

The Natural Course of Immediate-Type Cow's Milk and Egg Allergies in Children

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Keywords

Cow's milk · Egg · Food allergy · Natural course · Tolerance

Abstract

Background: Most of children with cow's milk (CM) and hen's egg allergies are known to outgrow their diseases with time, but recent studies have demonstrated that children tend to continue to have allergic symptoms in adolescence and adulthood. The aim of this study was to investigate the natural course of CM and egg allergies in Korean children and analyze prognostic factors. **Methods:** In this retrospective study, we reviewed data of children with CM allergy and with egg allergy using medical records and parental telephone interviews. Diagnosis of CM or egg allergy was based on positive oral food challenge test or convincing history of allergic symptoms in combination with positive allergen-specific IgE. Acquisition of tolerance was defined by the absence of allergic symptoms after reintroduction of the offending foods. **Results:** Half of the children outgrew CM allergy at a median age of 8.7 years. CM-specific IgE level at the first reaction was a significant prognostic factor for oral tolerance in CM allergy ($p < 0.05$). The median age to acquire oral

tolerance in 50% of patients with egg allergy was 5.6 years. Egg-specific IgE level at the first reaction and family history of allergic diseases significantly affected the prognosis in children with egg allergy ($p < 0.05$). **Conclusions:** Half of Korean children with CM and egg allergies had symptom resolution at 8.7 and 5.6 years of age, respectively. Our results also suggest that CM- and egg-specific IgE levels at the first reaction are the most significant prognostic factors in predicting acquisition of oral tolerance. © 2019 S. Karger AG, Basel

Introduction

Food allergies are common in children and can cause serious life-threatening conditions [1]. For this reason, this disease entity has become an important medical issue. In all food allergies, cow's milk (CM) and hen's eggs are the most common food allergens in infants and young children [1, 2]. The incidences of CM and egg allergies are estimated to be 0.9–3.8% and 0.3–2.0%, respectively, although they vary

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according to studies [3–5]. Since CM and eggs are important sources of nutrition for children and included in a wide range of manufactured food products, strict avoidance of these allergens is difficult. Therefore, accidental ingestions frequently occur, and patients along with their families are greatly concerned about the poor quality of life [6]. An understanding of the natural course of food allergy not only reduces the uncertainty on the outcome but also helps to make decisions on rechallenge of the offending foods or active treatment options such as immunotherapy.

It has generally been accepted that CM and egg allergies spontaneously resolve at preschool ages [7–9]. However, recent studies have demonstrated that children tend to outgrow their CM and egg allergies at a slower rate and develop persistent allergic symptoms in adolescence and adulthood [10–12]. Prognostic factors acquiring tolerance to CM or egg, such as the severity of allergic symptoms, age at diagnosis, wheal size of skin prick test, and food allergen-specific IgE antibody levels have been suggested in previous studies, but the results were inconsistent due to differences in study methodology and follow-up duration [12, 13].

Although CM and eggs are the most important food allergens in Korea, little is known about their natural courses [14, 15]. In the present study, we aimed to investigate the natural course of CM and egg allergies and identify prognostic factors for acquisition of tolerance to CM or egg in Korean children.

Materials and Methods

Study Population

We enrolled infants and young children who were diagnosed with CM or egg allergy between January 2010 and November 2016. Diagnosis of CM or egg allergy was based on a positive oral food challenge test or convincing history of adverse reactions within 2 h of food ingestion plus positive serum-specific IgE (≥ 0.35 kU/L). Immediate adverse reactions included urticaria, eyelid edema, facial edema, lip edema, cough, wheezing, dyspnea, vomiting, diarrhea, abdominal pain, hypotension, and altered mentality. Acquisition of oral tolerance was determined by either negative open food challenge tests in the hospital or telephone interviews with the patient's parents to confirm absence of additional clinical reactions after reintroduction at home. We also asked when they acquired oral tolerance to CM or egg. Follow-up duration was defined as the period either from the first episode of allergic reactions to the last one in patients with persistent food allergy or from the first symptom onset to tolerance development in patients who outgrew the disease later.

The medical records of children with CM or egg allergy were retrospectively reviewed to identify sex, presence of other allergic diseases during follow-up, family history of allergic diseases, duration of breastfeeding, age at the introduction of solid food, pres-

ence of CM or egg-induced anaphylaxis, serum total and allergen-specific IgE levels at the first reactions, sensitization to other foods, and peak allergen-specific IgE level during follow-up. A family history of allergic diseases was defined as at least one family member having food allergy, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, or asthma. Anaphylaxis was defined based on the criteria suggested in the second symposium on the definition and management of anaphylaxis [16]. Total and specific IgE levels were measured by ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden). The specific IgE level at the initial reactions was determined as the value within 3 months of onset of the first symptoms after ingestion of causative food. Sensitization to food allergens was defined when the food-specific IgE level was higher than 0.35 kU/L. When the allergen-specific IgE level was >101.0 kU/L, the value was assigned as 101.0 kU/L. All methods were performed in accordance with the relevant guidelines and regulations. All participants or parents in this study provided written consent form. This study was approved by the Institutional Review Board of Samsung Medical Center, Seoul, Korea (IRB No. 2016-08-014).

Statistical Analysis

The natural courses of CM and egg allergies were described with cumulative persistence curves using the Kaplan-Meier method. For comparisons between the tolerance and persistence groups, we used the χ^2 test or Fisher's exact test for qualitative variables and the Wilcoxon rank sum test for quantitative variables. Probable prognostic factors in the analysis included sex, feeding type during infancy (exclusive breast milk feeding, exclusive formula feeding, mixed feeding), duration of breast milk feeding, age at introduction of solid food, age at the first reaction, presence of other allergic diseases during follow-up, family history of allergic diseases, sensitization to other foods, presence of CM or egg-induced anaphylaxis, total IgE level and allergen-specific IgE levels at the first reaction and peak specific IgE level during follow-up. The effect of each prognostic factor was examined in the univariate analysis. After selecting the factors showing marginal significance with a p value <0.2 in the univariable analysis, we analyzed their effects in the multivariable analysis. In both analyses, Cox's proportional hazard regression method was used to determine the prognostic factors to predict the persistence of CM and egg allergies. For each allergy, the probability of persistence according to the age and specific IgE at the first reaction was estimated in the 3-dimensional plot. SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 3.31 (Vienna, Austria; <http://www.R-project.org/>) were used for the statistical analysis. A p value <0.05 was considered significant.

Results

Development of Tolerance

A total of 189 patients with CM allergy and 171 with egg allergy were enrolled in the study (Table 1). Of the 189 patients with CM allergy, 142 (75.1%) were diagnosed based on a convincing history and positive CM-specific IgE, while 47 (24.9%) showed allergic reactions in food challenge tests. For egg allergy, 48 patients (28.1%) were confirmed by positive food challenge tests.

Table 1. Characteristics of the study population

	CM allergy (n = 189)	Egg allergy (n = 171)
Male sex	113 (59.8)	106 (62.0)
Feeding during infancy		
Absolute BMF	157 (83.1)	101 (59.1)
Absolute formula feeding	2 (1.1)	11 (6.5)
Mixed feeding	30 (15.9)	59 (34.5)
Duration of BMF, months	12 (2–48)	10 (0–50)
Age at introduction of solid food, months	6 (4–18)	6 (3–18)
Concomitant allergic diseases		
Food allergy other than egg or CM allergy	60 (31.8)	60 (35.1)
Atopic dermatitis	147 (77.8)	130 (76.0)
Asthma	33 (17.5)	29 (17.0)
Allergic rhinitis	60 (31.8)	56 (32.8)
Family history of allergic diseases	133 (70.4)	122 (71.3)
Age at the first reaction, months	9.0 (0.0–30.0)	14.0 (3.0–39.0)
Total IgE level at the first reaction, kU/L	123.0 (3.5–9,930.0)	130.0 (6.3–4,514.0)
Specific IgE level at the first reaction, kU/L	6.4 (0.1–101.0)	8.6 (0.4–101.0)
Peak specific IgE level during follow-up, kU/L	14.2 (0.3–101.0)	16.9 (0.6–101.0)
Sensitization to other food allergens	116 (92.8)	100 (82.0)
Follow-up duration, months	32.4 (6.0–150.5)	23.4 (6.0–207.0)

Values are presented as median (range) or *n* (%). CM, cow's milk; BMF, breast milk feeding.

In patients with CM allergy, the median age at the first reaction was 9.0 months (range 0.0–30.0 months). The median level of CM-specific IgE at the first reaction was 6.4 kU/L (0.1–101.0 kU/L), and the median level of total IgE was 123.0 kU/L (3.5–9,930.0 kU/L). During the follow-up period (median 32.4 months; range 6.0–50.5 months), CM allergy resolved in 65 patients. CM tolerance was confirmed in 27 patients (41.5%) by open challenge test in our clinic and in 38 (58.5%) by reintroduction of CM at home. In the Kaplan-Meier survival analysis, 25 and 50% of the patients with CM allergy developed tolerance at 43.1 and 104.8 months, respectively (Fig. 1).

In patients with egg allergy, the first allergic reactions after ingestion of hen's egg were found at a median age of 14.0 months (range 3.0–39.0 months). The median level of egg-specific IgE and total IgE at the first reaction was 8.6 kU/L (0.4–101.0 kU/L) and 130.0 kU/L (6.3–4,514.0 kU/L), respectively. Follow-up duration ranged from 6.0 to 207.0 months with the median period of 23.4 months. Of 171 patients, 69 developed oral tolerance which was confirmed by open challenge test in 35 (50.7%) and reintroduction at home in 34 (49.3%). The Kaplan-Meier analysis in our patients showed that 25 and 50% outgrew egg allergy at 46.7 and 67.6 months, respectively (Fig. 2).

Prognostic Factors of Tolerance Development

The univariable analysis showed that age at introduction of solid food, sensitization to other food allergens, CM-specific IgE levels at the first reaction, and peak CM-specific IgE levels during follow-up were associated with tolerance of CM allergy ($p < 0.05$; Table 2). In patients with egg allergy, family history of allergic diseases, sensitization to other food allergens, egg-specific IgE levels at the first reaction, and peak egg-specific IgE level during follow-up was associated with tolerance of egg allergy in the univariable analysis ($p < 0.05$, respectively; Table 2). Total IgE in CM allergy was not significant (HR 1.000; 95% CI 1.000–1.000), while total IgE in egg allergy was weakly associated (HR 0.999; 95% CI 0.999–1.000). In the multivariable analysis using variables with $p < 0.2$ in the univariable analysis, CM-specific IgE levels at the first reaction (HR 0.980; 95% CI 0.961–0.999) were the only prognostic factor in the development of tolerance to CM. In egg allergy, egg-specific IgE levels at the first reaction (HR 0.981; 95% CI 0.962–1.000) and family history of allergic diseases (HR 0.527; 95% CI 0.283–0.979) were prognostic factors in the resolution of egg allergy (Table 3). The multivariate analysis showed that total IgE in egg allergy was not statistically significant as a predictor of tolerance (HR 1.000; 95% CI 0.999–1.001).

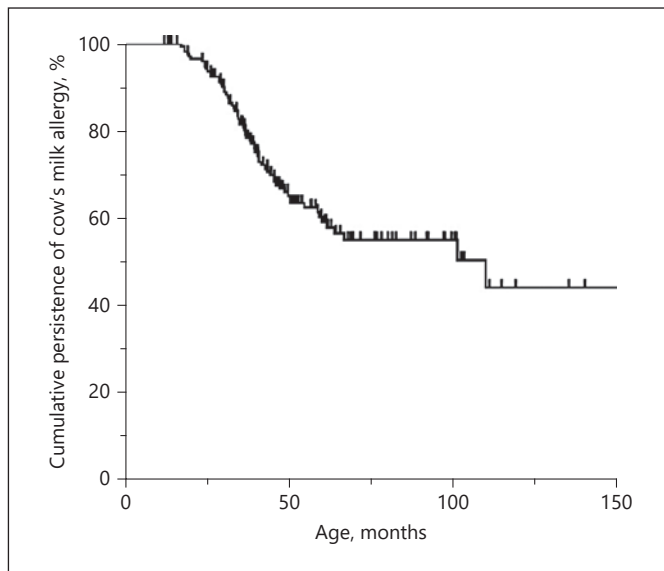


Fig. 1. Kaplan-Meier curve showing cumulative persistence of cow's milk allergy over time.

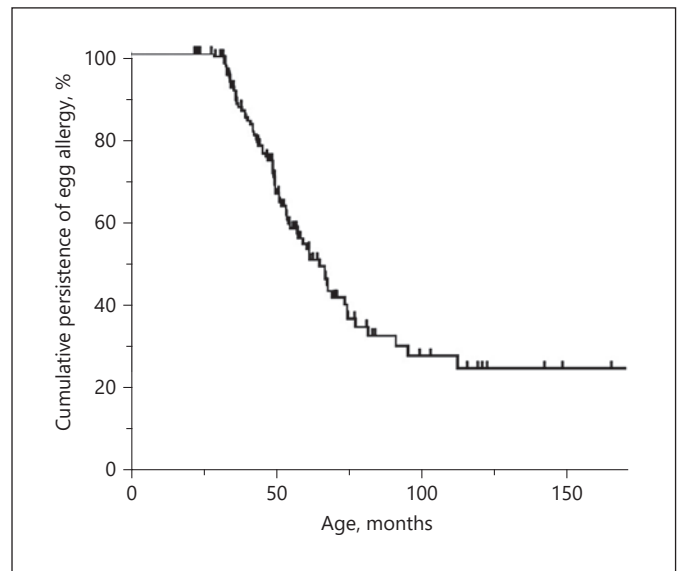


Fig. 2. Kaplan-Meier curve showing cumulative persistence of egg allergy over time.

Table 2. Predictors of tolerance according to the univariate analysis

	Cow's milk			Egg		
	HR	95% CI [†]	<i>p</i> value	HR	95% CI	<i>p</i> value
Female sex	1.287	0.789–2.101	0.3122	0.842	0.517–1.371	0.4893
Duration of breast milk feeding, months	0.958	0.917–1.001	0.0557	1.005	0.966–1.044	0.8177
Age at introduction of solid food, months	0.733	0.539–0.997	0.0476	0.988	0.877–1.113	0.8459
History of atopic dermatitis	0.831	0.481–1.435	0.5061	0.793	0.462–1.361	0.4007
Family history of allergic diseases	0.700	0.423–1.158	0.1649	0.457	0.280–0.746	0.0017
Presence of anaphylaxis	0.784	0.426–1.444	0.4352	0.524	0.250–1.097	0.0863
Sensitization to other food allergens	0.351	0.165–0.745	0.0064	0.487	0.257–0.924	0.0277
Total IgE level at the first reaction, kU/L	1.000	1.000–1.000	0.265	0.999	0.999–1.000	0.0606
Specific IgE level at the first reaction, kU/L	0.974	0.955–0.995	0.0136	0.981	0.967–0.994	0.0055
Peak specific IgE level during follow-up, kU/L	0.961	0.945–0.977	0.0001	0.983	0.974–0.993	0.0004

The hazard ratio (HR) >1 suggests an increased risk of persistent allergy, and the HR <1 suggests an increased risk of developing tolerance. CI, confidence interval.

We estimated the probability of persistence based on the specific IgE level at the first reaction and time (Fig. 3, 4). In a child with CM allergy, the probability of developing tolerance at 24 months of age was 30% in those with CM-specific IgE level of 5 kU/L at the first reaction and 10% in those with 52 kU/L. Tolerance at 48 months of age was likely to develop in 50% of the patients with CM-specific IgE level of 19 kU/L, 30% of those with 44 kU/L and 10% of those with 91 kU/L. The probability of devel-

oping tolerance at 96 months was 80% in patients with CM-specific IgE level of 2 kU/L, 50% in those with 35 kU/L, and 30% in those with 60 kU/L (Fig. 3).

Egg allergy was likely to resolve at 24 months in 30% of patients with 13 kU/L of egg-specific IgE level at the first reaction and in 10% of those with 76 kU/L. The probability of developing tolerance to egg at 48 months was 80% in children with egg-specific IgE level of 5 kU/L, 50% in those with 48 kU/L, and 30% in those with 82 kU/L. At

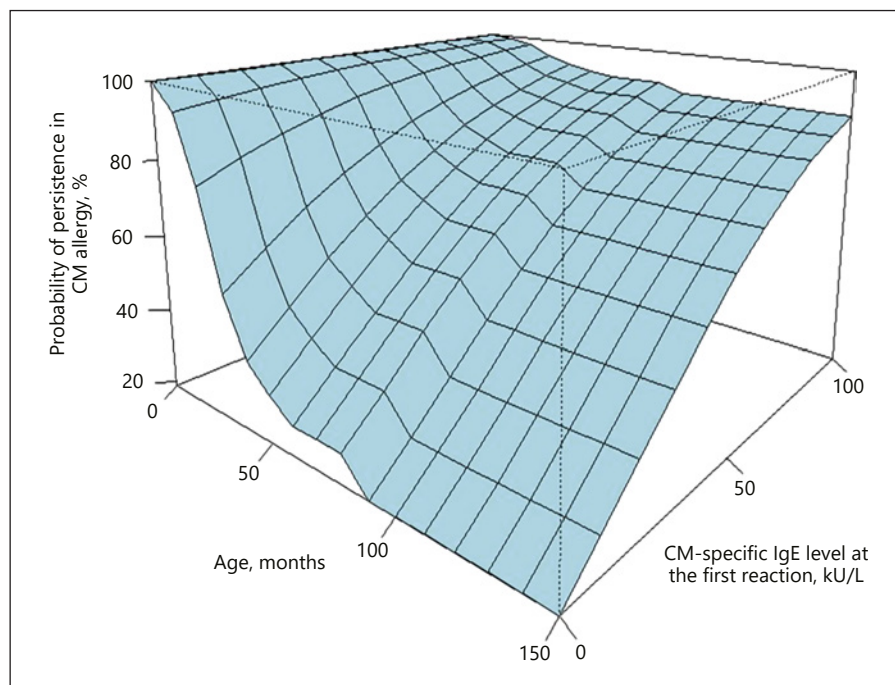


Fig. 3. The probability of persistence of cow's milk (CM) allergy according to the age and CM-specific IgE at the first reaction.

Table 3. Predictors of tolerance according to the multivariate analysis

	Cow's milk			Egg		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
Duration of breast milk feeding, months	0.961	0.913–1.011	0.1229	–	–	–
Age at introduction of solid food, months	0.745	0.534–1.041	0.0849	–	–	–
Family history of allergic diseases	0.707	0.409–1.222	0.2142	0.527	0.283–0.979	0.0425
Presence of anaphylaxis	–	–	–	0.359	0.127–1.016	0.0536
Sensitization to other food allergens	0.564	0.240–1.329	0.1904	0.594	0.292–1.210	0.1516
Total IgE level at the first reaction, kU/L	–	–	–	1.000	0.999–1.001	0.5742
Specific IgE level at the first reaction, kU/L	0.980	0.961–0.999	0.0421	0.981	0.962–1.000	0.0471

The hazard ratio (HR) >1 suggests an increased risk of persistent allergy, and the HR <1 suggests an increased risk of developing tolerance. CI, confidence interval.

72 months of age, egg allergy was likely to disappear in 80% of patients with egg-specific IgE level of 32 kU/L and 50% of those with 75 kU/L (Fig. 4).

Discussion/Conclusion

To the best of our knowledge, this is the first study to investigate the natural course and prognostic factors of CM or egg allergy based on food challenge test or convincing history in Korean children. Although there were

studies on tolerance to CM or egg allergy in Korean patients with atopic dermatitis, the diagnosis of food allergy was made on the basis of food-specific IgE levels [17, 18]. In this study, we found that spontaneous resolution rates were 50% at 104.8 months of age in patients with CM allergy and 67.6 months of age in patients with egg allergy. This means that half of children with CM or egg allergy outgrew the disease when they were 8.7 or 5.6 years old, respectively. We also demonstrated that probability of resolution over time was associated with CM- or egg-specific IgE level at the first reaction.

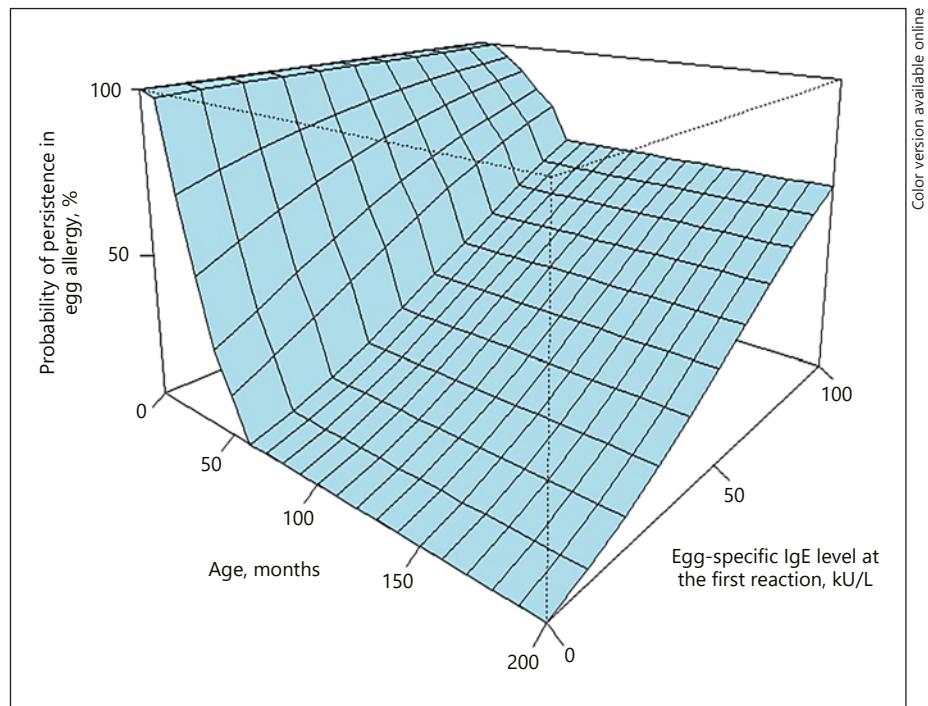


Fig. 4. The probability of persistence of egg allergy according to the age and egg-specific IgE at the first reaction.

CM or egg allergy has been considered a transient condition, and most patients are likely to outgrow it over time. A study in Finland showed that 44% of the patients with CM allergy developed tolerance by the age of 1.6 years, 51% by 2.0 years, and 89% by 8.6 years [9]. In a prospective cohort study of Israeli infants with IgE-mediated CM allergy, 40.7% tolerated CM within the first 2 years [19]. In children with challenge-proven CM allergy from the EuroPrevall birth cohort, 69% of patients with non-IgE-associated CM allergy and 57% of those with IgE-associated CM allergy tolerated CM by the age of 2 years [20]. In an observational cohort of 293 US children, Sampson et al. [16] reported that CM allergy resolved in 52.6% at a median age of 63 months [13]. In contrast, it seemed that Korean children with CM allergy have worse prognosis. However, our results are consistent with the findings of several previous studies. Of Portuguese children with CM allergy, 55% acquired tolerance by 5 years of age and approximately 70% by 15 years of age [10]. A retrospective study of 807 US children conducted in 2007 showed that 19% of patients with IgE-mediated CM allergy tolerated CM by 4 years of age, 42% by 8 years, and 79% by 16 years [21]. A similar tendency toward food allergy persistence is also observed in egg allergy. In a study of the Spanish population, 50% of patients with egg allergy acquired tolerance to egg by 3 years of age and 66% by 5 years [22]. An Australian study showed that egg al-

lergy resolved in half of patients with egg allergy at 2 years of age [8]. However, a retrospective study in the US population demonstrated that resolution occurred in 12% of patients with egg allergy by 4 years of age, 37% by 10 years, and 68% by 16 years [11]. In another study conducted in the US population, egg allergy was more persistent, since 50% of patients tolerated egg by 6 years of age [12]. In 226 Japanese children with immediate-type egg allergy, tolerance was acquired in 30% by 3 years of age, 59% by 5 years, and 73% by 6 years [23]. The exact reasons for different resolution rates remain unclear, but one possibility is the difference in the study design. In retrospective studies, neither food challenges nor assessment of specific IgE levels was performed at a regular interval, and it tends to result in unnecessary restriction. Follow-up duration in retrospective observations was also longer than that in prospective studies. Another reason may be that our study was performed in a tertiary center where more severe cases were enrolled. The different rates of acquiring tolerance might also be influenced by other factors such as ethnicity, sample size, bias in the study population, method for the diagnosis and assessment of tolerance development, and type of allergic reactions (IgE mediated vs. non-IgE mediated). Taken together, the real resolution rate in general Korean children with CM or egg allergy would be better than the results from our study.

Previous studies have shown that children with high initial CM or egg-specific IgE levels are less likely to out-grow CM or egg allergy than those with low levels [12, 13, 24–26]. In the present study, specific IgE level at the first reaction was the strongest prognostic factor of CM or egg allergy. We also estimated the probability of persistent food allergy according to food-specific IgE levels and age to provide the likelihood that resolution may occur in each individual. Although the specific IgE level is a good marker in predicting the prognosis of CM or egg allergy, it is not known which level, either initial or peak with age, is more useful as a predictor. Besides specific IgE levels, the presence of family history of allergic diseases was associated with the persistence of egg allergy in our study. Indeed, the prognosis of food allergy appears to be affected by many other factors including symptom severity after ingestion, size of skin prick test reaction, age at diagnosis, presence of other allergic diseases, changes in the food-specific IgE level, and IgE/IgG4 ratio [11–13, 19, 20, 24]. Although several studies showed significant linear epitopes related to persistent food allergy, they did not explain the reason why patients reacting to specific epitopes tend to have persistent allergy [27, 28].

Our results must be interpreted with caution. First, there is a selection bias in the study population, because the present study was performed in a single tertiary referral clinic where the patients with mild symptoms may not be brought by the parents. Second, the diagnosis of food allergy or assessment of tolerance acquisition was limited. Not all diagnoses were made by double-blind, placebo-controlled food challenges, and the resolution of food allergy was determined by self-report of the parents in telephone interviews. Finally, the specific IgE level at a specific timing was not measured in all patients analyzed, because our study design is retrospective, not prospective. We could not obtain the peak specific IgE level and failed to find the statistical significance. A prospective study in unselected populations is ideal to obtain a more correct result. Despite these limitations, we have provided the first data on the natural course of CM or egg allergy in

Korean children. Our data can be used by physicians in explaining to the patients or parents when reintroduction of CM or hen's egg is possible. It might also be helpful to screen patients who are likely to have persistent allergy and may benefit from other treatment options like oral immunotherapy.

In conclusion, approximately 50% of Korean children with CM and egg allergies had resolution of symptoms at 8.7 and 5.6 years of age, respectively. Our results also suggest that CM- and egg-specific IgE levels at the first reaction are the most significant prognostic factor to predict acquisition of oral tolerance.

Statement of Ethics

This study was approved by the Institutional Review Board of Samsung Medical Center, Seoul, Korea (IRB No. 2016-08-014).

Disclosure Statement

The authors have no conflicts of interest to declare pertaining to this article.

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This study has no relevant financial relationships.

Author Contributions

M.K.: analyzed and interpreted the patient data, wrote the manuscript. J.Y.L. and H.Y.: reviewed and revised the manuscript and provided important intellectual content. H.J.W. and K.K.: analyzed and interpreted the patient data and conceived the concept. J.K. and K.A.: supervised all aspects of manuscript preparation and assisted with the study formulation, data analysis, manuscript writing, and interpretation of the findings. All authors contributed to the analysis, interpretation, revision, and final preparation of the manuscript.

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