

Risk factors for failing a repeat oral food challenge in preschool children with hen's egg allergy

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Editor: Alexandra Santos

Abstract

Background: Children with hen's egg (HE) allergy and a positive initial oral food challenge (OFC) require rechallenge to assess for tolerance. However, the risk factors for a positive repeat OFC remain unclear.

Methods: We retrospectively analyzed data from 243 preschool children who failed an initial OFC with half a heated HE and repeated the same OFC after 6–24 months. Logistic regression models were used to determine risk factors for a positive repeat OFC, including factors that were ascertainable immediately after the initial OFC and at the repeat OFC as variables.

Results: The median age, egg white-, and ovomucoid-specific IgE (sIgE) were 3.5 years, 12.7, and 7.2 kU_A/L, respectively. The median interval between OFCs was 12.4 months and repeat OFCs were positive in 132 (54%) patients. One multivariate analysis model indicated that risk factors for a positive repeat OFC included cumulative dose (adjusted odds ratio [aOR]: 0.58), anaphylaxis (aOR: 3.09), total serum IgE (aOR: 0.41), ovomucoid-sIgE (aOR: 3.21), and age (aOR: 1.68) at the initial OFC. Another model indicated that the risk factors were cumulative dose (aOR: 0.59) and anaphylaxis (aOR: 3.41) at initial OFC and total serum IgE (aOR: 0.36), ovomucoid-sIgE (aOR: 4.93), and age (aOR: 1.30) at repeat OFC.

Conclusion: Low threshold dose and severe symptoms at initial OFC, and low total serum IgE, high ovomucoid-sIgE and higher age at initial and repeat OFCs are risk factors for the persistence of HE allergy and they may be useful when deciding the rechallenge interval for heated HE in preschool children.

KEYWORDS

allergy, children, hen's egg, oral food challenge, repeat, risk factors

1 | INTRODUCTION

Hen's egg (HE) allergy is one of the most common food allergies in childhood, with a prevalence of 1.3%–2.5% among children younger than 5 years.^{1–3} In Japan, HE is the most frequent cause (39%) of food allergy.⁴ Despite some variation in the results owing to differences

in the study population, 49%–73% of the patients outgrow the HE allergy in early childhood by age 6.^{5–8} Therefore, the European Academy of Allergy and Clinical Immunology issued guidelines that recommend a repeat oral food challenge (OFC) every 6–12 months in the absence of an accidental reaction.⁹ The American Academy of Allergy, Asthma, and Immunology practice guideline suggests a

reevaluation every 1–2 years, accompanied by an OFC if needed.¹⁰ Although skin-prick tests and serum-specific immunoglobulin E (sIgE) levels are useful for reevaluating patients with HE allergy,¹¹ OFCs are needed to confirm the acquisition of tolerance.^{9,10} There are limited reports on the risk factors for failing a repeat OFC; moreover, owing to the small sample size of previous studies, the risk factors remain unclear.^{12–14} In addition, previous studies comprised children of all ages, and no report has focused solely on preschool children. In this study, we aimed to clarify the risk factors for failing a heated HE OFC that was repeated in preschool children who had a positive initial OFC.

2 | METHODS

2.1 | Patient selection

We retrospectively reviewed medical records of preschool children (age ≤6 years) with suspected HE allergy who were confirmed to tolerate heated egg yolk that was slightly contaminated with egg white in an OFC or on consumption at home¹⁵ and subsequently underwent an initial OFC with half a heated HE (3690 mg HE protein) at the National Hospital Organization Sagamihara National Hospital between December 2005 and September 2014. Patients with a positive initial OFC and a repeat OFC after 6–24 months were included in the analysis dataset. Patients with inconclusive results in the initial OFC (owing to mild and/or transient symptoms that subsided without treatment), with an undeterminable OFC result (owing to insufficient HE intake), or with missing clinical or laboratory data were excluded from the analysis.

2.2 | Oral food challenge

Open OFCs were performed with half a heated HE (3690 mg HE protein) in a pumpkin cake or hamburger steak, made by mixing half of a whole egg with pumpkin or pork, respectively, and heating in a microwave to a core temperature of 95°C (1000 W, 90 s). OFCs were performed in five doses (measured as fractions of half an egg: 1/16, 1/16, 1/8, 1/4, and 1/2) with a 15-min interval, three doses (1/8, 3/8, and 1/2) with a 30-min interval, or two doses (1/4 and 3/4) with a 60-min interval, based on the period when the OFC was conducted. Initial and repeat OFCs were judged as positive when apparent objective symptoms, such as urticaria, cough, wheezing, vomiting, and diarrhea, or prolonged subjective symptoms, such as abdominal pain, and oral symptoms that necessitated treatment were observed. Repeat OFCs with inconclusive results were considered positive when symptoms were reproducible with the intake of the same amount of the challenged food at home. Symptom severity during the initial OFC was defined as Grade 1 (mild), Grade 2 (moderate), or Grade 3 (severe) according to the Japanese guidelines for food allergy (Appendix S1).⁴ Anaphylaxis was defined according to the World Allergy Organization anaphylaxis guidelines.¹⁶

Key Messages

In preschool children with hen's egg allergy, risk factors for a positive repeat oral food challenge included low threshold dose and severe symptoms at the initial oral food challenge, and low total serum IgE levels, high ovomucoid-specific IgE levels, and higher age at the initial and repeated oral food challenges.

These risk factors could guide the decision to repeat an oral food challenge after an interval without accidental reactions and indicate the possibility of tolerance.

2.3 | Clinical and laboratory data

Data on demographic characteristics, comorbid atopic diseases, and laboratory data were obtained from the medical records of the patients. Total serum IgE, egg white-sIgE, and ovomucoid-sIgE levels were measured using ImmunoCAP (Thermo Fisher Scientific/Phadia) within 1 year before or after each OFC. Details of the OFCs were collected from the OFC database at our hospital.

2.4 | Statistical analysis

The results of the analyses are expressed as medians and interquartile ranges. The Fisher's exact and Mann–Whitney *U*-tests were used for intergroup comparison. A *p*-value < .05 was considered to be statistically significant. In multivariate analysis, after removing factors that were associated or highly correlated, logistic regression analysis was performed with variables of importance that were fitted simultaneously. All analyses were performed using R version 4.1.1 (R Core Team).¹⁷

2.5 | Ethical considerations

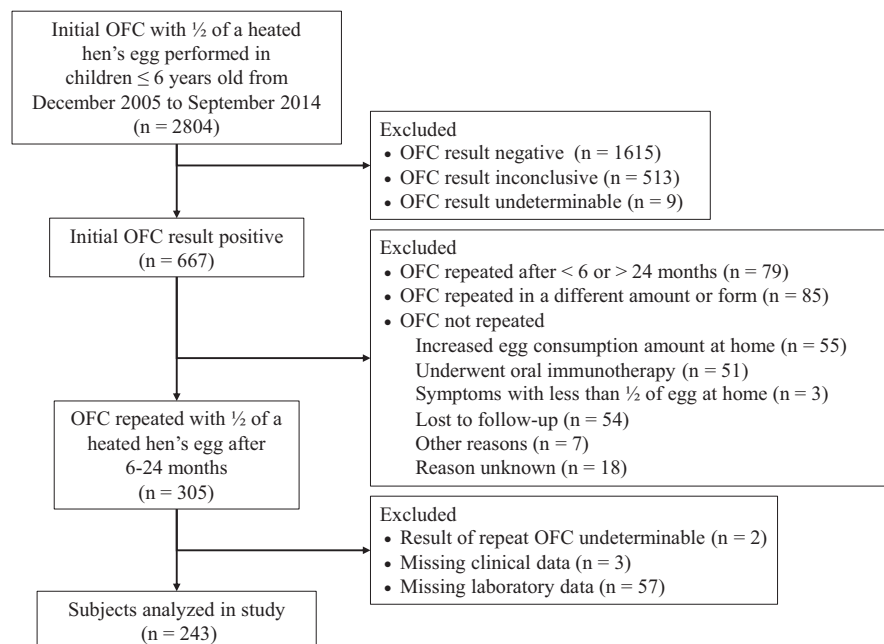
This study was approved by the ethics committee of the National Hospital Organization Sagamihara National Hospital, and informed consent was obtained from the guardians of all patients before each OFC.

3 | RESULTS

3.1 | Patient characteristics and results of the initial OFC

In total, 2804 preschool children underwent an initial OFC with half a heated HE, and 667 had a positive result. We analyzed data from 243 of the 667 patients who repeated an OFC with the same challenge food amount after 6–24 months (Figure 1). The median age of

FIGURE 1 Flowchart of patient selection. The OFC results were defined as inconclusive when mild and/or transient symptoms, which required no treatment, were observed. OFC results were defined as undeterminable when no apparent symptoms were induced but the patient refused to consume the total dose. OFC, oral food challenge



the 243 patients was 3.5 years. Atopic dermatitis, asthma, and food allergies besides HE were present in 196 (81%), 80 (33%), and 140 (58%) patients, respectively. The median egg white- and ovomucoid-sIgE levels were 13.0 and 7.96 kU_A/L, respectively.

The median cumulative dose in the initial OFC was 2994 mg HE protein; 187 (77%) patients presented with a symptom grade ≥ 2 , including 5 (2%) patients with Grade 3 symptoms. Symptoms in 63 (26%) patients were defined as anaphylaxis. Two hundred (82%) patients required treatment, and 9 (4%) required intramuscular adrenaline (Table 1).

3.2 | Data available at the time of the repeat OFC

OFCs were repeated after a median interval of 12.4 months and the median age at repeat OFC was 4.8 years. Median egg white- and ovomucoid-sIgE levels were 8.04 and 4.77 kU_A/L, respectively. The change in sIgE levels between the OFCs was assessed by the ratio of egg white- and ovomucoid-sIgE level at the repeat OFC to that at the initial OFC (median 0.64 and 0.62, respectively, Table 2).

Among the 243 patients, the repeat OFC was initially classified as positive in 120 (49%), negative in 85 (35%), and inconclusive in 41 (17%) patients. After the OFC, 12 of the patients with inconclusive results were determined to have a positive OFC because the symptoms were reproducible with an intake of the same amount at home. Therefore, 132 (54%) patients were defined as having a positive repeat OFC.

3.3 | Univariate analysis of risk factors

Age, total serum IgE, egg white-sIgE, and ovomucoid-sIgE levels at both the initial and repeat OFC were significantly higher in

patients with a positive repeat OFC. There was no significant difference in the rates of comorbid allergic diseases. Patients with a positive repeat OFC had a significantly lower cumulative dose and higher rate of anaphylaxis at the initial OFC. The ratio of egg white-sIgE and ovomucoid-sIgE at repeat OFC to that at initial OFC was significantly lower in patients with a negative repeat OFC (Table 3).

3.4 | Multivariate analysis of risk factors

In the first model, we performed multivariate analysis of only the data available immediately after the positive initial OFC. Risk factors included a low cumulative dose, anaphylaxis, high ovomucoid-sIgE level, low total serum IgE level, and higher age at the initial OFC (Table 4). In the second model, we also included the data available at the time of the repeat OFC. Risk factors included a low cumulative dose and anaphylaxis during the initial OFC, and high ovomucoid-sIgE level, low total serum IgE level, and higher age at the repeat OFC (Table 5).

In both models, Grade 2–3 symptoms during the initial OFC were called as independent risk factors when included instead of anaphylaxis. Receiver operating characteristic analysis showed that the area under the curve of egg white-sIgE was lower than that of the ovomucoid-sIgE at the time of the initial (0.655 vs. 0.678) and repeat OFC (0.687 vs. 0.719). Therefore, egg white-sIgE was excluded in both models owing to high correlation. A comparison of the total serum IgE, ovomucoid-sIgE, and age of patients with a positive and negative repeat OFC result is shown in Figures S1–S3. The rate of positive repeat OFCs in patients with and without anaphylaxis was 76% (48/63) and 47% (84/180), respectively. The rate of positive repeat OFCs in patients with Grade 1, 2, and 3 symptoms was 34% (19/56), 59% (108/182), and 100% (5/5), respectively.

TABLE 1 Patient characteristics and results of the positive initial oral food challenges

Characteristics	n = 243
Patient characteristics at initial OFC	
Sex (male)	168 (69)
Age (years)	3.5 (2.3–5.2)
Comorbid allergic disease	
Atopic dermatitis	196 (81)
Asthma	80 (33)
Allergic rhinitis	57 (23)
Other food allergy	140 (58)
Total serum IgE (IU/ml) ^a	308 (113–818)
Egg white-sIgE (kU _A /L)	13.0 (6.11–25.3)
Ovomucoid-sIgE (kU _A /L)	7.96 (3.59–18.0)
Results of initial OFC	
Cumulative dose (milligrams of hen's egg protein)	2994 (1845–3690)
Symptom severity	
Symptom grade ^b	
Grade 1 (mild)	56 (23)
Grade 2 (moderate)	182 (75)
Grade 3 (severe)	5 (2)
Anaphylaxis	63 (26)
Symptoms	
Skin	185 (76)
Oral	43 (18)
Respiratory	147 (60)
Gastrointestinal	129 (53)
Neurological	12 (5)
Cardiovascular	0 (0)
Treatment	
No treatment	43 (18)
Oral antihistamine	141 (58)
IV or IM antihistamine	57 (23)
Oral corticosteroid	19 (8)
IV corticosteroid	26 (11)
Nebulized β_2 -agonist	116 (48)
Nebulized adrenaline	2 (1)
IM adrenaline	9 (4)

Note: Data are presented as n (%) or median (interquartile range).

Abbreviations: IM, intramuscular; IV, intravenous; OFC, oral food challenge; sIgE, specific IgE.

^aTotal serum IgE data were missing for two patients (n = 241).

^bAccording to the Japanese guidelines for food allergy, symptom severity was classified as Grade 1 (mild), Grade 2 (moderate), or Grade 3 (severe), based on the organ which was most affected.

4 | DISCUSSION

In this study of preschool children with HE allergy, we found that a low cumulative dose, anaphylaxis or grade 2–3 symptoms at the initial OFC, and low total serum IgE, high ovomucoid-sIgE, and higher age at both the initial and repeat OFC were risk factors for failing a

TABLE 2 Patient characteristics at repeat oral food challenge and changes in egg white- and ovomucoid-specific IgE levels

Characteristics	n = 243
Age (years)	4.8 (3.3–6.3)
Total serum IgE (IU/ml) ^a	418 (138–1013)
Egg white-sIgE (kU _A /L)	8.04 (3.09–17.2)
Ovomucoid-sIgE (kU _A /L)	4.77 (1.78–12.9)
Interval between initial and repeat OFC (months)	12.4 (10.2–15.9)
Increase in egg white-sIgE	51 (21%)
Increase in ovomucoid-sIgE	61 (25%)
Egg white-sIgE ratio (Repeat OFC/ Initial OFC)	0.64 (0.42–0.92)
Ovomucoid-sIgE ratio (Repeat OFC/ Initial OFC)	0.62 (0.40–1.00)

Note: Data are presented as n (%) or median (interquartile range).

Abbreviations: OFC, oral food challenge; sIgE, specific IgE.

^aTotal serum IgE data were missing for one patient.

repeat OFC. Awareness about these risk factors may be useful in deciding the interval for a reevaluation for HE allergy after an initial positive heated HE OFC, in the absence of an accidental reaction.

Mudd et al. have previously reported results of repeat OFCs in 101 children, including 38 patients with HE allergy. A higher proportion of patients with severe symptoms during the initial OFC failed the repeat OFC (70.4% vs. 29.6%), but a significant difference was only seen in patients with milk allergy. The challenge dose that provoked symptoms during the initial OFC was not predictive of the repeat OFC results and a difference in allergen-sIgE at repeat OFC was only seen in patients with milk allergy.¹² However, the results of the abovementioned study are limited by the small sample size. There are retrospective reports of HE-allergic children who received a baseline OFC and were rechallenged over time to assess the relationship between the course of egg white- and ovomucoid-sIgE levels and tolerance; however, owing to the small sample size, multivariate analysis including other factors, such as cumulative dose and symptom severity during baseline OFCs, was not performed.^{13,14}

In our study of 243 preschool children with HE allergy, the severity of symptoms during the initial OFC, which was assessed by symptom grade and the presence of anaphylaxis, was a risk factor of a positive repeat OFC. Previous reports on the natural history of HE allergy indicate that a history of anaphylaxis or systemic reactions that are not limited to the skin were factors associated with persistent HE allergy, which is in agreement with our findings.^{5,6,8}

Furthermore, we found that children with a lower cumulative dose, and consequently, a lower threshold dose during the initial OFC, were more likely to have a positive repeat OFC. Gradman et al. previously reported that a lower threshold dose at the baseline OFC with raw egg was associated with persistent HE allergy.¹³ Similarly, Okada et al. reported that children with HE allergy who were reactive to heated egg yolk that was slightly contaminated with egg white had greater odds of persistent HE allergy than those who were unreactive.¹⁸ The results of these studies support our findings,

TABLE 3 Univariate analysis of risk factors for a positive repeat oral food challenge

Variables	Positive repeat OFC (n = 132)	Negative repeat OFC (n = 111)	p-Value
Patient characteristics at initial OFC			
Sex (male)	94 (71)	74 (67)	.445
Age (years)	4.1 (3.1–5.5)	2.6 (1.8–4.2)	<.001
Comorbid allergic diseases			
Atopic dermatitis	104 (79)	92 (83)	.422
Asthma	45 (34)	35 (32)	.672
Allergic rhinitis	37 (28)	20 (18)	.068
Other food allergy	78 (59)	62 (56)	.611
Total serum IgE (IU/ml) ^a	425 (146–1003)	204 (73–683)	.002
Egg white-sIgE (kU _A /L)	16.0 (7.58–35.7)	10.3 (4.23–16.2)	<.001
Ovomucoid-sIgE (kU _A /L)	11.6 (5.28–27.0)	5.0 (1.90–13.3)	<.001
Result of initial OFC			
Cumulative dose (milligrams of hen's egg protein) ^b	1845 (1845–3690)	1845 (1845–3690)	<.001
Symptom severity			
Symptom grade ^c			
Grade 1 (mild)	19 (14)	37 (33)	<.001
Grade 2 (moderate)	108 (82)	74 (67)	
Grade 3 (severe)	5 (4)	0 (0)	
Anaphylaxis	48 (36)	15 (14)	<.001
Symptoms			
Skin	99 (75)	86 (77)	.652
Oral	30 (23)	13 (12)	.027
Respiratory	92 (70)	55 (50)	.002
Gastrointestinal	80 (61)	49 (44)	.011
Neurological	8 (6)	4 (4)	.384
Cardiovascular	0 (0)	0 (0)	NA
Data available at the time of repeat OFC			
Age (years)	5.3 (3.4–6.5)	3.9 (2.7–5.6)	<.001
OFC interval (months)	12.4 (10.3–15.9)	12.4 (10.1–16.0)	.989
Total IgE (IU/ml) ^d	558 (209–1138)	371 (112–848)	.008
Egg white-sIgE (kU _A /L)	11.3 (4.31–27.2)	5.3 (1.9–12.2)	.023
Ovomucoid-sIgE (kU _A /L)	8.32 (2.70–21.6)	3.25 (0.90–6.68)	<.001
Egg white-sIgE ratio (Repeat OFC/Initial OFC)	0.72 (0.47–1.06)	0.54 (0.37–0.76)	<.001
Ovomucoid-sIgE ratio (Repeat OFC/Initial OFC)	0.65 (0.48–1.08)	0.55 (0.33–0.97)	.011

Note: Data are presented as n (%) or median (interquartile range). A p-value < .05 was considered significant and is presented in bold font.

Abbreviations: CI, confidence interval; NA, not applicable; OFC, oral food challenge; OR, odds ratio; sIgE, specific IgE.

^aTotal serum IgE data at the time of initial OFC were missing for two patients.

^bMedian and interquartile range of cumulative dose were identical in the patients with positive and negative results on the repeated OFC.

^cAccording to the Japanese guidelines for food allergy, symptom severity was classified as Grade 1 (mild), Grade 2 (moderate), or Grade 3 (severe) based on the organ which was most affected.

^dTotal serum IgE data at the time of repeat OFC was missing for one patient.

suggesting that it would take longer for patients with a lower threshold dose to outgrow their HE allergy.

Higher age was a risk factor of a positive repeat OFC. However, in contrast to our study, a previous study has reported that younger

TABLE 4 Multivariate analysis of only the data available immediately after the initial oral food challenge

Variables	Adjusted OR (95% CI)	p-Value
Patient characteristics at initial OFC		
Sex (male)	1.27 (0.67–2.43)	.468
Age (years)	1.68 (1.30–2.18)	<.001
Atopic dermatitis	0.86 (0.38–1.95)	.725
Asthma	0.63 (0.30–1.28)	.201
Total serum IgE (IU/ml)	0.41 (0.19–0.90)	.027
Ovomucoid-sIgE (kU _A /L)	3.21 (1.62–6.35)	<.001
Result of initial OFC		
Cumulative dose	0.58 (0.44–0.76)	<.001
Anaphylaxis	3.01 (1.46–6.20)	.003

Note: Variables of importance were fitted simultaneously in the multivariate analysis. The symptom grade during the initial OFC was excluded from multivariate analysis as it was considered to be associated with anaphylaxis. Moreover, the egg white-sIgE level was excluded from multivariate analysis owing to a high correlation with the ovomucoid-sIgE level. Adjusted ORs of the total serum IgE level and the ovomucoid-sIgE levels are per 10-fold increase. Adjusted OR of cumulative dose is per 1000mg increase. A *p*-value < .05 was considered significant and is presented in bold font.

Abbreviations: CI, confidence intervals; OFC, oral food challenge; OR, odds ratio; sIgE, specific IgE.

children had a higher HE OFC positivity rate.¹⁹ This difference may be attributable to a selection bias in our study, as patients with more accidental reactions may have received the initial OFC at a higher age.

With regard to laboratory data, high ovomucoid-sIgE levels and low total serum IgE at initial and repeat OFC were risk factors for failing the repeat OFC. Previous studies have reported that high baseline egg-sIgE is associated with persistent HE allergy.^{5,6,8} In more recent studies, ovomucoid-specific IgE has been reported to predict heated HE OFC results more accurately than egg white-sIgE,^{20–23} whereas in baked HE OFCs, the ovomucoid-sIgE was not superior to egg white-sIgE in predicting the results.^{24,25} This difference may be attributable to the degree of heating, the food matrix effect caused by wheat, or both.^{26,27} In the OFCs in our study, we used heated HE which did not contain wheat and we found that the ovomucoid-sIgE was more useful than egg-white-sIgE. Horimukai et al. reported that children with a higher total serum IgE were significantly less responsive in OFCs,²⁸ as observed in our study. This may be due to the high rate of patients with atopic dermatitis, who frequently have high total serum IgE levels and elevated antigen sIgE but without clinical relevance.²⁹

Previous studies have reported that the decrease in egg white- and ovomucoid-sIgE levels was significantly greater in patients who became tolerant to HE.^{8,13,14} We found that egg white- and ovomucoid-sIgE levels decreased at a significantly higher rate in patients with a negative repeat OFC in the univariate analysis; however, the change in sIgE levels was not identified as an independent risk factor in the multivariate analysis. The difference between the results of our study and those of previous studies may be due to the longer intervals between the measurements of sIgE levels in the previous studies.

Variables	Adjusted OR (95% CI)	p-value
Patient characteristics at initial OFC		
Sex (male)	1.30 (0.67–2.52)	.435
Atopic dermatitis	0.75 (0.33–1.71)	.540
Asthma	0.64 (0.32–1.31)	.248
Result of initial OFC		
Cumulative dose	0.59 (0.45–0.79)	<.001
Anaphylaxis	3.41 (1.60–7.26)	.002
Data available at time of repeat OFC		
Age (years)	1.43 (1.15–1.77)	.001
Total serum IgE (IU/ml)	0.36 (0.16–0.79)	.011
Ovomucoid-sIgE (kU _A /L)	4.93 (2.36–10.30)	<.001
Ovomucoid-sIgE ratio (Repeat OFC/Initial OFC)	1.32 (0.53–3.32)	.553

Note: Variables of importance were fitted simultaneously in the multivariate analysis. The symptom grade during the initial OFC was excluded from multivariate analysis as it was considered to be associated with anaphylaxis. The egg white-sIgE levels at the repeat OFC and the egg white-sIgE ratio (Repeat OFC/Initial OFC) were excluded from multivariate analysis owing to the high correlation with the ovomucoid-sIgE level at the repeat OFC and the ovomucoid-sIgE ratio (Repeat OFC/Initial OFC), respectively. Adjusted ORs of the ovomucoid-sIgE level and the ovomucoid-sIgE ratio are per 10-fold increase. Adjusted OR of cumulative dose is per 1000mg increase. A *p*-value < .05 was considered significant and is presented in bold font.

Abbreviations: CI, confidence intervals; OFC, oral food challenge; OR, odds ratio; sIgE, specific IgE.

TABLE 5 Multivariate analysis of the data available at the time of repeat oral food challenge

This study has some limitations. First, the OFCs were open OFCs and not double-blind placebo-controlled food challenges. However, as most of the OFCs were adjudged positive owing to objective symptoms, and patients with inconclusive initial OFC results were excluded from this study, the effect of this limitation would be considered minimal. Second, since only patients who could consume egg yolk with slight contamination of egg white received the initial OFC, patients with a very low threshold, and therefore with the most severe HE allergy, were not included in this study. Third, selection bias may have affected the results. For example, patients with high egg white- and ovomucoid-sIgE may not have received the initial OFC. In addition, patients who experienced severe symptoms during the initial OFC may not have received a repeat OFC. However, as 76% of the patients who received a repeat OFC had Grade 2 or 3 symptoms during the initial OFC, and as 26% experienced anaphylaxis, we infer that most of the patients who underwent the initial OFC received the repeat OFC. Fourth, although we routinely perform repeat OFCs after approximately 1 year, in the absence of accidental reactions, the timing would have been affected by the preference of the attending physician and/or guardian of the child. To minimize the effect of this limitation, we excluded patients who repeated their OFCs before 6 months or after 24 months.

In conclusion, as the majority of preschool children outgrow HE allergy, repeat OFCs are necessary after an initially positive OFC. The knowledge that a low threshold dose and severe symptoms at the initial OFC, and a low total serum IgE, high ovomucoid-sIgE and higher age at the initial and repeat OFC are risk factors for a positive repeat OFC with heated HE, may be useful for providing an outlook about the child's HE allergy status and progression after an initially positive OFC. Furthermore, these markers can guide the decision of rechallenge when the child is reevaluated after an interval without accidental ingestions. Further studies with OFCs in different populations, using HE heated to different degrees, are needed as these factors may alter the risk factors that are involved in a positive repeat HE OFC.

AUTHOR CONTRIBUTIONS

Makoto Nishino conceptualized and designed the study, collected data, undertook statistical analysis of the data, interpreted the results, and drafted the manuscript. Noriyuki Yanagida contributed to the conceptualization and designing of the study, interpretation of the results, and critically reviewed the manuscript. Sakura Sato contributed to the interpretation of the results, and critically reviewed the manuscript. Kyohei Takahashi contributed to the statistical analysis of the data and critically reviewed the manuscript. Ken-ichi Nagakura, Kiyotake Ogura, and Motohiro Ebisawa critically reviewed the manuscript.

ACKNOWLEDGMENTS

The authors thank the pediatricians, dietitians, and nurses who helped perform the oral food challenges. We also thank Editage (www.editage.jp) for English language editing.

CONFLICTS OF INTEREST

Motohiro Ebisawa and Sakura Sato have received speaker honoraria from Mylan. The other authors declare that they have no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/pai.13895>.

DATA AVAILABILITY STATEMENT

The datasets used to support the findings of this study are available from the corresponding author on reasonable request.

IMPACT STATEMENT

In preschool children with hen's egg allergy, risk factors for failing a repeat oral food challenge with heated hen's egg were low threshold dose and severe symptoms at the initial oral food challenge, and low total serum IgE levels, high ovomucoid-specific IgE levels, and higher age at the initial and repeat oral food challenges. Awareness of these risk factors could facilitate prognostication of the child's hen's egg allergy after an initial positive oral food challenge and guide the decision to repeat an oral food challenge when the child is reevaluated after an interval without accidental reactions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Nishino M, Yanagida N, Sato S, et al. Risk factors for failing a repeat oral food challenge in preschool children with hen's egg allergy. *Pediatr Allergy Immunol*. 2022;33:e13895. doi:[10.1111/pai.13895](https://doi.org/10.1111/pai.13895)