of atopic manifestations showing a sequence of atopic dermatitis (AD) progressing into allergic asthma (AA) and allergic rhinitis (AR)<sup>1</sup>. An estimated one-third of patients with AD develop asthma, and two-thirds develop AR<sup>1,2</sup>. The exact mechanism underlying the development of atopic march is still debatable; however,

most studies stress the causal relationship between AD and onset of other respiratory allergic diseases; a defective skin barrier during childhood eczema contributes to epidermal water loss, and entry of high molecular weight allergens, bacteria, and viruses leads to eventual onset of airway hyper-responsiveness<sup>3</sup>.

Because atopic march is a phenomenon of sequential events, longitudinal cohort studies are widely performed on the topic, with the study periods mostly concentrated during infancy and childhood<sup>2,4-8</sup>. From a general point of view, early onset of childhood eczema<sup>4</sup>, more severe eczema in childhood<sup>2,6-10</sup>, and family history of atopic diseases all possess possible contribution to the development of atopic march.

The usual course of atopic march after childhood presents with resolving eczema but with persistent asthma and rhinitis<sup>9</sup>. Yet, there is still a small portion of patients with atopic march who visit dermatologists with persistent

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dermatitis or delayed onset of eczema well after childhood<sup>11</sup>. Until now, the characterization of patients with atopic march who retain AD after childhood was never fully explored. Thus, in this brief study attempting to observe only at a single point, we aimed to compare the phenotypes of the patients with AD after childhood on the basis of their atopic march tendency.

## MATERIALS AND METHODS

The study examined patients aged between 10 and 30 years who were diagnosed with AD on the basis of the Hanifin and Rajka criteria. On the patient's initial visit, family history of allergic diseases was determined in accordance with an investigator-designed survey questionnaire. If the patients had any history of allergic diseases other than AD, regardless of its activity at the time of their initial visit, the patients were classified into the atopic march group. Those without atopic march tendency and presenting only with AD were classified into the non-atopic march group. Blood tests, including the serum-specific IgE (sIgE) test with the ImmunoCAP system (Phadia, Uppsala, Sweden) and skin prick test (SPT), were performed to compare the sensitization rates to commonly noted allergens in AD.

The following allergens were included for the sIgE analysis: *Dermatophagoides farinae* (d2), egg white (f1), milk cow (f2), soybean whole (f14), pork (f26), and wheat (f4). If the quantitative result was <0.35 kIU/L, the sIgE was determined as absent (class 0). An sIgE of >0.35 was considered a positive allergic response, and the values were further classified as follows: 0.35 to 0.7 kIU/L (class 1), 0.7 to 3.5 kIU/L (class 2), 3.5 to 17.5 kIU/L (class 3), 17.5 to 50 kIU/L (class 4), 50 to 100 kIU/L (class 5), and >100 kIU/L (class 6).

SPT with 55 inhalant allergens was performed as stated in

a previous study<sup>12</sup>. For the analysis, we grouped similar allergens into 7 groups as follows: tree pollen, grass pollen, fungal allergens, dust mite, animal dander, cockroach, and food allergens.

For the designation of allergy testing performed in the patients, those with eczema on their back, history of urticaria or dermatographism could not undergo SPT; instead, the sIgE was measured. Further, those who refused to undergo SPT owing to its time-consuming nature were candidates for sIgE measurement. No other strict criteria were set for designating the patients for sIgE and SPT. Basic laboratory workups for serum total IgE and serum eosinophil were performed, and the results are shown as mean standard deviations (mean±SDs). The severity of AD was evaluated using the Eczema Area and Severity Index (EASI). Data management and statistical analyses were performed using the IBM Statistical Package for Social Sciences Statistics, version 18 software (SPSS Inc., Chicago, IL, USA).

## RESULTS

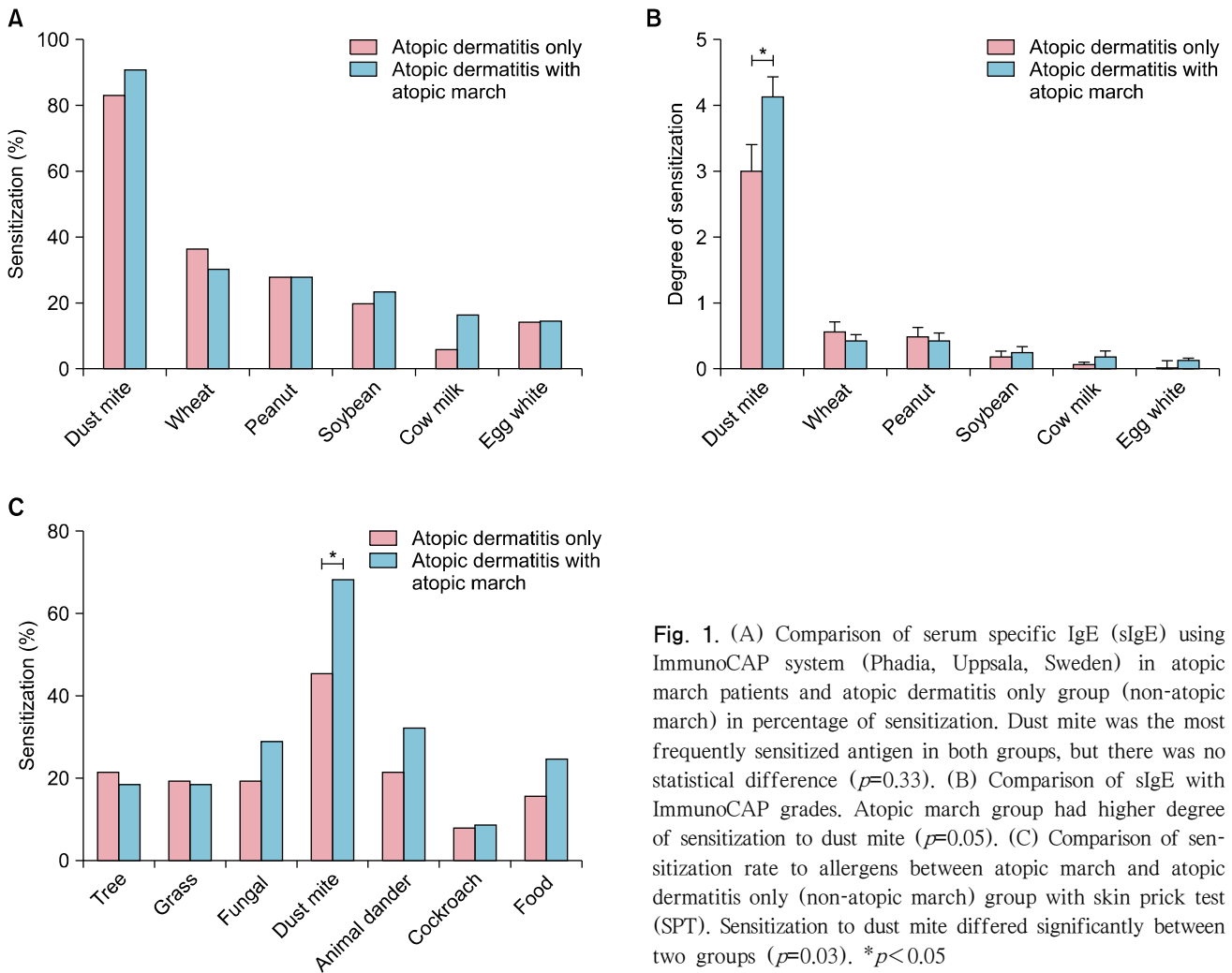
A total of 93 patients with atopic march and 89 patients with non-atopic march were observed. After the allocation of the patients into two allergen tests, 79 patients (36 non-atopic march, 43 atopic march) underwent sIgE testing, and 103 patients (53 non-atopic march, 50 atopic march) underwent SPT.

A relatively comparable number of patients for both sexes were included in the two groups. The characteristics of the enrolled patients are described in Table 1. No significant difference existed concerning the patients' baseline demographics.

Analysis of the sIgE allergen sensitization rate showed that both patients with atopic march and non-atopic march most strongly sensitized to dust mite. In the non-atopic

**Table 1.** Characteristics of study population, divided according to allergen tests performed

	Serum specific IgE			Skin prick test		
	Non-atopic march (n=36)	Atopic march (n=43)	<i>P</i> -value	Non-atopic march (n=53)	Atopic march (n=50)	<i>P</i> -value
Male	22	27	0.87	21	22	0.65
Female	14	16	0.87	32	28	0.65
Age	24.11±6.69	23.51±7.14	0.7	19.91±10.17	18.20±6.87	0.32
EASI	19.35±10.59	18.14±9.23	0.59	11.32±7.61	11.98±7.85	0.69
Total IgE	1963.91±1930.09	1385.89±1525.88	0.42	752.94±1096.02	927.36±1026.41	0.41
WBC count (×1000)	7.02±1.78	7.2±1.65	0.65	6.86±1.58	7.13±1.58	0.38
Eosinophil %	6.11±3.59	6.74±3.39	0.43	4.73±2.92	5.51±2.98	0.2



**Fig. 1.** (A) Comparison of serum specific IgE (sIgE) using ImmunoCAP system (Phadia, Uppsala, Sweden) in atopic march patients and atopic dermatitis only group (non-atopic march) in percentage of sensitization. Dust mite was the most frequently sensitized antigen in both groups, but there was no statistical difference ( $p=0.33$ ). (B) Comparison of sIgE with ImmunoCAP grades. Atopic march group had higher degree of sensitization to dust mite ( $p=0.05$ ). (C) Comparison of sensitization rate to allergens between atopic march and atopic dermatitis only (non-atopic march) group with skin prick test (SPT). Sensitization to dust mite differed significantly between two groups ( $p=0.03$ ). \* $p<0.05$

march group, 83.3% of the patients were sensitized to dust mite, whereas in the atopic march group, 90.7% were sensitized to the same allergen (Fig. 1A). However, the difference between the two groups was not statistically significant ( $p=0.33$ ). However, when the sIgE sensitization rate was further analyzed for grades of sensitization (class 0 to class 6), the mean sensitization degree to dust mite sIgE in the non-atopic march group was 2.51 and that in the atopic march group was 4.12. The difference between the two groups was statistically significant ( $p=0.05$ ) (Fig. 1B). Sensitization degree to other allergens showed no difference.

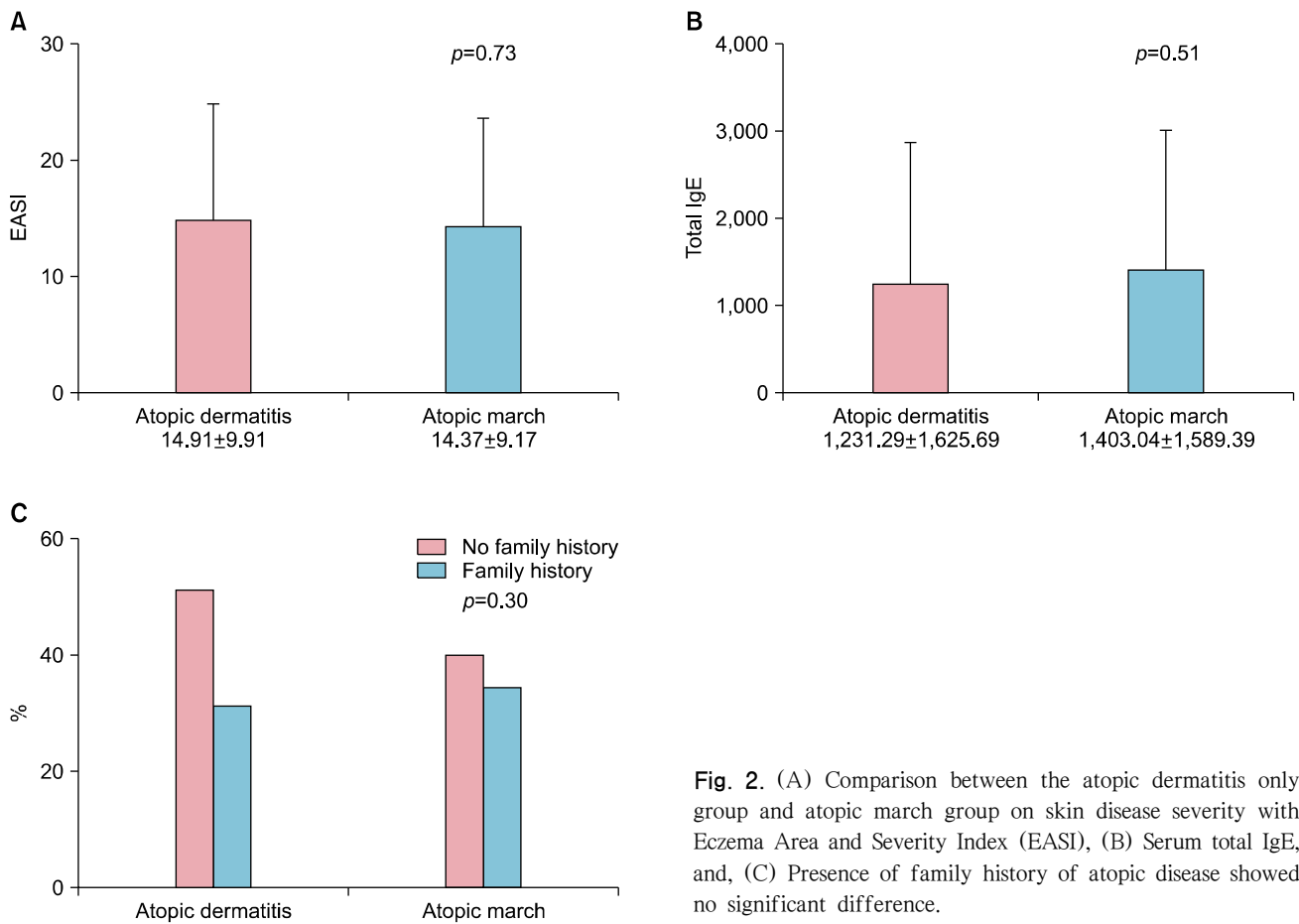
In the SPT group, majority of the patients also showed sensitization to dust mite as shown in the sIgE-tested group. The atopic march group showed a 68% sensitization rate to dust mite, whereas the non-atopic march group showed 45.3% (Fig. 1C). The difference between the two groups was statistically significant ( $p=0.03$ ). The enrolled patients

only showed minimal sensitization to other groups of allergens, including grass pollen, tree pollen, and animal dander.

Comparison of AD severity with EASI, serum total IgE, and presence of family history between the two groups revealed no remarkable differences (Fig. 2A~C). There was no difference in the level of serum eosinophil as well (data not shown). In summary, the only notable difference between the patients with AD with and without atopic march was the presence of a “greater” degree of sensitization to dust mite.

## DISCUSSION

Most patients with atopic march have resolving eczema after childhood. If symptoms of atopy persist, they are often present in forms of rhinitis or asthma. However, there is a



**Fig. 2.** (A) Comparison between the atopic dermatitis only group and atopic march group on skin disease severity with Eczema Area and Severity Index (EASI), (B) Serum total IgE, and, (C) Presence of family history of atopic disease showed no significant difference.

small portion of a subpopulation with consistent flare-ups of AD even after childhood. Further, a concept of “reverse atopic march” has once been suggested by one study showing 20% of children with asthma only at baseline eventually developing AD around a mean age of 7 years<sup>11</sup>.

In our study, we observed that the sensitization to dust mite is possibly important in differentiating between patients with AD with and without atopic march. Sensitization to dust mite in AD is common, and the greatest concentration of IgE in the patients with AD is known to be specific for dust mite<sup>13</sup>. More prevalent rates to dust mite sensitization in the patients with AD are observed when compared with those in asthmatic patients<sup>14</sup>. However, with findings of dust mite even more strongly sensitized in the patients with atopic march—a group with possibly more defects in the skin barrier—it is possible to theorize that skin sensitization to dust mite may occur prior to airway sensitization, contributing to the future development of other allergic diseases<sup>15,16</sup>.

For other aeroallergens, such as pollen and animal dander,

sensitization was detected in both groups; however, the difference was not noticeable. Our result is in contrast with that of a recent study by Celakovska et al.<sup>17</sup>, which reported animal dander as one of the most important allergens in atopic march. Considering the results from a longitudinal study of a birth cohort of New Zealand children, which showed sensitivities to house dust mite and cat dander being highly significant independent risk factors associated with the development of asthma, the prevalence of other aeroallergens could not be entirely ignored<sup>18</sup>. Nevertheless, sensitization to allergens aside from dust mite is often dependent on local community climate, lifestyle, and socio-economic features; thus, in the future, appropriateness of various allergens in post-childhood Korean patients should be evaluated in more detail. Additionally, our study only explored one type of dust mite, *D. farinae*, as it is the most commonly detected dust mite allergen in Koreans. However, a more detailed analysis could be more useful if other dust mite allergens are utilized in further studies.

Hence, with our results, we suggest that although dust

mite sensitization is present in both patients with atopic march and non-march AD, the greater degree of sensitization present in the atopic march group could be due to a more prevalent defective barrier function that eventually leads to future airway sensitization.

Another interesting point of our observation was that contrary to a generally known phenomenon that the severity of AD is related to the development of atopic march, the difference in disease severity was not noted between the two groups when assessed after childhood. The lack of phenotype differences between the two groups could be because of a general tendency of eczema subsiding as age progresses; however, when adjusting for confounding factors, such as closer follow-up periods, frequent treatment of eczema or concomitant allergic diseases in the patients with atopic march might influence their outcomes into adulthood. We also cannot ignore that this study was based on patients who were referred to a tertiary level hospital. Selection bias could have included patients only requiring frequent follow-ups to hospitals, leaving out patients with AD with mild and infrequent eczematous lesions.

The use of an investigator-designed survey questionnaire is another limitation that needs improvement in future studies. A lack of clinical verification for some allergic disease diagnoses led to a rather crude study design. Further, as the onset of diseases could not be determined in the questionnaire, a sub-analysis on the comparison between the onset of atopic march diseases and other allergic diseases and comparison of AD onset between the atopic march and non-march groups could not be performed. Thus, the reliability and accuracy of the investigator-designed survey questionnaire should be verified in future studies.

Lastly, because our study was not a longitudinal prospective cohort study, which can oversee the natural history of the atopic march and non-atopic march groups, there could be a portion of patients whose phenotypes may evolve into atopic march in later years along with a possible portion of patients who would demonstrate a "reverse atopic march." Nevertheless, our study has strengths in terms of attempting to observe, at one point, the key characteristic differences between the two groups after childhood for the first time.

## CONCLUSION

In conclusion, there were no significant differences between the patients with AD with and without atopic march, except for the sensitization degree to dust mite. This finding could be portrayed as no apparent phenotype difference between the two groups was found when judged solely on the basis

of the clinical characteristics. However, if a patient shows a high-class sensitization rate to dust mite, clinicians should watch out for the onset of other allergic diseases or reconfirm the patient's allergic disease histories.

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