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Original article

Natural history of immediate-type hen's egg allergy in Japanese children

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EW, egg white; HE, hen's egg; Immunoglobulin E, IgE; OFC, oral food challenge; OM, ovomucoid; SEM, standard error of the mean

ABSTRACT

Background: Hen's egg (HE) allergy develops during infancy. We investigated tolerance acquisition in Japanese children allergic to HE aging <6 years.
Methods: In this retrospective study, 226 children born in 2005 with a history of immediate-type HE allergy underwent an oral food challenge (OFC). Tolerance was defined as no reaction to an OFC with half of whole heated HE or accidental HE consumption at home. Participants were divided into three groups based on age at tolerance acquisition: group I (<3 years) ($n = 66$), group II (3–6 years) ($n = 98$), and group III (prolonged allergic groups) ($n = 62$).
Results: Tolerance acquisition occurred in 30% (66/226) by 3 years of age, 59% (133/226) by 5 years of age, and 73% (164/226) at 6 years of age. At 3 years, incidences of allergy-related complications (bronchial asthma, $p = 0.02$; atopic dermatitis, $p = 0.04$) were higher in the group III than in the group I. Anaphylaxis to any food occurred more frequently in the group III than in the group I ($p = 0.03$); anaphylaxis to HE was more common in the group III ($p = 0.04$). Egg white (EW)- and ovomucoid (OM)-specific immunoglobulin E (IgE) levels were higher in the group III than in the group I ($p < 0.05$).
Conclusions: The group III experienced HE-related anaphylaxis and complications more frequently and exhibited sustained, high EW- and OM-specific IgE levels.
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Introduction

Diagnosis of a food allergy is associated with a significant deterioration in quality of life. In Japan, the most common food allergy is to hen's egg (HE).[1] Food allergies are common among infants aging <1 year and they diminish with age, indicating that tolerance develops with age. The estimated prevalence of food allergy in Japan is 5%–10% among infants and 1%–2% among schoolchildren.[1,2] The basis of food allergy treatment is elimination of the offending food from the diet.[3] Regarding the clinical practice of food allergy medicine, it is important to determine the timing of tolerance acquisition, so that elimination of the allergen from the diet is no longer necessary.

In Western countries, many investigators have studied the natural history of food allergy in children and have discussed the factors associated with the prolongation of food allergy.[4–14] In contrast, only two reports have been published so far about the natural history of food allergy in Japan.[15,16] Ikematsu *et al.*[15] investigated the rate of tolerance acquisition in children aging <3 years allergic to HE, cow's milk, and wheat, and Imai *et al.*[16] investigated the prolongation of food allergies in children up to 6 years who were diagnosed with food allergy to HE by a definitive history of positive food allergic reactions or food provocation tests.

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In this study, based on an oral HE challenge in Japanese children aged 6 and under years, and the large number of the study population in Japan, we retrospectively investigated tolerance acquisition and factors related to the prolongation of immediate-type HE allergy.

Methods

Study population

We conducted a retrospective study using the clinical records of children with HE allergy born in 2005 who presented at our hospital with a history of an immediate-type reaction. The cohort was followed up at our department until 6 years of age. HE allergy was defined as the presence of an allergic reaction after the ingestion of a raw or heated HE, or a positive physician-supervised OFC with HE.

The history of an immediate-type reaction to HE can vary from urticaria to severe responses, such as anaphylaxis. Children were included if they were instructed to eliminate HE from their diet after presentation, and if an immediate-type allergic reaction occurred following accidental ingestion of HE after HE elimination. Patients who were not given HE because of their levels of antigen-specific immunoglobulin E (IgE) or who did not ingest HE were excluded. Additionally, patients where follow-up to the age of 6 was impossible or who received oral immunotherapy were excluded. Moreover, children were excluded from this study if they presented at our department with severe atopic dermatitis and unstable asthma had no history of HE ingestion, or started an egg-elimination diet because of a high level of egg white (EW)-specific IgE but had a negative result to the OFC. This study was approved by the ethics committee of Sagamihara National Hospital.

Oral food challenge

For patients on an egg-elimination diet, OFC using heated whole HE yolk was conducted in our department. In our department, OFC was undertaken based on the Japanese Guideline for Food Allergy. It was undertaken more than 1 year after the last immediate allergic responses to HE because of confirmed tolerance to HE allergy. The age at which OFC could be undertaken was decided by a primary doctor. However, if the diagnosis of HE allergy was unclear, we confirmed it by performing OFC.[2] If the result was negative, OFC using pumpkin cake containing half of whole heated HE was undertaken. The half of whole heated HE was cooked at 1000 W for 90 s in a microwave. The result of the OFC was deemed positive or negative based on the presence or the absence of clear objective symptoms on the skin or of the respiratory, digestive, cardiovascular, and nervous systems. Patients with objective symptoms who did not require treatment were designated undetermined. Undetermined patients were considered negative when no clear objective symptoms were observed after repeated ingestion of HE at home. Tolerance acquisition was recorded when a negative or undetermined response to the OFC was achieved after a 2- to 4-week period when half of whole heated HE was regularly ingested at home.

OFC to determine tolerance acquisition was conducted when more than 1 year had passed since the last episode of symptoms caused by accidental ingestion of egg, or if OFC was requested by parents or guardians on the precondition that a reduction in the level of EW-specific IgE was measured during the elimination period. Open challenges are routine at our clinic for very young children and follow the recommendations of the European Academy of Allergology and Clinical Immunology.[17]

Study selection

OFC with half of whole heated HE at home was only conducted in children that had no history of anaphylaxis when an immediate-type reaction occurred more than 12 months before the OFC and measurement of the level of HE-specific IgE was found to be reduced or below 0.70 kU_A/L. Participants underwent OFC using half of whole heated HE and ingested half of whole heated EW as a trial at home (Fig. 1). The participants were divided into three groups based on the age at which tolerance to half of whole heated HE was acquired: group I (<3 years), group II (3–6 years), and group III (prolonged allergic groups), the individuals in which continued to present allergic symptoms after the OFC. The rate of tolerance acquisition against half of whole heated HE was investigated over time according to age.

Clinical information

We recorded patient characteristics (gestational age, body weight at birth, type of delivery, sex, breast-feeding during infancy, age at weaning, presence of pets in the home, passive smoking, number of siblings, age at first presentation, presence of symptoms of bronchial asthma, atopic dermatitis, and allergic rhinitis or allergic conjunctivitis at 3 years), family history of complications of allergic diseases (bronchial asthma, atopic dermatitis, allergic rhinitis, and allergic conjunctivitis), and food allergy factors (disease type, age of occurrence, age at which food elimination diets were started, and any history of anaphylaxis caused by any foods or triggered by HE).

Serologic findings

Serologic findings (changes in antigen-specific IgE levels over time) were obtained by measuring specific IgE antibodies to EW and ovomucoid (OM) (ImmunoCAP; Phadia AB, Uppsala, Sweden) after the OFC. However, skin tests were not performed in all participants.

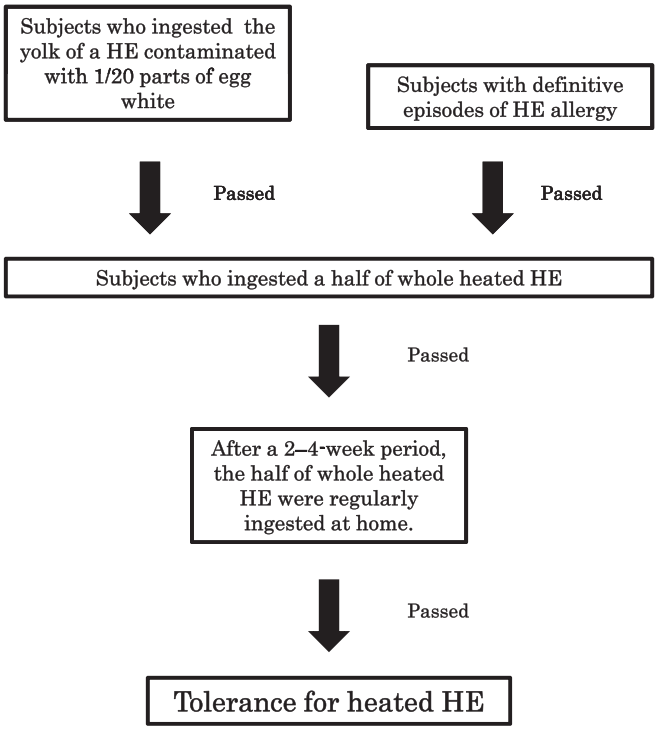

Fig. 1. Oral food challenge and tolerance.

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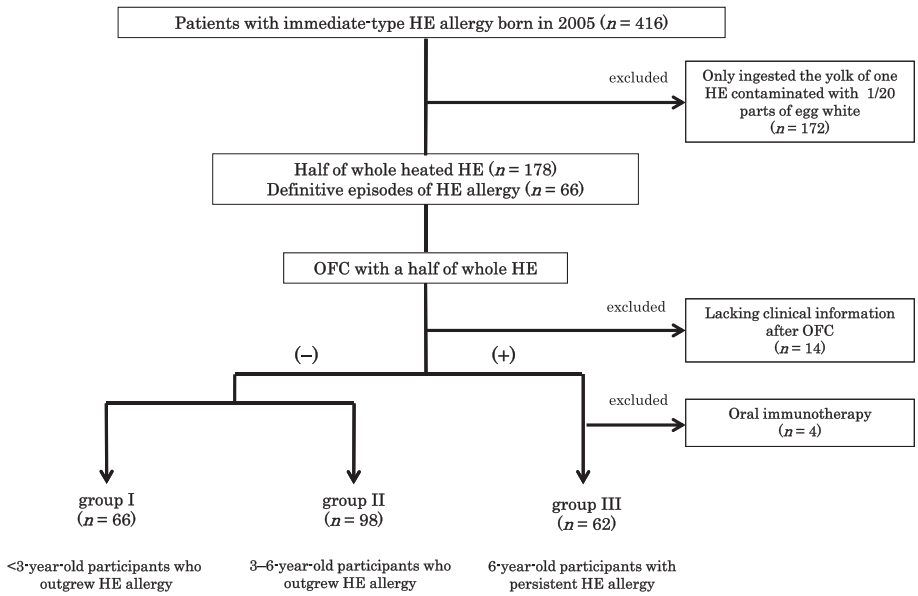


Fig. 2. Natural history of patients with a hen's egg (HE) allergy.

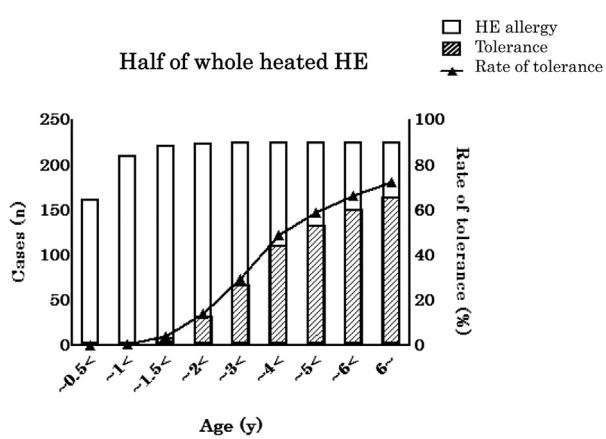
Statistical analysis

Data were analyzed using GraphPad Prism 5 for Windows (GraphPad Software Inc., La Jolla, CA, USA). Data are presented as the mean ± standard error of the mean (SEM). For statistical analysis, Fisher' s exact test or the Mann–Whitney *U*-test was used for intergroup comparisons of discontinuous variables, and the Kruskal–Wallis test was used for comparisons among the three groups. A *p*-value of <0.05 was considered statistically significant.

Results

Study population

A total of 416 children born in 2005 with a history of immediate-type allergic reaction following HE ingestion presented at our department. We excluded 172 patients who underwent OFC using only heated whole HE yolk contaminated with 1/20 parts of egg white, because these patients could not confirm the tolerance of HE. Two hundred forty-four children met the criteria for this study: 178 underwent OFC using half of whole heated HE, and 66 children ingested half of whole heated HE as a trial at home. Of the 244 children, only 226 were included in this study. Fourteen children were excluded because of incomplete clinical information after OFC, and six were excluded because they received oral immunotherapy. Consequently, 66 children were included in the group I, 98 in the group II, and 62 in the group III (Fig. 2).



Age (years)	~0.5<	~1<	~1.5<	~2<	~3<	~4<	~5<	~6<	6~
Cases (*n*)	162	211	222	225	226	226	226	226	226
Tolerance (*n*)	0	1	8	31	66	110	133	150	164
Rate of tolerance (%)	0	0.01	0.04	14	30	49	59	66	73

Fig. 3. Tolerance acquisition with increasing age.

Table 1
Analysis of factors associated with tolerance acquisition and food allergies.

	Group I (*n* = 66)	Group II (*n* = 98)	Group III (*n* = 62)	*p*-Value
Gestational age	39.5 ± 0.1	39.4 ± 0.1	39.5 ± 0.2	ns
Birth weight (g)	3112.3 ± 39.5	3055 ± 37.3	3054.7 ± 46.3	ns
Normal delivery, *n* (%)	61 (92)	80 (82)	50 (81)	ns
Male, *n* (%)	33 (50)	61 (62)	37 (60)	ns
Breast feeding, *n* (%)	20 (30)	43 (44)	19 (31)	ns
Age at weaning (m)	5.6 ± 0.2	5.6 ± 0.1	5.6 ± 0.1	ns
Pets in the home, *n* (%)	6 (9)	3 (3)	2 (3)	ns
Passive smoking, *n* (%)	25 (38)	37 (38)	26 (42)	ns
Number of siblings (*n*)	1.6 ± 0.1	1.5 ± 0.1	1.6 ± 0.1	ns
First visit (m)	14.1 ± 1.6	31.2 ± 2.2†	34.1 ± 3.0†	<0.001
Initial type				
FA/AD, *n* (%)	41 (62)	69 (70)	48 (77)	ns
Immediate, *n* (%)	25 (38)	29 (30)	14 (23)	ns
Months at onset				
FA/AD (m)	1.9 ± 0.3	2.4 ± 0.3	2.1 ± 0.3	ns
Immediate (m)	9.0 ± 0.7	8.4 ± 0.7	9.8 ± 1.9	ns
Start of food elimination (m)	6.9 ± 0.4	7.4 ± 0.4	6.1 ± 0.4	ns
History of anaphylaxis (any foods; times)	0.3 ± 0.1	0.5 ± 0.1	0.7 ± 0.1†	0.03
History of anaphylaxis (HE; times)	0.1 ± 0.04	0.1 ± 0.03	0.3 ± 0.1†	0.04

Kruskal–Wallis test (gestational age, birth weight, age at weaning, number of siblings, months at onset, start of food elimination, first visit, and history of anaphylaxis [(any foods and hen's egg)].
HE, hen's egg; FA/AD, infant atopic dermatitis associated food allergy; g, grams; m, months; ns, not significant.
Mean ± standard error of the mean.
† Versus group I.

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Table 2
Analysis of allergy factors associated with tolerance acquisition.

		Group I ($n = 66$)	Group II ($n = 98$)	Group III ($n = 62$)	p-Value
Subjects	BA, n (%)	11 (17)	22 (22)	31 (50)†	0.02
	AD, n (%)	42 (64)	65 (66)	51 (82)†	0.04
	AR, n (%)	3 (5)	3 (3)	3 (5)	ns
	AC, n (%)	3 (5)	2 (2)	4 (6)	ns

Complications of allergic diseases were assessed in children at age 3.
AD, atopic dermatitis; AC, allergic conjunctivitis; AR, allergic rhinitis; BA, bronchial asthma; FA, food allergy; ns, not significant.
† Versus group I.

Changes over time in tolerance rates according to age are shown in Fig. 3. The rate of tolerance for half of whole heated HE 30% (66/226) by 3 years of age, 59% (133/226) by 5 years of age, and 73% (164/226) at 6 years of age.

Clinical information

Age at first visit was significantly higher in the group II and group III compared with the group I ($p < 0.001$). No significant differences were evident among the three groups for gestational age, body weight at birth, type of delivery, sex, breast-feeding during infancy, age at weaning, presence of pets in the home, passive smoking, and number of siblings (Table 1). The incidences of bronchial asthma and atopic dermatitis were significantly higher in the group III than in the group I (Table 2). No significant difference was observed between the three groups in the family history of allergic disease (data not shown). Similarly, no significant differences were observed for disease type, age at occurrence, and age at the start of food elimination. The total number of episodes of anaphylaxis caused by exposure to any food was significantly higher in the group III than the group I ($p = 0.03$). The number of episodes of anaphylaxis due to HE exposure was also significantly higher in the group III ($p = 0.04$) (Table 1).

Serologic findings

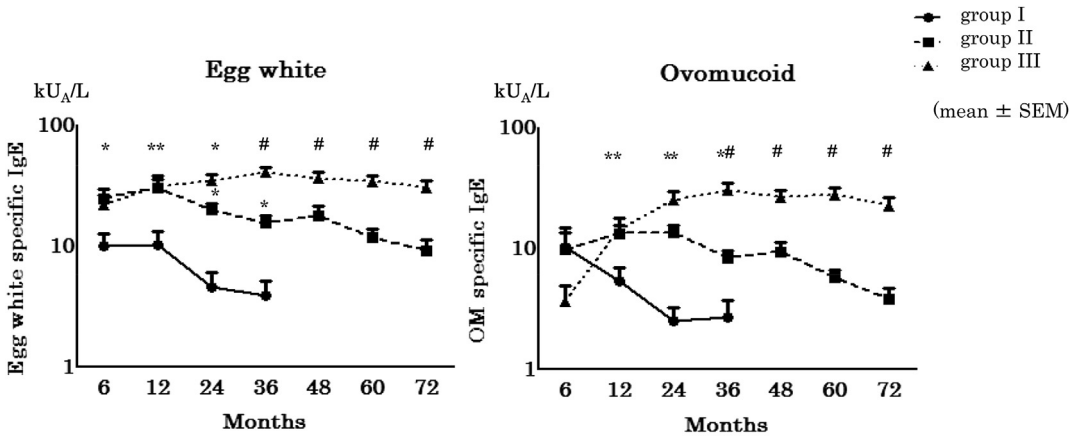
Levels of EW- and OM-specific IgE in the group III remained significantly higher than those in the group I ($p < 0.05$). Additionally, levels of OM-specific IgE remained raised, but not significantly so, after infancy in the group III. Levels of EW-specific IgE gradually decreased with age in the group I and group II (Fig. 4). The levels of OM-specific IgE in those who passed the OFC to half of whole heated egg were 2.8 ± 0.7 kU_A/L (mean ± SEM) in the group I and 7.9 ± 1.2 kU_A/L in the group II. In those who failed the OFC, OM-specific IgE levels were 5.5 ± 1.8 kU_A/L in the group I, 22.8 ± 2.3 kU_A/L in the group II, and 27.2 ± 3.2 kU_A/L in group III. The number of patients who underwent serologic testing varied in this study, because the timing of the test was not necessarily consistent, and there was a period during which the test was undertaken within 6 months.

Discussion

In this retrospective study, based on the results of the OFC (rate of tolerance acquisition against half of whole heated HE), we investigated the natural history of immediate-type HE allergy in Japanese children aged <6 years. Approximately 70% of the enrolled patients acquired tolerance to HE by 6 years of age.

In Western countries, a considerable number of reports have been published on the natural history of food allergies,[5–12,17,18] however few reports have been published in Japan.[15,16] A study by Ikematsu *et al.*[15] showed a 30% rate of tolerance acquisition against half of whole heated HE by 3 years of age. In our investigation, we similarly found a 30% (66/226) rate of tolerance acquisition against half of whole heated HE by 3 years of age.

Kim *et al.*[18] investigated HE allergy in 106 children who had developed atopic dermatitis and egg allergies at <2 years of age. They demonstrated a 58% (62/106) rate of HE allergy children aged up to 5 years or less. Boyano-Martinez *et al.*[4] investigated HE allergy in children aged <2 years with a history of an immediate-type allergic reaction; they showed a 66% (38/58) tolerance rate by 5 years of age. Pyziak *et al.*[6] investigated IgE-dependent HE allergy



Months	6	12	24	36	48	60	72
group I ($n = 66$)	39	49	47	29			
group II ($n = 98$)	43	59	68	70	69	56	39
group III ($n = 62$)	35	43	46	55	54	49	39

Months	6	12	24	36	48	60	72
group I ($n = 66$)	25	43	46	28			
group II ($n = 98$)	22	51	59	68	60	49	36
group III ($n = 62$)	19	37	42	52	51	45	39

Fig. 4. Changes in the levels of egg white- and ovomucoid-specific immunoglobulin E (IgE) with increasing age.

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and showed a 90% (17/19) rate of tolerance acquisition at 6 years of age. In these reports, Kim *et al.*[18] defined tolerance acquisition as tolerance to heated whole HE, Boyano-Martinez *et al.*[4] defined it as tolerance to half-raw whole HE, and Pyziak *et al.*[6] defined it as tolerance to a sufficient amount of HE as part of a usual dietary intake.

Results from this study and three previous reports[4,5,18] indicate that acquisition of tolerance to HE is possible in approximately 60%–90% of children allergic to HE before the age of 6 years, despite the variation in patient populations and definition of tolerance between these studies. Pyziak *et al.*[6] reported the following predisposing factors to the development of tolerance: immediate symptoms present at only one organ site; no complications such as bronchial asthma, and no family history of food allergies. Imai *et al.*[16] suggested that factors delaying tolerance acquisition include complications related to various food allergies, a history of anaphylaxis, and other allergic diseases (atopic dermatitis as well as high levels of antigen-specific IgE antibody). In this investigation, a history of anaphylactic episodes caused by any food ($p = 0.03$) or HE ($p = 0.04$) and complications such as bronchial asthma at the age of 3 years ($p = 0.02$) and atopic dermatitis ($p = 0.04$) were significantly higher in the allergic group than in the two groups in which tolerance was acquired.

This study has some limitations. First, because this is a retrospective study, the timing of the OFC may not align with the defined age. Second, the enrolled children did not undergo double-blind, placebo-controlled food challenges, which is the gold standard for food allergy diagnosis. Finally, patients with mild egg allergy do not visit tertiary hospitals during the initial stage. Patients severe symptoms that are resistant to usual treatments tend to visit tertiary hospitals only after becoming older. Therefore, limited epidemiological data can be obtained from our study. In practice, the tolerance rate may be higher than that observed in our study.

In conclusion, we determined the rates of tolerance acquisition in Japanese children with immediate-type HE allergy in each age group up to the age of 6 years. We identified a history of anaphylactic episodes, complications such as bronchial asthma and atopic dermatitis, as well as persistent high levels of IgE specific to EW and OM over time as factors involved in delaying the acquisition of tolerance to HE in children with HE allergy.

Acknowledgments

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Conflicts of interest

The authors have no conflicts of interest to declare.

Authors' contributions

KO, SS, AS and ME designed the study and wrote the manuscript. TA, KOg, YK, KI, NY and TI contributed to the data collection. KO performed the statistical analysis and interpreted the results. All authors read and approved the final manuscript.

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