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Reduction Rate of Specific IgE Level as a Predictor of Persistent Egg Allergy in Children

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ABSTRACT

Purpose: Egg is the most common food allergen in infants. However, the natural course of egg allergy has not been fully elucidated. This study aimed to describe clinical characteristics and to identify prognostic factors associated with tolerance acquisition of immunoglobulin E (IgE)-mediated egg allergy in children.
Methods: Children who underwent more than 1 follow-up egg white-specific immunoglobulin E (EWsIgE) test between November 2005 and November 2015 at -Severance Children's Hospital were assessed. Children were diagnosed as having IgE-mediated egg allergy based on immediate allergic reaction after egg consumption and an EWsIgE level of > 0.35 kU/L. The children were divided into "tolerant" and "persistent" groups according to tolerance acquisition defined as egg consumption without adverse allergic reactions.
Results: Of 124 participants, egg allergy resolved in 101 (81.5%) children. The persistent group had more atopic dermatitis ($P = 0.039$), and more wheat ($P = 0.009$) and peanut ($P = 0.012$) allergies compared to the tolerant group. The EWsIgE levels at diagnosis ($EWsIgE_{diag}$) were higher in the persistent group than in the tolerant group ($P = 0.001$). The trend of the EWsIgE levels in the tolerant group decreased markedly over time compared to the persistent group ($P < 0.001$). In predicting egg allergy tolerance acquisition, the reduction rate of EWsIgE level after 12 months from diagnosis ($\Delta EWsIgE_{12mo}$) tended to be more accurate than $EWsIgE_{diag}$ (area under the curve: 0.835 *vs.* 0.731). When $\Delta EWsIgE_{12mo}$ was ≥ 30%, tolerance acquisition was more frequent than that of < 30% (91.9% *vs.* 57.9%; $P < 0.001$).
Conclusions: $\Delta EWsIgE_{12mo}$ can be used as an early independent predictor of tolerance acquisition of IgE-mediated egg allergy in children.

Keywords: Egg hypersensitivity; immunoglobulin E; egg white; food allergy; child

INTRODUCTION

Food allergy is an adverse food reaction arising from a specific immune response that occurs reproducibly on exposure to a certain food, including immunoglobulin E (IgE)-mediated, non-IgE-mediated, mixed, or cell-mediated reactions.[1] Food allergies are more common in children than in adults.[2,3] The prevalence of food allergies in children tends to increase gradually, and based on the data released by the American Centers for Disease Control in

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2013, the prevalence rate of food allergy in children aged 0–17 years was 3.4% from 1997 to 1999, which increased to 5.1% from 2009 to 2011.[4] In Korea, the prevalence rate of food allergy increased from 0.6% to 3.15% in children aged 6–7 years and from 1.6% to 4.01% in children aged 12–13 years between 2010 and 2015.[5,6] IgE-mediated food allergies can cause symptoms such as acute urticaria, angioedema, atopic dermatitis and asthma, as well as anaphylactic reactions. With regard to the treatment of food allergies, the intake of food that caused allergic reactions should be avoided.[1,7] However, several food allergens are difficult to avoid because they are ingested in different forms through food processing, which can cause an accidental exposure.[7,8]

Egg is one of the most common allergens in children, accounting for 0.5%–2.5% of allergies in children.[9-12] An Australian study reported that the prevalence of IgE-mediated egg allergy in infants aged 12 months is 9%.[13] Egg is also the most important cause of food allergy among single foods in Korea.[5,14] In 1995, based on the Food Allergen Cause Report, 22.7% of children with food allergy had egg allergy.[15] A recent questionnaire survey on children aged 0 to 6 years was conducted in 2014, and 20% of children with food allergy complained of egg allergy.[16]

Most egg allergy develops in the first year of life and the overall prognosis for tolerance has been considered good.[17,18] However, tolerance acquisition rates have been varyingly reported as 30%–50% by age of 3 years, 59%–66% by age of 5 years and 50%–70% at age of 6 years.[19-21] The median time to develop tolerance has been reported to be from 3 to 9 years of age, and 5%–10% of children reported that their egg allergy persisted until 18 years of age.[19,21,22] Therefore, prediction of future tolerance is useful for planning whether to apply interventions, such as oral immunotherapy, and providing individualized insights into prognostication. The prognostic factors associated with the egg allergy tolerance acquisition have been reported to include the following: characteristics of the initial reaction at the time of egg consumption, baseline egg skin prick test wheal size, and baseline egg-specific IgE level at diagnosis.[1,19-21]

Here, we sought to compare clinical characteristics between tolerant and persistent groups of children with egg allergy, and to identify an early predictor for future tolerance in children with IgE-mediated egg allergy.

MATERIALS AND METHODS

This was a retrospective clinical study of children who underwent egg white-specific immunoglobulin E (EWsIgE) testing twice or more at Severance Children's Hospital, Seoul, Republic of Korea, between November 2005 and November 2015. Of 960 children, 430 were diagnosed as having egg allergy and were included in this study. Among them, 226 were excluded because we could not confirm whether they acquired tolerance or not until their last visit based on the medical records. The remaining 124 children were enrolled.

Egg allergy was defined as follows: reports by a guardian of allergic reaction after eating eggs and an EWsIgE level of > 0.35 kU/L.[1,23] Other food allergies were defined as follows: reports by a guardian of allergic reaction after consumption of the relevant food and the specific IgE level of > 0.35 kU/L. The participants were divided into "tolerant" and "persistent" groups according to tolerance acquisition. Tolerance acquisition was defined as 1) a negative result from an open food challenge test conducted in the hospital using 1 whole cooked egg[24] or 2) no allergic reaction after ingesting eggs at home under the direction of a physician. The open food challenge test was performed in 34 (27.4%) patients.

The patients' sex, age, allergy history (atopic dermatitis, allergic rhinitis, asthma and other food allergies), family history of allergy (atopic dermatitis, allergic rhinitis, asthma and other food allergies), and other characteristics (history of breastfeeding, pets in the home and passive smoking) were collected using medical records. In each case, total serum IgE levels at the time of diagnosis and repeated EWsIgE levels from diagnosis until the end of the observation period were determined. To calibrate the EWsIgE test performed at irregular intervals, the reduction rate of the EWsIgE level was calculated at intervals of 12 months ($\Delta EWsIgE_{12mo}$), and the following formula was used:

$$\Delta \text{EWsIgE12mo } (\%) = \left[\frac{\{(\text{First value} - \text{second value})/\text{first value}\}}{\text{Interval from the first to the second date (months)}} \times 12\right] \times 100$$

Allergen-specific IgE and total serum IgE were measured using the ImmunoCAP system (Thermo Fisher, Uppsala, Sweden). The study design was approved by the Institutional Review Board (IRB) of Severance Hospital. The requirement for informed consent was waived due to the retrospective nature of the study (No. 4-2016-0779).

For the analysis in this study, we used SPSS version 23.0 for Windows (SPSS Inc., Chicago, IL, USA) and R version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria). The Mann-Whitney and χ^2 tests were used to compare the characteristics of the 2 groups. The linear mixed-model method was applied to compare EWsIgE values over time. Logistic regression analysis was used to plot receiver-operating characteristic (ROC) curves, and the predictive power of EWsIgE levels at diagnosis ($EWsIgE_{diag}$), $\Delta EWsIgE_{12mo}$ and peak EWsIgE to predict egg allergy tolerance acquisition were analyzed. Each cutoff value in the ROC curve was calculated using the Youden index. The survival analysis using the Kaplan-Meier curve was used to determine whether the predictor could effectively predict tolerance acquisition.

RESULTS

Tolerance to egg allergy compared to persistent egg allergy

Of a total of 124 children, egg allergy resolved in 101 (81.5%) children at a median age of 34 months. Median follow-up duration was 49.0 (range, 32.0–127.0) months in the persistent group, and the median duration to acquire tolerance was 18.0 (range, 8.0–61.0) months in the tolerant group. No significant differences were found between the 2 groups in age at diagnosis and sex. Of 64 (51.6%) children with other food allergies, wheat (26.1% *vs.* 5.9%; $P = 0.009$) and peanut (34.8% *vs.* 11.9%; $P = 0.012$) allergies were more frequent in the persistent group than in the tolerant group. Of 90 (72.6%) children with other allergic diseases, the persistent group (87.0%) had more atopic dermatitis compared to the tolerant group (66.3%; $P = 0.039$). No significant difference was found between the 2 groups in terms of the presence of parental allergic diseases and breastfeeding (**Table 1**).

Baseline EWsIgE levels and their trends between the persistent and tolerant groups

The median $EWsIgE_{diag}$ was higher in the persistent group (median [interquartile range; IQR], 21.12 [9.99–66.12] kU/L) than in the tolerant group (median [IQR], 7.71 [4.51–15.40]

Table 1. Subjects' characteristics

Characteristics	Persistent group (n = 23)	Tolerant group (n = 101)
Age at diagnosis of egg allergy (mon)	14.5 (10.75–26.0)	14 (10.0–18.0)
Sex (male)	15 (65.2)	65 (64.4)
Total serum IgE level at diagnosis (kU/L)	240.5 (88.35–485.0)	111.0 (46.7–371.0)
Presence of other food allergies	14 (60.9)	50 (49.5)
Milk allergy	7 (30.4)	38 (37.6)
Peanut allergy*	8 (34.8)	12 (11.9)
Wheat allergy*	6 (26.1)	6 (5.9)
Soybean allergy	1 (4.3)	5 (5.0)
Other food allergies	7 (30.4)	15 (14.9)
Presence of other allergic diseases	20 (87.0)	70 (69.3)
Atopic dermatitis*	20 (87.0)	67 (66.3)
Allergic rhinitis	5 (21.7)	18 (17.8)
Asthma	5 (21.7)	12 (11.9)
Presence of breastfeeding history (n = 79)	12 (100.0)	59 (88.1)
Presence of parental allergic diseases (n = 92)	15 (83.8)	45 (60.8)
Atopic dermatitis	2 (11.1)	15 (20.3)
Allergic rhinitis	10 (55.6)	29 (39.2)
Asthma	2 (11.1)	4 (5.4)
Food allergy	3 (16.7)	9 (12.2)

Data were expressed as median (interquartile range) or number (%).
IgE, immunoglobulin E.
*The $P < 0.05$.

kU/L; $P = 0.001$; **Fig. 1A**). The peak EWsIgE level during the individual follow-up period was also higher in the persistent group (median [IQR], 49.45 [17.87–100.00] kU/L) than in the tolerant group (median [IQR], 7.86 [4.54–17.1] kU/L; $P < 0.001$; **Fig. 1B**). The trends of repeated EWsIgE levels showed that the EWsIgE levels in the tolerant group decreased markedly over time compared to those in the persistent group ($P < 0.001$; **Fig. 2**).

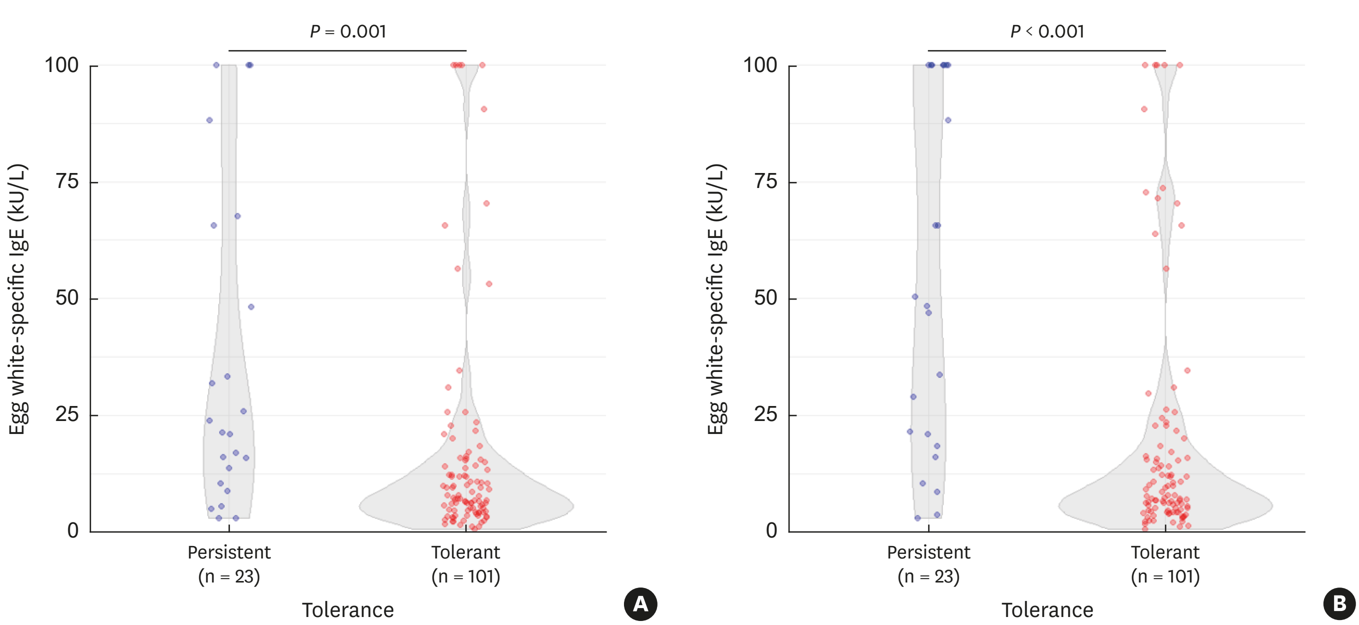

Fig. 1. The EWsIgE level at diagnosis between persistent and tolerant groups. The EWsIgE level at diagnosis was higher in the persistent group than in the tolerant group (A) median (interquartile range), 21.12 (9.99–66.12) kU/L *vs.* 7.71 (4.51–15.40) kU/L; $P = 0.001$). The peak EWsIgE level during the individual follow-up period also was higher in the persistent group than in the tolerant group (B) 49.45 (17.87–100.00) kU/L *vs.* 7.86 (4.54–17.1) kU/L; $P < 0.001$).
EWsIgE, egg white-specific IgE.

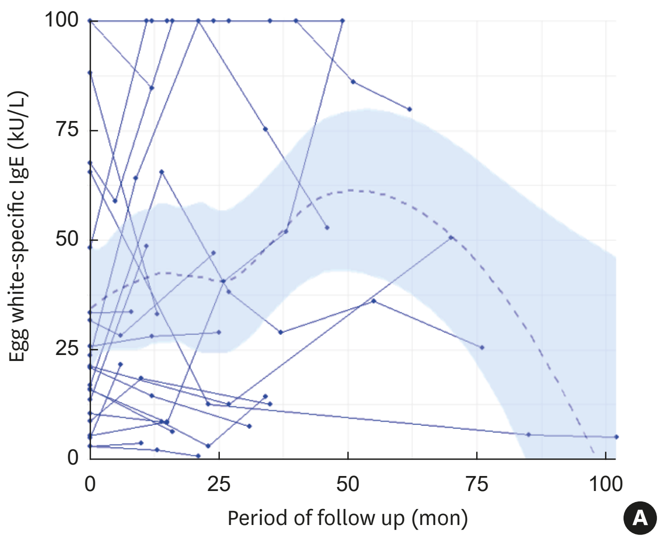

Fig. 2. The trends of EWsIgE levels over time. The EWsIgE levels in the tolerant group (B) decreased over time in contrast to those in the persistent group (A) (P = 0.002). EWsIgE, egg white-specific IgE.

The ΔEWsIgE$_{12mo}$ as a predictor of egg allergy tolerance

When EWsIgE$_{diag}$ and ΔEWsIgE$_{12mo}$ were compared for their predictive power for allergy tolerance acquisition, ΔEWsIgE$_{12mo}$ (area under the curve [AUC], 0.835; 95% confidence interval [CI], 0.763–0.907) tended to show better performance than EWsIgE$_{diag}$ (AUC, 0.731; 95% CI, 0.609–0.853); however, there was no statistically significant difference (P = 0.169). The cutoff values were 16 kU/L for EWsIgE$_{diag}$ and 30% for ΔEWsIgE$_{12mo}$. The predictive power of using both ΔEWsIgE$_{12mo}$ and EWsIgE$_{diag}$ (AUC, 0.805; 95% CI, 0.718–0.891) showed similar performance to using EWsIgE$_{diag}$ (P = 0.192) or ΔEWsIgE$_{12mo}$ alone (P = 0.255; **Table 2**). The Kaplan-Meier curves showed more egg allergy tolerance acquisition in the group with ΔEWsIgE$_{12mo}$ of ≥ 30%. In addition, we performed the analysis in the subgroup with a high EWsIgE$_{diag}$ of > 23.0kU/L, which was the level of 75th percentile in all participants, and confirmed that ΔEWsIgE$_{12mo}$ of ≥ 30% produced a similar result (**Fig. 3**).

The patients were further divided based on the cutoff ΔEWsIgE$_{12mo}$ value of 30% to perform additional analysis; 86 (69.4%) had a ΔEWsIgE$_{12mo}$ of ≥ 30% and 38 (30.6%) had a ΔEWsIgE$_{12mo}$ of < 30%. Of the children with a ΔEWsIgE$_{12mo}$ of ≥ 30%, 79 (91.9%) had acquired egg allergy tolerance, whereas of the children with a ΔEWsIgE$_{12mo}$ of < 30%, only 22 (57.9%) had acquired tolerance (P < 0.001; **Table 3**).

Table 2. Prediction model of egg allergy tolerance acquisition

Variables	AUC (95% CI)	Cutoff value	P value
EWsIgE$_{diag}$	0.731 (0.609–0.853)	16.0 kU/L	0.001
ΔEWsIgE$_{12mo}$	0.835 (0.763–0.907)	30%	< 0.001
EWsIgE$_{diag}$ + ΔEWsIgE$_{12mo}$	0.805 (0.718–0.891)	16 kU/L + 30%	< 0.001

AUC, area under the curve; CI, confidence interval; EWsIgE$_{diag}$, egg white-specific IgE level at diagnosis; ΔEWsIgE$_{12mo}$, reduction rate of egg white-specific IgE level after 12 months from diagnosis.

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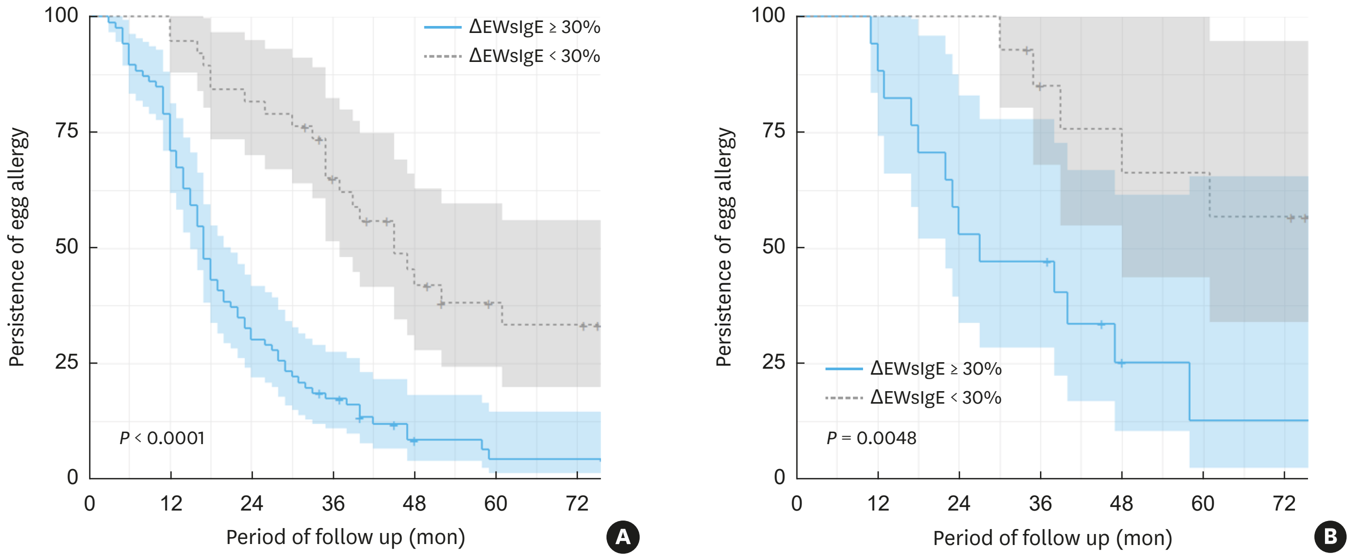

Fig. 3. Comparison of the incidence of egg allergy tolerance acquisition according to $\Delta EWsIgE_{12mo}$ using the Kaplan-Meier curve. More children with $\Delta EWsIgE_{12mo}$ of ≥ 30% acquired tolerance than those with $\Delta EWsIgE_{12mo}$ of < 30% among all the participants (A) and in the subgroup with high EWsIgE levels (> 23.0 kU/L) at diagnosis (B).
$\Delta EWsIgE_{12mo}$, reduction rate of EWsIgE level after 12 months from diagnosis; EWsIgE, egg white-specific IgE.

Table 3. Subjects' characteristics divided by the cutoff of $\Delta EWsIgE_{12mo}$

Characteristics	$\Delta EWsIgE_{12mo}$ ≥ 30% (n = 86)	$\Delta EWsIgE_{12mo}$ < 30% (n = 38)	*P* value
Tolerance acquisition	79 (91.9)	22 (57.9)	< 0.001
Sex (male)	57 (66.3)	23 (60.5)	0.337
Presence of other food allergies	44 (51.2)	20 (52.6)	0.518
Presence of other allergic diseases	59 (68.6)	31 (81.6)	0.099
Total IgE level at diagnosis (kU/L)	120.0 (49.35–382.5)	136.5 (56.18–472.0)	0.584
EWsIgE level at diagnosis (kU/L)	7.86 (4.54–15.95)	11.15 (5.16–25.1)	0.140

Data were expressed as median (interquartile range) or number (%).
$\Delta EWsIgE_{12mo}$, reduction rate of EWsIgE level after 12 months from diagnosis; IgE, immunoglobulin E; EWsIgE, egg white-specific IgE.

DISCUSSION

This study compared clinical characteristics between groups of children with tolerance to egg allergy and persistent egg allergy, and suggested an early predictor for future tolerance in children with IgE-mediated egg allergy. The group with persistent egg allergy had more other food allergies and more atopic dermatitis compared to the tolerant group. The $EWsIgE_{diag}$ and the peak EWsIgE were higher in the persistent group than in the tolerant group. The trend of the EWsIgE levels over time in the tolerant group decreased markedly compared to that in the persistent group. We propose $\Delta EWsIgE_{12mo}$ as an early predictor for future tolerance. It tended to show better performance than the $EWsIgE_{diag}$ and the peak EWsIgE, and comparable performance to the combination of $\Delta EWsIgE_{12mo}$ and $EWsIgE_{diag}$.

Egg allergy resolved in half of the children at the median age of 6 years; however, a wide range from 2 to 9 years has been reported for the age at resolution. The review by Savage *et al.*[18] revealed that the differences in resolution rates and ages in each study were due to the different study designs, and definitions of egg allergy and development of tolerance. The resolution rate most likely depended on the definition of development of tolerance including the method of food challenge test.[21,22,25] In this study, 81.5% of children developed tolerance

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to egg by the median age of 3 years. The resolution rate was much higher compared to the previous study, a retrospective study in a tertiary referral clinic with similar criteria of egg allergy and development of tolerance, which reported that only 19% of children acquired tolerance to egg allergy by age 4 years.[22] Forty percent of Korean children with atopic dermatitis[26] and 30% of Japanese children[20] had tolerance to egg by the age of 3 years. These Asian studies reported favorable resolution rates of 70% by the age of 6 years and 85% by the age of 10 years compared to the previous Western studies.[21,22,25] The differences may be due not only to different populations but also different lifestyles including dietary habits.

Persistence of egg allergy has been associated with more severe symptoms,[19,21] the presence of other allergic diseases and their severity.[21,22] The clinical characteristics associated with the natural history of egg allergy in this study were presence of other food allergies and atopic dermatitis. More than half of the children had other food allergies and children with comorbid peanut or wheat allergies had persistent egg allergy. Eighty percent of children had other comorbid allergic diseases and the majority was atopic dermatitis. Our results showed that comorbid atopic dermatitis in children with egg allergy was an indicator of poor prognosis, which is consistent with other studies, while the resolution rate in our study was much higher compared to that of previous studies that reported lower resolution rates in children with atopic dermatitis.[21,22] We collected participants' information using only medical records and excluded more than half of the children due to insufficient information on tolerance acquisition, which might have skewed the resolution rate.

Larger skin prick test wheal size[19,21] or high egg-specific IgE levels[21,22,27,28] were associated with persistent egg allergy. Moreover, we showed that the $EWsIgE_{diag}$ and the peak EWsIgE were higher in the persistent group than in the tolerant group. The $EWsIgE_{diag}$ has been suggested as a predictor of tolerance acquisition. Tolerance acquisition was reported to be significantly delayed when the baseline egg-specific IgE level was ≥ 6.2 kU/L[29] or ≥ 10 kU/L,[21] and failed in almost all children when the peak egg-specific IgE level was ≥ 50 kU/L.[22] In this study, the $EWsIgE_{diag}$ level of ≥ 16 kU/L was less likely to resolve egg allergy by the age of 3 years, and with a relatively insufficient AUC, it cannot be used as a predictor. There were 24 (19.4%) children with peak egg-specific IgE level ≥ 50 kU/L; however, only half had persistent egg allergy. For the next step, we compared the trends of EWsIgE between the tolerant and persistent groups and found that the EWsIgE levels decreased markedly over time in the tolerant group compared to those in the persistent group. Therefore, we tested $\Delta EWsIgE_{12mo}$ as an early predictor for future tolerance and confirmed that its performance tended to be better than the $EWsIgE_{diag}$ based on the cutoff $\Delta EWsIgE_{12mo}$ value of 30% with a sufficient AUC regardless of the $EWsIgE_{diag}$. Small sample size, a limitation of this study, might be attributed to the failure in reaching statistical significance. Our results were consistent with those of Shek *et al.*[30] who reported that the rate of decrease in EWsIgE over time was significantly related to the probability of developing egg allergy tolerance, and the probability of developing tolerance due to decreased EWsIgE level was 52% for a 50% reduction and 78% for a 90% reduction. However, the $\Delta EWsIgE_{12mo}$ value of 30% would be easy to use by applying simple mathematics in clinics.

It is important to predict which children with egg allergy are likely to have persistent allergy because it is necessary to identify the candidates for emerging food allergy therapies including oral immunotherapy, which can carry risks and be costly. If we predict tolerance to egg, then regular consumption of baked egg, if tolerated, can be recommended to accelerate the development of tolerance to less cooked egg.[25] Thus, IgE epitope specificity,[31]

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IgE/IgG4 ratio,[32] and specific IgA and IgA2[33] have been associated with the development of tolerance; however, assays for these are less readily available. Allergen component-resolved diagnostics[34] and cellular-based assays[35-37] may be candidates in predicting the natural course of food allergy.

This study had a few limitations. Firstly, this study was conducted retrospectively in a single tertiary clinic; thus, the children did not participate in the study at a similar time, and each medical observation schedule varied. Therefore, we reinforced this by using more effective statistical methods stepwise and by conducting an additional subgroup analysis. Secondly, we did not perform double-blind, placebo-controlled food challenges for all subjects to diagnose egg allergy and check for tolerance acquisition, which is the gold standard. To overcome these limitations, the criteria for diagnosis and tolerance acquisition proposed in this study were applied more strictly to the medical record review, and the open challenge test was used as a tolerance acquisition confirmation method. Therefore, we excluded more than half of the children due to insufficient information on tolerance acquisition, which might have led to overestimating the egg allergy resolution rate. However, this is a real-world practical study, which on the other hand, can be a strength of this study. Another limitation was a variable and relatively short follow-up period. For example, the shortest follow-up duration was 29 months in the persistent group, which is an insufficient time to confirm a persistent egg allergy, and can be a factor in underestimating the egg allergy resolution rate.

In conclusion, children with egg allergy are less likely to have tolerance to egg when they show concomitant allergies to other food, atopic dermatitis, or EWsIgE level of ≥ 16 kU/L at diagnosis. We suggest $\Delta EWsIgE_{12mo}$ as a good independent predictor for future tolerance in children with IgE-mediated egg allergy.

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