

The Natural History and Prognostic Factors of Egg Allergy in Korean Infants with Atopic Dermatitis

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SUMMARY The aim of this study was to understand the natural course of egg allergy and to identify the prognostic factors for tolerance. A retrospective study that included 106 children with atopic dermatitis and egg allergy diagnosed at less than 2 years of age was conducted using medical records and parental telephone interviews. Tolerance was defined as the absence of an allergic reaction in response to the parental introduction of cooked eggs to the diet of children whose egg white specific IgE level had decreased to less than 1.5 kU_A/l. The median age of tolerance to egg allergy was 4 years. Kaplan-Meier analysis predicted that 41% of children had developed tolerance to egg allergy by age 3, while 60% of children had developed tolerance by age 5. The age at the diagnosis of egg allergy was the only significant prognostic factor of egg allergy tolerance identified by the Cox proportional regression model.

Thirty-five to 40% of patients with atopic dermatitis (AD) are known to have food allergies.^{1,2} In addition, sensitization to eggs is common in children with AD and is often associated with the persistence of the skin symptoms.³ Moreover, an egg allergy or sensitization to eggs may precede the appearance of an inhalant allergy later in life and predict the development of asthma.^{4,5} Therefore, understanding the natural history and prognosis of egg allergies is important for preventing the development of other allergic diseases as well as for managing AD properly.

Although the timing and prognostic factors of the development of tolerance to egg allergies have been the subject of debate, it is believed that most egg allergies are outgrown.⁶⁻⁸ Indeed, the results of previous studies have shown that 24 to 70% of patients outgrow egg allergies.⁹⁻¹¹ In addition, recent

studies have reported that approximately 50% of children with an egg allergy tolerate the food by 4 to 12 years of age.^{6,7}

Previous studies have suggested various prognostic factors for the development of tolerance to egg allergies, including the severity of symptoms following ingestion,^{6,9} the size of skin prick tests reactions,⁶ egg specific IgE antibody levels,^{7,9,12} and the rate of change in egg specific IgE levels.¹³ However, it is difficult to compare the results of these studies due to differences in the follow-up durations and the age at which the initial evaluation was conducted.

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The most reliable technique utilized to confirm the diagnosis of a food allergy is the double-blind, placebo controlled food challenge (DBPCFC);¹⁴ however, this procedure is time consuming and burdensome. In contrast, the quantification of food specific IgE antibody levels is a useful method for diagnosing symptomatic allergy to foods in the pediatric population that may eliminate the need to perform DBPCFC in a large number of children. The presence of an egg specific IgE level exceeding 2 kU_A/l using the CAP system in infants less than 2 years old indicates that there is a 95% chance of detecting a clinical allergy in response to egg ingestion.^{15,16} To date, few studies have been conducted to evaluate the natural course of egg allergies and its related factors in Korea, although several reports are available from other countries.^{6,7,9-11}

Therefore, it is the purpose of this study to retrospectively evaluate the genesis of egg allergies in those Korean children diagnosed with AD. Since Korean children have differing genetic make-ups, socioeconomic levels and dietary patterns than westernized children, these findings may contribute to a more understanding of the natural history of egg hypersensitivity. Additionally, a secondary purpose was to identify relevant prognostic factors instrumental in developing tolerance to eggs in these children.

MATERIALS AND METHODS

This study was conducted on 106 children who had been diagnosed with concomitant AD and egg allergies in the allergy clinic of Samsung Medical Center, Seoul, based on medical records and parental telephone interviews. All patients enrolled in this study had developed AD and egg allergies at less than 2 years of age. The diagnosis of AD was based on the criteria defined by Hanifin and Rajka, which is delineated as pruritus, lichenification, chronic course and atopy history.¹⁷ Egg allergy was determined when egg white specific IgE level measured by immunoCAP (Pharmacia, Uppsala, Sweden) system was greater than 2 kU_A/l with more than 95% certainty of egg allergy diagnosis.^{15,16} Patients with anaphylaxis to any kind of food were excluded in this study.

For each child, a detailed clinical history was

recorded. The severity of skin lesions was determined by the six area, six sign in atopic dermatitis (SASSAD) severity score.¹⁸ This score is obtained by grading each of six clinical signs of disease intensity (erythema, exudation, excoriation, dryness, cracking, and lichenification) on a scale of 0-3 at each of six defined body sites (head and neck, trunk, arms, hands, legs, and feet) to give an overall score with a maximum of 108. Following diagnosis, the children's parents were advised to strictly avoid providing eggs to their children. In addition, egg ingestion was also restricted in lactating mothers. All patients were then regularly followed up at an outpatient clinic, with serum total IgE and specific IgE antibodies to egg whites being measured at least once a year. The specific IgE antibodies to other common food allergens including cow's milk, wheat, soy, peanut and buckwheat were also measured, with concentrations ≥ 0.7 kU_A/l being regarded as sensitization. This limit was chosen to exclude possibly ambiguous or transient events of sensitization caused by variations in measurement sensitivity.

All patients and their parents were asked about possible reactions as a result of accidental or intentional ingestion of eggs during the follow-up period. In 32 patients who had never eaten eggs, parents were asked to introduce egg in the patients' diet at home using one whole cooked egg when the specific IgE levels became less than 1.5 kU_A/l. Tolerance was determined as the absence of an allergic reaction to the open challenge test. At the end of the study, we obtained further information regarding egg ingestion and possible allergic reaction in patients who had not developed tolerance at the time of their last follow-up visits by subsequent parental telephone interviews.

In addition, several prognostic factors were evaluated, including gender, duration of exclusive breastfeeding, age at which AD developed, age at which egg allergy was diagnosed, family history of allergic diseases, maternal dietary restriction of eggs during breastfeeding prior to diagnosis, whether or not hydrolyzed formula was provided, and sensitization to other foods. A family history of allergic disease was defined as at least one family member having AD, allergic rhinitis, allergic conjunctivitis, or asthma.

This study was approved by the institutional review board at Samsung Medical Center in Seoul, and written informed consent was obtained from each patient prior to participation in this study.

Statistic analysis

The data generated in this study were analyzed using SPSS for Windows (version 13.0, SPSS, Chicago, USA). For purposes of statistical analysis, values of >100 kU_A/l were assigned a value of 101 kU_A/l. 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 a log-rank test. Factors in the analysis included gender, duration of exclusive breastfeeding (< 6 months or ≥ 6 months), age at the development of AD (< 6 months or ≥ 6 months), age at the diagnosis of egg allergy (< 6 months or ≥ 6 months), family history of physician-diagnosed allergic diseases (0 or ≥ 1), maternal dietary restriction of egg during breastfeeding prior to diagnosis, feeding of hydrolyzed formula, severity of AD based on an SASSAD severity score (< 30 or ≥ 30) and sensitization to other foods. The influence of the total IgE and egg white specific IgE on tolerance was statistically evaluated by univariate Cox regression analyses. The relative importance of multiple prognostic factors on allergic disease survival was analyzed using multivariate analysis in conjunction with the Cox proportional regression model. A *p* value < 0.05 was considered to be significant.

RESULTS

Development of tolerance to egg

The median age at the initial visit of the 61 boys and 45 girls included in this study was 7 months (range 1-23 months), which was divided into 38 subjects with age < 6 months, 50 subjects with age between 6-11 months, and 18 subjects with age between 12 and 23 months. The median follow-up duration was 49 months (range 23-132 months). At the time of the initial visit, the median total IgE level was 148.5 kU_A/l with a range between 11.8-26588 kU_A/l and the median egg white specific IgE level was 13.25 kU_A/l (range 2.3-101). In addition, 74 patients (69.8%) had convincing history of clinical reactions in response to egg ingestion, while 32 pa-

tients (30.2%) had never eaten eggs. Among 74 children, the predominant AD symptoms associated with egg allergies was eczema (87.8%) followed by a grouping of urticaria, angioedema and rash (6.8%) with respiratory symptoms present in only 4 subjects.

During the follow-up period, 62 (58%) children developed tolerance to egg. Fig. 1 shows the Kaplan-Meier curve about the egg allergy tolerance in children with AD. The median survival age, which was defined as the age of cumulative survival probability that includes 50% of the population, was 4 years. In addition, 41% of the patients had recovered from their allergy by age 3, 60% by age 5 and 85% by age 10.

Prognostic factors of the development of tolerance

Table 1 enumerates prognostic factors without statistical significance such as sex, duration of exclusive breastfeeding, age at the onset of AD, family history of physician-diagnosed allergic diseases, maternal dietary restriction of eggs during breastfeeding before diagnosis, feeding of hydrolyzed formula, severity of AD and the presence of sensitization to other foods. Univariate analysis using the log-rank test showed that the development of tolerance was only related to the age when egg allergy was diagnosed. The median age of developing tolerance

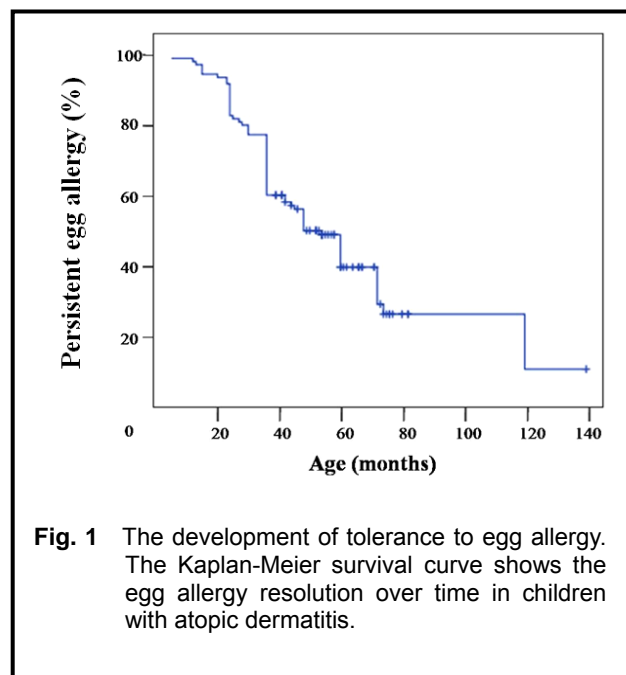


Fig. 1 The development of tolerance to egg allergy. The Kaplan-Meier survival curve shows the egg allergy resolution over time in children with atopic dermatitis.

was 36 months for patients whose egg allergy were diagnosed before 6 months of age, while it was 60 months for those diagnosed with egg allergy at 6 months or older ($p = 0.002$). However, the SASSAD severity score was close to statistical significance ($p = 0.051$).

Table 2 shows that persistent egg allergy was associated with total IgE and egg white specific IgE according to univariate Cox regression analysis. The median time to develop egg tolerance was greater in children who had higher levels of logarithm of total IgE or egg white specific IgE at the

time of the initial evaluation ($p = 0.012$, and $p = 0.044$, respectively). Similar to the initial values, the tolerance was inversely related to the logarithm of the peak total IgE and specific IgE observed during the follow-up period ($p = 0.000$, and $p = 0.003$, respectively). The hazard ratio was 0.81 for every 1 unit increase in the logarithm of total IgE level at initial visit and 0.80 in the logarithm of specific IgE level at initial visit. The hazard ratio was 0.74 for every 1 unit increase in the logarithm of the peak total IgE level during follow-up period and 0.73 in the logarithm of the peak specific IgE level.

Table 1 Predictors of egg tolerance according to the log-rank test

Variable	No. of tolerance (%)	Median survival (months)	95% CI	<i>p</i> value
Sex				
Male	34/61 (55.7)	60	41 – 79	0.548
Female	28/45 (62.2)	48	36 – 60	
Duration of breastfeeding				
< 6 months	26/42 (61.9)	60	53 – 67	0.591
≥ 6 months	36/64 (56.3)	44	36 – 52	
Age at development of AD				
< 6 months	56/96 (58.3)	48	38 – 58	0.899
≥ 6 months	6/10 (60.0)	54	22 – 86	
Age at diagnosis of egg allergy				
< 6 months	22/33 (66.7)	36	28 – 44	0.002
≥ 6 months	40/73 (54.8)	60	49 – 71	
Family history of allergic diseases				
None	45/73 (61.7)	48	37 – 59	0.424
≥ 1 member	17/33 (51.5)	60	39 – 81	
Maternal dietary restriction of egg during breastfeeding				
No	47/79 (59.5)	54	43 – 65	0.925
Yes	15/27 (55.6)	48	25 – 71	
Feeding of hydrolyzed formula				
No	26/47 (55.3)	60	28 – 92	0.401
Yes	36/59 (61.0)	48	39 – 57	
SASSAD severity score				
< 30	56/87 (64.4)	48	33 – 63	0.051
≥ 30	6/19 (31.6)	NA	NA	
Sensitization to other foods				
No	17/22 (77.3)	36	32 – 40	.060
Yes	45/84 (53.6)	60	47 – 74	

AD, atopic dermatitis; CI, confidence interval; SASSAD, six area, six sign atopic dermatitis; NA, not available.

Table 3 shows the prognostic factors of egg allergy tolerance according to multivariate Cox proportional regression analysis. The age when egg allergy was diagnosed was the only significant prog-

Table 2 Predictors of egg tolerance according to univariate analysis by the Cox proportional hazard model

Variable	Median		Hazard ratio	95% CI	p value
	Tolerance	Intolerance			
Logarithm of total IgE at initial visit	4.59	5.23	0.81	0.68 – 0.95	0.012
Logarithm of egg white specific IgE at initial visit	2.38	3.19	0.80	0.64 – 0.99	0.044
Logarithm of the peak total IgE	6.06	5.88	0.74	0.63 – 0.88	0.000
Logarithm of the peak egg white specific IgE	3.21	2.84	0.73	0.59 – 0.90	0.003

CI, confidence interval; specific IgE, specific IgE.

Table 3 Predictors of egg tolerance according to multivariate analysis

Variable	Hazard ratio	95% CI	p value
Sex			
Male	0.83	0.48 – 1.41	0.486
Female	1		
Duration of breastfeeding			
< 6 months	0.84	0.46 – 1.54	0.575
≥ 6 months	1		
Age at development of AD			
< 6 months	0.68	0.27 – 1.74	0.423
≥ 6 months	1		
Age at diagnosis of egg allergy			
< 6 months	1		
≥ 6 months	0.45	0.23 – 0.86	0.016
Family history of allergic disease(s)			
None	1		
≥ 1 member	0.93	0.52 – 1.65	0.793
Maternal dietary restriction of egg during breastfeeding			
No	1		
Yes	0.66	0.31 – 1.37	0.259
Feeding of hydrolyzed formula			
No	0.62	0.36 – 1.06	0.081
Yes	1		
SASSAD severity score			
< 30	1		
≥ 30	0.55	0.22 – 1.41	0.216
Sensitization to other foods			
No	1		
Yes	0.74	0.36 – 1.50	0.405
Logarithm of total IgE at initial visit	0.92	0.71 – 1.20	0.545
Logarithm of egg white specific IgE at initial visit	0.90	0.62 – 1.30	0.569

AD, atopic dermatitis; CI, confidence interval; SASSAD, six area, six sign atopic dermatitis; specific IgE, specific IgE; NA, not available.

nostic factor of egg allergy tolerance ($p = 0.016$). Furthermore, the likelihood of tolerance decreased by 0.45 in children diagnosed with egg allergy at 6 months of age and older. Gender, duration of breastfeeding, age at the onset of AD, family history of allergic diseases, maternal dietary restriction of eggs during breastfeeding, feeding of hydrolyzed formula, SASSAD severity score and the presence of sensitization to other foods were not found to be statistically related to the resolution of egg allergy.

DISCUSSION

The results of the present study reinforce the notion that the majority of patients with egg allergy will eventually develop tolerance. However, the timing of the development of tolerance to eggs observed in the present study was inconsistent with the results of Savage *et al.*⁷ In that study, the Kaplan-Meier curves revealed only 4% of children outgrew egg allergy by age 4, but that 48% of children outgrew it by age 12. In contrast, Boyano-Martinez *et al.*⁶ reported that 50% of children with egg allergy developed tolerance by age 4 to 4.5 years. In the present study, approximately 50% of children with egg allergy developed tolerance by 4 years of age, which is consistent with the results of Boyano-Martinez *et al.* However, it is difficult to compare these data, because the proportion of patients with AD in the previous studies varies between 50% and 81%, while in the present study 100% of the children had AD. The length of follow-up, the definition of egg allergy and the population size may also have influenced the results. Furthermore, the patients enrolled in the present study had a different race, genetic background, and dietary habits compared with children in the aforementioned studies.

The natural course of egg allergy is poorly understood; cutaneous or gastrointestinal symptoms following the ingestion of eggs,^{6,9,11} low levels of specific IgE antibodies to egg,^{6,7} a small reaction size in response to the skin prick test⁶ or an early high IgG/IgE antibody ratio¹² have been found as good prognostic factors for the development of tolerance to egg allergy. In addition, the degree of reduction in food specific IgE antibody concentration over time was used to predict the likelihood of the development of tolerance to egg allergy.¹³ In the present study, univariate analysis showed a significant asso-

ciation between levels of egg white specific IgE antibodies and egg allergy tolerance, but not in multivariate analysis, which is different from previous studies.^{6,7} Differences of age, the population size and specific IgE levels between our study and previous reports are postulated as the cause. In addition, the age when egg allergy was diagnosed was the only significant prognostic factor of the tolerance identified by the univariate and multivariate Cox proportional regression model. In terms of age at diagnosis, our results correspond with those of earlier studies, in which children diagnosed before 4 years of age were more likely to develop clinical tolerance to allergy to eggs than those diagnosed at greater than 4 years of age.¹³

There are possible explanations for better prognosis in the early diagnosis group. One possible reason may be the route of exposure to egg allergens. Indeed, the majority of children who were diagnosed with egg allergy before reaching 6 months of age had never ingested an egg, although they may have been exposed to egg allergens through other routes. Clinical adverse reactions to eggs can occur in response to the first known ingestion or skin contact with eggs.^{19,20} It has been suggested that sensitization can occur by transplacental transfer or through breast feeding.^{21,22} Animal studies have revealed that age, route of exposure and age at the time of exposure contributed to the development of oral tolerance in food allergy.²³⁻²⁵ Similarly, it has been shown that early exposure to the ingestion of cow's milk is related to delayed development of the tolerance to cow's milk.²⁶ Another possible explanation is that early detection of the egg allergy and avoidance of the offending food could lead to earlier tolerance of egg allergy. Although there is no good evidence that exposure to egg allergens delays the acquisition of tolerance,^{27,28} the cornerstone of the management of food allergies is believed to be avoidance of the relevant food allergens.²⁹ In this study, patients diagnosed with egg allergy before 6 months of age had been managed from an early age by using a multidisciplinary approach including consultation with a well-trained dietitian. The patients in the early diagnosis group may have benefited from the early intervention. Finally, children without true clinical allergy to eggs might be included in the early diagnosis group, because they were diagnosed on the basis of specific IgE levels alone. This may have resulted in

asymptomatic sensitized patients being counted in the tolerance group.

It should be noted that there are several potential limitations to this study. The evaluation of tolerance development was not established by DBPCFC in the hospital setting. In addition, approximately 30% of the initial diagnoses of egg allergy were based on specific IgE antibody levels alone, but not DBPCFC. However, the Kaplan-Meier survival curves for the tolerance development in children with a convincing history of egg allergy were similar to those of children who were diagnosed based on the specific IgE levels alone (data not shown), as previous study.⁷

In conclusion, half of children with egg allergy and AD which developed before 2 years of age outgrow the egg allergy at 48 months of age. The age at the diagnosis of egg allergy might be an important prognostic factor to predict development of tolerance.

ACKNOWLEDGEMENTS

This work was supported by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD). (KRF- 2008-532-E00016).

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