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Effect of moderate to severe atopic dermatitis on the prognosis of egg allergy resolution

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Abstract

Background: Few studies have examined the effect of atopic dermatitis (AD) on the resolution of food allergies in Asia, and the predictors of egg allergy resolution are not yet well defined.

Objective: We evaluated whether AD severity could predict the resolution of egg allergy.

Methods: This retrospective cohort study included infants under 24 months of age diagnosed with IgE-mediated egg white allergy. We included subjects who completed a 60-month follow-up. Open oral food challenges (OFCs) and serologic tests were performed at the time of initial diagnosis and at 36 ± 3 and 60 ± 3 months.

Results: We analyzed 68 patients (39 boys and 29 girls). OFCs were performed in 88.2% of the patients. The egg allergy remission rates were 23.5% and 47.1% by 3 and by 5 years of age, respectively. Persistent egg allergy was significantly associated with moderate to severe AD and house dust mite sensitization. Kaplan–Meier curve analysis revealed that patients with moderate to severe AD had higher persistent egg allergy rates than patients with no and mild AD ($p = 0.012$). Multivariable analysis identified moderate to severe AD as strongly associated with persistent egg allergy ($p = 0.001$).

Conclusion: In this study, 47.1% of infants had resolved egg white allergies at 60 months. Moderate to severe AD may be a practical and important prognostic factor for persistent egg allergy in clinical settings.

Key words: Egg allergy, atopic dermatitis, food allergy, prognosis, child

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Introduction

Evaluation and prediction of food allergy resolution are important. Prognostic factors should also be investigated to understand the natural course and management of food allergies in patients. Moreover, due to differences in race, food allergy prevalence, and food intake culture, more studies on the natural course of food allergies in Asian countries, including Korea, are required.

Atopic dermatitis (AD) is a common skin disease characterized by inflammatory, chronically relapsing, and pruritic eczematous flares and marked by skin barrier dysfunction and impaired quality of life.[1] AD is the first manifestation of an atopic march which begins in early infancy. Recently, the hypothesis that impaired skin barrier in AD initiates progression to epicutaneous sensitization, food allergy, and respiratory allergy in later life has become an important topic in the study of allergies. Recent cohort studies showed an increased risk of food allergy and allergic airway disease in late childhood in patients with early-onset persistent AD.[2,3] Strong evidence indicates a link between early-onset AD and the development of other allergic diseases, especially food allergy.[1,4] Approximately 40% of AD patients have a food allergy, the prevalence of which is higher in children with severe AD.[1,5,6] Previous studies on the association between AD and food allergy focused on the development of food allergy in AD patients. Some examined the effects of AD on the natural course of food allergy, mostly in western countries.[7,8]

Therefore, we hypothesized that the skin barrier dysfunction in AD is a predictor of poor prognosis of food allergy.

We focused on patients with egg allergy, one of the most common childhood food allergies, and assessed whether AD severity could predict the resolution of egg allergy in Korean children.

Methods

This retrospective cohort study included infants under 24 months of age diagnosed with immunoglobulin E (IgE)-mediated egg white allergy between January 2011 and December 2013 at Pusan National University Hospital, Busan, Republic of Korea. The eligibility criteria were: (1) diagnosed egg allergy defined by the presence of a positive oral food challenge test (OFC) with egg white or anaphylaxis or repeated episodes of clinical reactions after the ingestion of egg white within 3 months. Patients who could not be administered egg white because of their inherent antigen-specific IgE levels were excluded. (2) Complete follow-up to 60 months of age, and (3) both OFC and serologic tests performed at initial diagnosis and 36 ± 3 and 60 ± 3 months. This study protocol was approved by the Institutional Review Board of Pusan National University Hospital (PNUHIRB 1801-028-063).

Open OFC was performed initially and at 36 ± 3 and 60 ± 3 months under the supervision of allergists according to Korean guidelines.[9,10] Briefly, the patients were challenged with boiled egg white at a total dose of 0.15–0.3 g protein per kilogram body weight. The total challenging dose did not exceed 3 g of protein. Over 90 minutes, the patients received egg white in increments of 1, 4, 10, 20, 20, 20, and 25% of the total amount every 15 minutes. The tests were considered positive when the attending pediatric allergist confirmed the appearance of one or more of the following objective symptoms within 2 hours of the last challenge dose; urticaria, angioedema, cough, rhinorrhea, wheezing, stridor, breathing difficulty, vomiting, or low blood pressure.[9,11,12]

Sera from all 68 patients were obtained at the time of the initial visit and at 36 ± 3 and 60 ± 3 months. Levels of specific IgE (sIgE) antibodies against the allergens (egg white, house dust mite [HDM] *Dermatophagoides pteronyssinus* [DP] and *D. farina* [DF]) were measured by ImmunoCAP (Thermo Fisher Scientific Inc., Waltham, MA, USA). Sensitization was defined as sIgE levels of 0.35 kU/L or greater. sIgE antibody levels above 100 kU/L were assigned a value of 101 kU/L for analysis.

AD was diagnosed based on the criteria proposed by Hanifin and Rajka.[13] AD severity was classified using the Scoring Atopic Dermatitis system (SCORAD) as mild (< 15), moderate (15-40), or severe (> 40) depending on the area, intensity, and subjective symptoms.

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). Data for continuous variables were shown as median and interquartile ranges. Fisher's exact test, Mann–Whitney U test, or one-way analysis of variance (ANOVA) with post hoc comparison tests were used for intergroup comparisons. Cumulative survival curves were estimated by the Kaplan–Meier method and relationships between the cumulative probability of egg tolerance and the prognostic factors were analyzed using log-rank tests. The influence of prognostic factors on egg allergy resolution was evaluated by univariable Cox regression analyses. The relative importance of multiple prognostic factors on egg allergy resolution was analyzed using multivariable analysis in conjunction with the Cox proportional regression model. Variables with p-values < 0.2 in univariable analysis were included in the multivariable analysis. Candidate variables for adjustment included sex, age at diagnosis (< 1 or ≥ 1 year), vaginal delivery (yes or no), exclusive breastfeeding under 6 months (yes or no), anaphylaxis (yes or no), concomitant allergic diseases (presence or absence), family history of allergic diseases (presence or absence), AD severity (none, mild, or moderate to severe), HDM sensitization (negative or positive), total IgE (< 200 or ≥ 200 kU/L), eosinophils (< 4 or ≥ 4%), baseline egg white sIgE at diagnosis (< 20 or ≥ 20 kU/L). $P < 0.05$ was considered statistically significant.

Results

The medical records of 165 patients with IgE-mediated egg white allergy were longitudinally reviewed. Of the patients, 92 received regular follow-up by pediatric allergists. We analyzed 68 patients (39 boys and 29 girls) who both completed the follow-up and underwent regular serologic testing to assess their current status up to 60 months. Sixty participants (88.2%) underwent OFC, 8 (11.8%) of whom had a history of egg allergy (**Figure 1**).

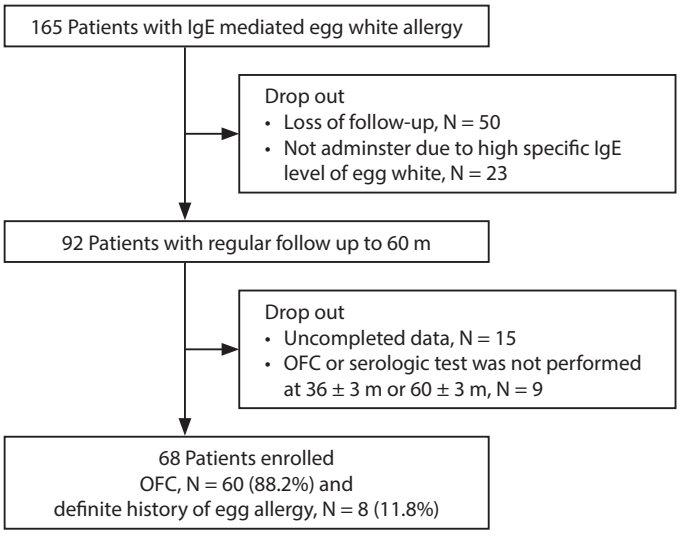

Figure 1. Flow chart showing the inclusion and exclusion of the study participants
m, months; OFC, oral food challenge

The demographic data of these patients are shown in **Table 1**. The median age of the study subjects at diagnosis was 10.2 years (range 7–16) and anaphylaxis was present in 16 (23.5%) patients. At diagnosis, 20, 23, and 25 patients had no, mild, and moderate to severe AD. The baseline median egg white sIgE level was 19.1 (interquartile range [IQR] 6.7–35.7) kU/L. Forty-seven (69.1%) patients were sensitized to HDM. Persistent egg allergy was significantly associated with moderate to severe AD and HDM sensitization (p = 0.002 and 0.037, respectively). The median egg white-sIgE levels at 36 and 60 months of age were higher in the persistent egg allergy group

Table 1. Demographic data of children with immunoglobulin E (IgE)-mediated egg white allergy (N = 68)

Characteristics	All	Egg allergy resolved				*p* value
		No		Yes		
		N	%	N	%	
Total subjects	68	36	52.9	32	47.1	
Sex						0.477
Male	39	21	53.84	18	46.15	
Female	29	15	51.72	14	48.72	
Age at diagnosis, months*	10.2 (8.6–13.1)	10.1 (8.5–12.9)		10.2 (8.7–13.3)		0.741
Vaginal delivery	40	21	52.50	19	47.50	0.321
Exclusive breast feeding for 6 months	16	9	56.25	7	43.75	0.101
Concomitant allergic diseases at diagnosis	48	25	52.08	23	47.91	0.256
Family history of allergic disease	33	17	51.21	16	49.49	0.247
Anaphylaxis	16	9	56.25	7	43.75	0.101
Baseline AD severity						**0.002**
None	20	7	35.00	13	65.00	
Mild	23	9	39.13	14	60.86	
Moderate to severe	25	20	80.00	5	20.00	
HDM sensitization	47	30	63.83	17	36.17	**0.037**

Abbreviations: AD: atopic dermatitis, HDM: house dust mite
*median (interquartile range)

than in those in the tolerance group (p = 0.015 and 0.010, respectively) (**Figure 2**).

Figure 3a shows the Kaplan–Meier curves for egg allergy resolution. The remission rates of the study population with egg allergy were 23.5 and 47.1% at 36 and 60 months, respectively. **Figure 3b** shows that patients with moderate to severe AD had higher persistent egg allergy rates than those in patients with no and mild AD (p = 0.008). The remission rates of egg allergy at 36 ± 3 and 60 ± 3 months in the non-AD group were 35 and 65%, respectively; 30 and 56.5% in the mild AD group, respectively; and 8 and 24% in the moderate to severe AD group, respectively. The median [IQR] egg white-sIgE levels

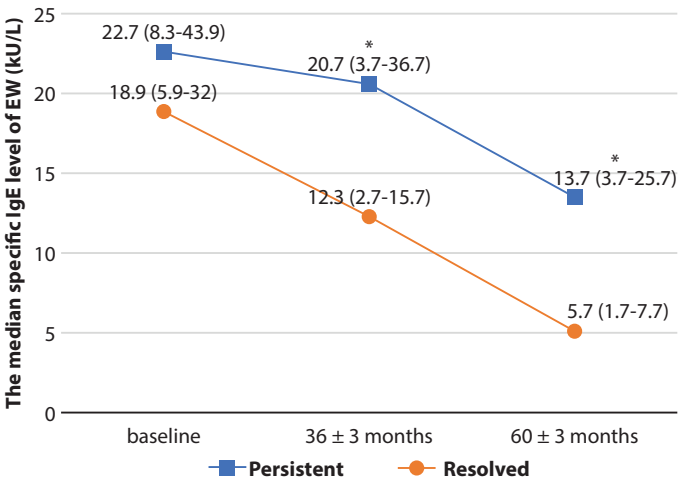

Figure 2. The median egg white-specific immunoglobulin E (IgE) levels in the resolved and persistent groups at 36 and 60 months of age (*p = 0.015, 0.010, respectively)
EW, egg white

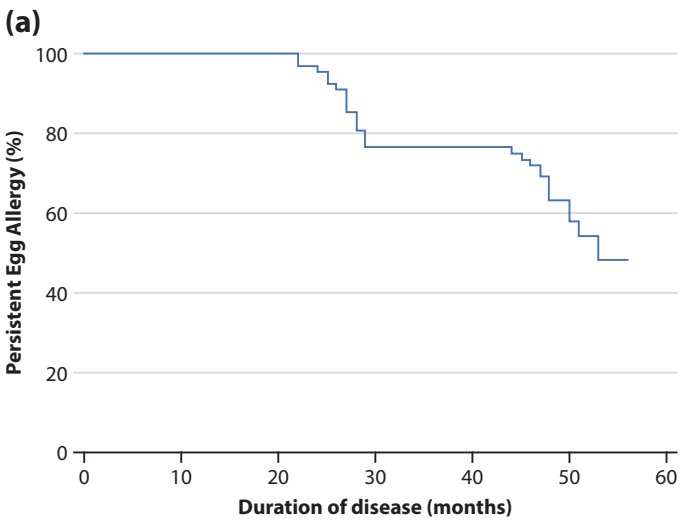

Figure 3. Kaplan–Meier analysis of egg allergy remission over time. (a) Remission rate of 68 patients

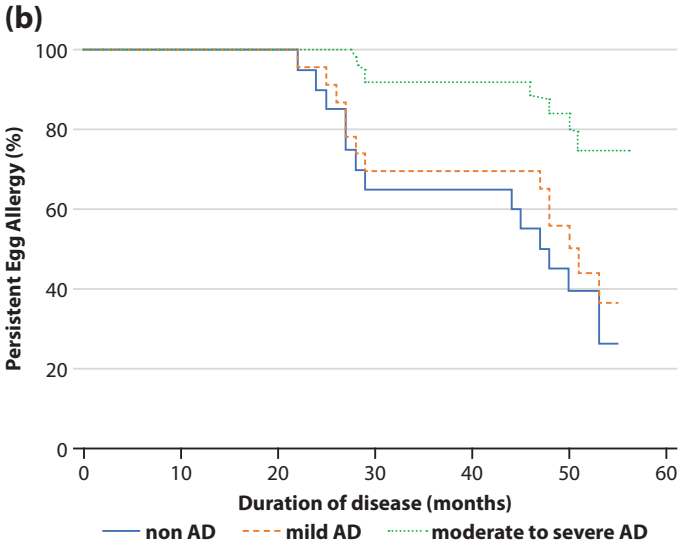

Figure 3. (Continued) (b) Remission rates of groups according to atopic dermatitis severity ($P = 0.008$)

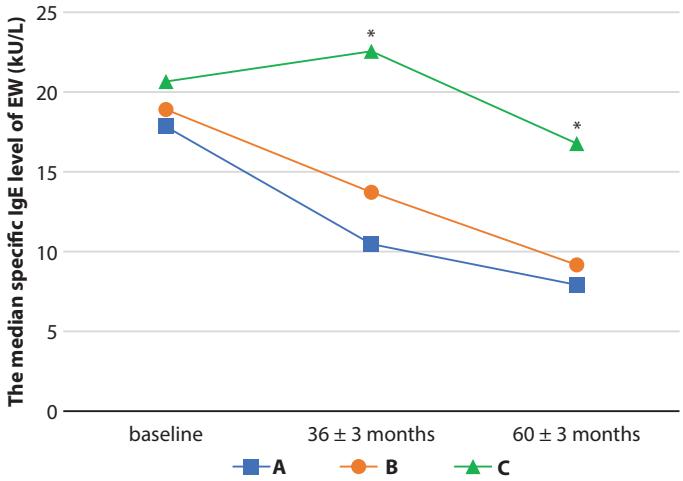

Figure 4. The median levels of specific immunoglobulin E (sIgE) to egg white
A: Egg allergy without atopic dermatitis
B: Egg allergy with mild atopic dermatitis
C: Egg allergy with moderate to severe atopic dermatitis
*$p = 0.01$

at the time of diagnosis in the no, mild and moderate to severe AD groups were 17.8 [5.4–30.5], 18.9 [7.9–30.3], and 20.7 [9.7–35.7] kU/L, respectively. No significant differences were found between the three groups at the time of egg allergy diagnosis. However, the median [IQR] egg white-sIgE levels at 36 ± 3 and 60 ± 3 months were 10.5 [2.0–12.8] and 7.9 [1.2–10.8] kU/L in the no AD, 13.8 [2.7–17.7] and 9.1 [1.9–16.9] kU/L in the mild AD, and 22.5 [9.0–40.1] and 16.8 [9.3–30.8] kU/L in the moderate to severe AD groups, respectively. The median egg white-sIgE levels at 36 ± 3 and 60 ± 3 months were higher in the moderate to severe AD group than in the other groups ($p = 0.010$) (**Figure 4**).

The prognostic factors for egg allergy resolution in the univariate and multivariate Cox regression analyses are shown in **Table 2**. Baseline moderate to severe AD, high baseline egg white-sIgE (≥ 20 kU/L), and HDM sensitization were significantly associated with persistent egg allergy in univariable analysis ($p = 0.010$, 0.031, and 0.042, respectively). However, only moderate to severe AD was a significant prognostic factor of persistent egg allergy in multivariable analysis (hazard ratio = 2.521, 95% confidence interval [CI]: 1.855–3.211, $p = 0.012$). Sex, age at diagnosis, vaginal delivery, exclusive breastfeeding, concomitant allergic disease, family history of allergic diseases, anaphylaxis, HDM sensitization, and laboratory findings were not statistically related to persistent egg allergy.

Table 2. Prediction of egg allergy resolution according to univariable and multivariable Cox analyses.

Variables	Univariable analysis			Multivariable analysis		
	Hazard ratio*	95% CI	p-value	Hazard ratio*	95% CI	p-value
Sex						
Male	1					
Female	0.945	(0.612–1.325)	0.797			
Age at diagnosis (years)						
< 1	1					
≥ 1	0.996	(0.762–1.292)	0.733			
Vaginal delivery						
No	1					
Yes	0.912	(0.779–1.263)	0.881			

Abbreviations: AD: atopic dermatitis., EW: egg white, HDM: house dust mite
**Under 6 months of age
*Hazard ratio > 1 indicates a proportional increase in the chance of persistent egg allergy

Table 2. (Continued)

Variables	Univariable analysis			Multivariable analysis		
	Hazard ratio*	95% CI	p-value	Hazard ratio*	95% CI	p-value
Exclusive breastfeeding*						
No	1					
Yes	0.927	(0.821–1.291)	0.679			
Concomitant allergic disease						
No	1					
Yes	1.231	(0.879–1.563)	0.381			
Family history of allergic disease						
No	1					
Yes	1.068	(0.770–1.479)	0.693			
Anaphylaxis						
No	1			1		
Yes	1.383	(0.861–1.722)	0.180	1.393	(0.837–2.320)	0.202
Baseline AD severity						
No	1			1		
Mild	1.321	(0.961–1.613)	0.098	1.287	(0.909–1.498)	0.062
Moderate to severe	2.768	(1.869–3.522)	0.010	2.521	(1.855–3.211)	0.012
Baseline EW-specific IgE (kU/L)						
< 20	1			1		
≥ 20	1.345	(1.052–1.774)	0.031	1.211	(0.892–1.447)	0.071
HDM sensitization						
No	1			1		
Yes	1.346	(1.074–2.63)	0.042	1.232	(0.891–1.932)	0.174
Total IgE at diagnosis (kU/L)						
< 200	1					
≥ 200	1.093	(0.791–1.511)	0.590			
Eosinophils at diagnosis (%)						
< 4	1					
≥ 4	1.059	(0.756–1.486)	0.737			

Abbreviations: AD: atopic dermatitis., EW: egg white, HDM: house dust mite
**Under 6 months of age
*Hazard ratio > 1 indicates a proportional increase in the chance of persistent egg allergy

Discussion

This retrospective cohort study based on OFC results investigated the natural history of immediate-type egg white allergy in Korean children. We found remission rates of 23.5% by 3 years of age and 47.1% by 5 years of age in the study subjects. The results of the Cox proportional regression model revealed that moderate to severe AD was the only significant predictor of poor egg allergy resolution.

The natural course of egg allergy is not yet fully understood. Most egg allergy develops in early infancy and resolves in most patients by school age.[14] However, previous studies have shown that the reported tolerance rates (11–81.5% by 3 years and 26–73% by 6 years) are highly variable.[14-20] In our study, 23.5% of the children developed tolerance towards eggs by 3 years of age and 47.1% by 5 years. This can be explained by differences in the present study population, such as race, concomitant atopic disease, and dietary habits as well as study methods.

The predictors for egg allergy resolution are also not yet well defined. Factors such as serum allergen-specific IgE level, skin prick test (SPT) wheal size, severity of previous reactions,

eczema, age at diagnosis, and initial baked egg reactivity have been proposed.[7,8,14,15] Several studies have examined the effect of AD on the resolution of food allergies in Asia. A Korean study reported that 90% of infants with egg allergy without AD had developed tolerance at 3 years of age, compared to 60% of patients with AD.[14] Recent Korean[20] and Japanese[21] retrospective studies have shown higher proportions of individuals with AD in the groups with persistent egg allergy compared to those in the tolerant groups. However, these studies did not evaluate AD severity in children with egg allergy.

The results of our study implied that egg allergy with moderate to severe AD was less likely to be resolved. The remission rates of egg allergy by 5 years of age in the no, mild, and moderate to severe AD groups were 65%, 56.5%, and 24%, respectively. The group with moderate to severe AD had a significantly lower tolerance acquisition rate of egg allergy compared to those in the no AD and mild AD groups (Kaplan–Meier curve, $P = 0.008$). The results of this study also showed higher median egg white-sIgE levels at 3 and 5 years of age in more severe AD compared to those for no and mild AD. Among participants with egg allergy and moderate to severe AD, the median egg white-sIgE level had increased at 3 years (22.5 kU/L) of age compared to that at the time of diagnosis (20.7 kU/L). Epicutaneous sensitization through severely damaged skin may cause increased food-specific IgE levels, which could further delay food allergy resolution. This important finding suggests that active treatment of impaired skin barriers may expedite egg allergy resolution in patients with moderate to severe AD.

The baseline egg white-sIgE level is considered as a predictor of tolerance acquisition.[14] Several studies have demonstrated a poor prognosis in patients with high egg white-sIgE levels.[22-25] However, multivariable analysis in our study showed that high baseline egg white-sIgE level (≥ 20 kU/L) was not significantly related to persistent egg allergy. A Korean study also reported that initial egg white-sIgE level was not statistically related to persistent egg allergy in multivariable analysis.[26] Other studies have also shown an association between tolerance development and the rate of decrease in egg white-sIgE levels over time.[7,20,27] The baseline egg white-sIgE level and the trend of reduced egg white-sIgE over time might be affected by the severity of skin barrier dysfunction in patients with egg allergy.

This study also showed significantly higher HDM sensitization in the persistent egg allergy group. While previous studies revealed reported that egg allergy or severe AD increased the risks of inhalant sensitization in late childhood,[1,22,28,29] HDM sensitization was not statistically related to persistent egg allergy in multivariable analysis in the present study. Further well-designed prospective large-population studies are needed to evaluate the correlation between food allergy resolution and inhalant allergen sensitization.

Our study had several limitations. First, this was a single-center study, and the patients may have had more severe allergies than those in general hospitals or clinics. Furthermore, this was a retrospective study and therefore might involve selection bias. The change in AD severity over time was also not evaluated. Nevertheless, the criteria for diagnosis and tolerance acquisition proposed in this study were applied more strictly to the medical record reviews. Patients who could not be administered egg whites because of their inherent antigen-specific IgE levels were excluded. In this investigation, 60 (88.2%) patients underwent OFC, 8 (11.8%) of whom had a definite history of egg allergy.

Conclusion

In conclusion, the results of this study showed a remission rate of 47.1% by 5 years of age and that moderate to severe AD may be a practical and important prognostic factor to predict persistent egg allergy.

Conflicts of Interest

The authors have no potential conflicts of interest to declare with respect to the authorship and/or publication of this article.

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None

Author Contributions

SHK, HYY, YHJ, YMK and HYK participated in the study design and conduct. SHK and HYK drafted the manuscript and performed the statistical analysis. All authors read and approved the final manuscript.

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