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Development of Tolerance in Children with Hen's Egg Allergy Using the Egg Ladder

Gulce BARANLI AYDINLIOGLU[1], Melike OCAK[2], Demet CAN[1]

[1] Department of Pediatrics, Balıkesir University Faculty of Medicine, Balıkesir, Türkiye
[2] Division of Pediatric Allergy and Immunology, Health Sciences University, İzmir Faculty of Medicine, Dr. Behçet Uz Children's Hospital, İzmir, Türkiye

Corresponding Author: Demet Can ddcan15@hotmail.com

ABSTRACT

Objective: Hen's egg is one of the most common causes of food allergy worldwide. A hen's egg ladder is used to accelerate the acquisition of tolerance. This study investigated the frequency of tolerance achieved with the hen's egg ladder and the factors influencing tolerance.

Materials and Methods: Patients with IgE-mediated hen's egg allergy younger than five years of age who underwent egg laddering were reviewed.

Results: The study group consisted of 85 patients with a median (min-max) age at diagnosis of 11 months (3-48 months) with a male predominance (61.2%). The most common symptoms, in terms of frequency, were eczema (53%), urticaria (15.2%), angioedema (10.5%) and vomiting (9.4%). Six patients had anaphylaxis. The most common co-allergens were cow's milk and peanuts. Of the 85 patients, 76 (89.4%) patients tolerated baked whole hen's eggs, and 9 (10.6%) were allergic to baked hen's eggs, including 5 to egg yolk and 4 to egg white. The median age at diagnosis was statistically significantly lower and the eosinophil count was significantly higher in the allergic group (p=0.010, p=0.033, respectively). In the study group, 70 (82.4%) were tolerant to whole hen's eggs and 15 (17.6%) who had a positive OFC at any stage were allergic. The median age at diagnosis and the presence of anaphylaxis were found to be significantly higher in the persistent group (p=0.031 and p=0.008, respectively). Caesarean section was also found to be a factor delaying tolerance in all forms of hen's egg allergy.

Conclusion: The frequency of tolerance is high in hen's egg allergy. Tolerance to baked forms develops at an earlier age. The use of an egg ladder that gives priority to egg yolk is thought to induce early tolerance.

Keywords: Hen's egg allergy, hen's egg ladder, infant, natural history, tolerance

INTRODUCTION

Hen's egg is one of the most common causes of food allergy worldwide, with a reported prevalence of 1.6-10.1% (1). The HealthNut study reported that the prevalence of hen's egg allergy (HEA) at one year of age was 9.5%, higher than with other major food allergies such as peanut (3.1%) and cow's milk (1.5%) (2). The natural history of HEA has been reported in several studies. The rate of tolerance varies between reports, ranging from 12% to 73% by 6 years of age (1, 3, 4). Peters et al. (2) studied 140 infants with challenge-confirmed HEA at one year of age and reported resolution of HEA in 47% by two years of age (2).

Recent studies have shown that despite this natural history of the egg, over 70% of children with hen's egg allergy can tolerate eggs in baked foods (5). Leonard et al. have shown that when baked egg-tolerant children were introduced to heated eggs in their diet, the time required for tolerance induction was reduced to 50 months as opposed to 78 months in the egg avoidance group (6). Diets starting with baked eggs to induce tolerance are the basis of the egg ladder (7).

A food ladder is a form of home food challenge therapy that gradually increases exposure to an allergenic food and is widely used around the world for children with milk and

ORCID Gulce Baranli Aydinlioglu / 0000-0002-1258-9348, Melike Ocak / 0000-0001-07841-4690, Demet Can / 0000-0002-1258-9348

egg allergies. This approximation is based on the sensitivity of proteins to different types of processing including heating, fermentation, and enzymatic or chemical degradation. Heating reduces the allergenicity of food proteins through disruption of conformational epitopes with limited effect on sequential epitopes (8-10). This is used to accelerate the acquisition of tolerance in those who would outgrow it on their own, or as a form of modified oral immunotherapy in persistent allergy. It is widely used in Europe and was originally developed for the management of non-IgE mediated food allergy. Subsequently, the use of the food ladder has been extrapolated to the management of IgE-mediated milk and egg allergy and has generally been found to be safe and effective (7, 11, 12). The egg ladder goal is to facilitate the development of natural tolerance by gradually introducing egg-containing foods of increasing quantity and allergenicity through different cooking processes, typically with a gradual progression from baked products (e.g. biscuits, muffins) to well-cooked forms (e.g. pancakes, waffles, hard-boiled eggs) and finally to less processed products (e.g. soft boiled or lightly scrambled eggs). De Vlieger et al. have conducted a study of 78 baked egg-tolerant children randomized to follow a short (18 months) or long (30 months) home introduction of the egg ladder. A total of 58 children achieved tolerance to raw eggs; of these, 80% achieved this in the short introduction protocol while the 69% in the long introduction protocol achieved tolerance within 30 months. No severe reactions were reported (11). In another recent study of 287 children with egg allergy and symptoms of anaphylaxis at diagnosis, 85.2% successfully completed the ladder compared with 92.9% who did not have symptoms of anaphylaxis (13). Therefore, starting the egg ladder with egg yolk instead of whole egg may make it easier for people with a hen's egg allergy to tolerate (14). The aim of this study was to investigate the frequency of tolerance achieved using the hen's egg ladder starting with egg yolk and the factors affecting tolerance in children with egg allergy.

MATERIALS and METHODS

Study Population

This retrospective cross-sectional study was conducted in the Pediatric Allergy and Immunology Department of Balıkesir University School of Medicine. Children younger than five years of age who were diagnosed with IgE-mediated HEA between 1 May 2015 and 1 February 2020 and had complete medical records were included in the study. The diagnosis of IgE-mediated HEA was defined as a positive skin prick test (SPT; 3 mm or more above the negative control) and/or a positive specific IgE (≥0.35 kU/L). In addition, patients had to meet one of the following two criteria: a consistent and clear history of an immediate type reaction strictly related to food consumption (urticaria, angioedema, anaphylaxis), and benefit from an elimination diet, or a positive food challenge. Patients were excluded from the study if their records were incomplete or if their tests were inconsistent with egg allergy.

The patients' medical history was recorded using a standard collection form that included gender, mode of delivery, age at onset of symptoms, initial symptom with hen's egg, history of atopic disease, co-allergies, oral food challenge (OFC)'s results, and family history of atopy. Complete blood cell count, eosinophil percentage, absolute eosinophil count (AEC), and total serum IgE (tIgE) were noted. The study protocol was approved by the Ethics Committee of Balıkesir University Faculty of Medicine (Number: 2020/112, Date: 22 July 2020).

Hen's Egg Ladder Protocol

Oral food challenge tests were performed to confirm the diagnosis and assess tolerance (15). The OFC was not undergone in patients who had a history of anaphlyaxis in the previous 12 months. Patients were recommended open OFC with hen's egg according to the PRACTALL consensus (16). The procedure was conducted as an open food challenge. The risks associated with OFCs have been minimised by appropriate dosing and by conducting the tests in a controlled environment with experienced personnel.

According to our hen's egg ladder protocol, the first OFC was usually performed with one cooked egg yolk; if the test was negative, the patient consumed the same amount of cake with 2 egg yolks daily at home 7-10 days later. The patient underwent an OFC with baked egg white (whole egg) in the hospital 7-10 days later and the dose was increased to 2 whole hen's eggs at home. The baked hen's egg was cooked at 180°C for 45 minutes. If the patient tolerated the two whole baked hen's eggs, the challenge was continued with the heated yolk and white, respectively, with an interval of one month. One month later, the patient who tolerated heated whole hen's egg consumed lightly scrambled eggs at home. Heated hen's egg means that it was boiled for at least 10 minutes. Patients were observed

for at least 2 hours after each OFC. OFCs were defined as positive if there was objective evidence of an allergic reaction. The patient was also considered to be tolerant to hen's egg when consuming whole heated hen's egg. The hen's egg ladder protocol is shown in Figure 1. Patients continued to take the tolerated dose daily at home after performing the OFC and increased the daily dose as recommended. Besides, patients and their families were educated on the recognition and management of symptoms and the use of epinephrine auto-injectors. Written informed consent was obtained from the parents before OFC.

Laboratory Parameters

All children underwent SPT with a commercially available hen's egg yolk and egg white allergen extract (ALK-Abell_o, Hørsholm, Denmark). In addition, raw hen's egg was applied using the prick to prick technique. Histamine or hen's egg extract was taken from a well using a device (Oryum, Gaziantep, Turkey), and then vertical pressure was applied with 90° clockwise rotation to the volar side of the children's forearms (17). The mean wheal diameter was measured after 15 minutes by determining the longest and orthogonal diameter. A positive SPT was defined as 3 mm or more above the negative control as usual. and orthogonal diameters. Total IgE was measured in the sera by a quantitative turbidimetric method (Beckman Coulter AU680, California, USA). Eosinophilia was defined as ≥500/μ.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v.22.0 (IBM Corp., Armonk, NY, USA). Descriptive analysis was used to characterise the patients. Pearson's x2 test or Fisher's exact test was used for comparisons between groups. Values are presented as median and minimum-maximum for non-normally distributed data. The Mann-Whitney U test or Kruskal-Wallis test was used to compare values. All statistical tests were 2-sided and the level of statistical significance was set at $P < 0.05$.

RESULTS

Characteristics of Patients

A total of 110 patients with IgE-mediated hen's egg allergy were studied. Of the patients, 25 were excluded due to incomplete medical records and 85 were included in the study. Of these, 61.2% (n = 52) were male. The median age at symptom onset was 4 months (min-max: 1-30 months), while the median age at diagnosis was 11 months (min-max: 3-48 months). There was no statistically significant difference between the median age at symptom onset for male and female (p=0.720). 77.6% of patients were term, and the rate of caesarean section delivery was 64.7% (n = 55). The most common symptoms, according to frequency, were eczema (53%), urticaria (15.2%), angioedema (10.5%) and vomiting (9.4%). Anaphylaxis occurred in 7%

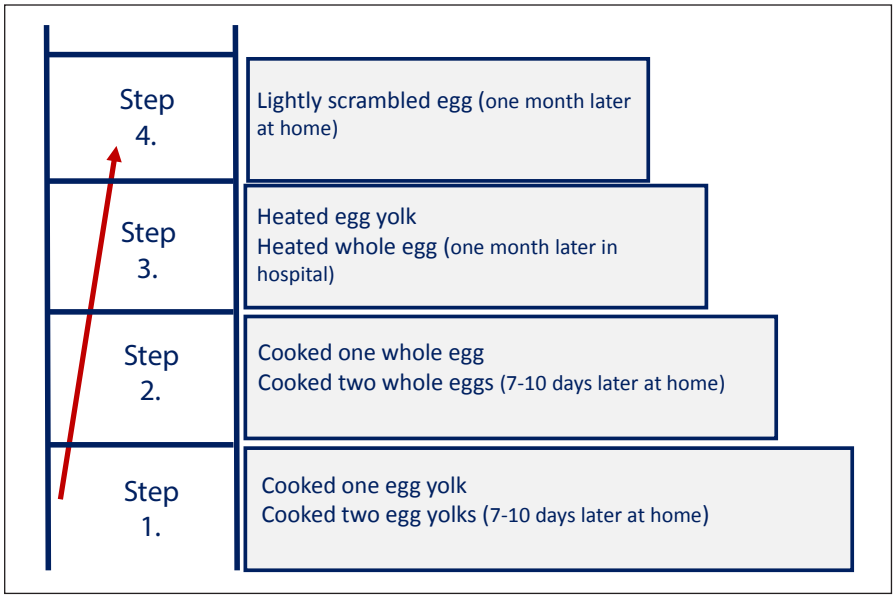

Figure 1. The hen's egg ladder protocol.

(n=6) of patients. The most common co-allergens were cow's milk (44.7%) and peanuts (4.7%). Of the patients, 47 (55.3%) had atopic dermatitis, 25 (29.4%) had food protein-induced allergic proctocolitis, and 19 (22.3%) had a history of recurrent wheezing. The age of symptom onset was statistically significantly lower in patients with concomitant cow's milk allergy and in patients with FPIAP ($p<0.05$). A parental history of atopy was recorded in 54% (n=46) of the children. Table I shows the demographic and clinical characteristics of the patients.

Outcomes of hen's egg ladder

A total of 85 OFCs were performed with baked egg yolk, of which 80 (94.1%) were negative and 5 (5.9%) were positive. The median (min-max) age of tolerance to baked egg yolk was 12 months (5-32 months). Subsequently, 80 patients who tolerated baked egg yolk, of whom 76 were negative and 4 were positive, underwent OFC with baked egg white. The median (min-max) age of tolerance to baked egg white was 13 months (9-35 months). As a result, 76 (89.4%) patients tolerated baked whole hen's egg, and 9 (10.6%) were allergic to baked hen's egg, including 5 to egg yolk and 4 to egg white. The median (min-max) age at diagnosis was 9 months (3-42 months) in the tolerant group and it was statistically significantly lower than in the allergic group (p=0.010). The eosinophil count was significantly higher in the allergic group, with a median of 1200 mm^3 (p=0.033). However, there were no differences in gender, age at symptom onset, concomitant allergic diseases, family history of atopy, and total IgE levels (Table II).

Of the 76 patients who tolerated baked whole hen's eggs, 74 had negative OFC with heated egg yolk and 2 had positive OFC. The median (min-max) age of tolerance to heated egg yolk was 18 months (6-42 months). Seventy-

Table I: Demographic and clinical characteristics of patients.

	Study group
Total, no. of patients	85
Sex: male, n (%)	52 (61.2)
Age at symptom onset, mo*	4 (1-30)
Age at diagnosis, mo*	11 (3-48)
Delivery mode, cesarean section, n (%)	55 (64.7)
Initial symptom with sesame, n (%)	
Eczema	45 (53)
Urticaria	13 (15.2)
Angioedema	9 (10.5)
Nausea/vomiting	8 (9.4)
Anaphylaxis	6 (7)
Concomitant food allergy, n (%)	
Cow's milk	38 (44.7)
Peanut	4 (4.7)
Walnut	2 (2.4)
Hazelnut	1 (1.2)
Atopic dermatitis, n (%)	47 (55.3)
History of recurrent wheezing, n (%)	19 (22.3)
Food protein-induced allergic proctocolitis	25 (29.4)
Family history of atopy, n (%)	46 (54)
Eosinophil count, /mm^3*	400 (100-3000)
Total IgE, kU/L*	70 (3.6-2270)

*Median (min-max)

Table II: Comparison of allergic and tolerant patients to baked hen's egg.

	Tolerant to baked hen's egg n=76	Alergic to baked hen's egg n=9	p
Sex: male, n (%)	46 (60.5)	6 (66.7)	1.000
Age at symptom onset, mo*	4 (1-30)	3 (1-22)	0.931
Age at diagnosis, mo*	9 (3-42)	13 (9-48)	0.010
Delivery mode, cesarean section, n (%)	51(67.1)	4 (44.4)	0.268
Atopic dermatitis, n (%)	41 (53.9)	6 (66.7)	0.725
History of recurrent wheezing, n (%)	19 (25)	-	0.198
The presence of anaphylaxis, n (%)	1 (11.1)	5 (6.6)	0.500
Concomitant cow's milk allergy, n (%)	35 (46.1)	3 (33.3)	0.725
Family history of atopy, n (%)	43 (56.6)	3 (33.3)	0.290
Eosinophil count, /mm^3*	400 (100-3000)	1200 (150-2000)	0.033
Total IgE, kU/L*	66.5 (3.6-2270)	115 (58-500)	0.073

*Median (min-max)

four patients underwent OFC with heated egg white and 70 of them passed the OFC test. The median (min-max) age of tolerance to whole hen's egg was 20 months (6-48 months). The results of the hen's egg ladder are summarised in Figure 2. None of the patients had an adverse reaction during the hen's egg ladder procedure at home.

Of the 85 patients, 70 (82.4%) were tolerant to whole hen's egg and 15 (17.6%) who had a positive OFC at any stage were allergic. The median age at diagnosis and the presence of anaphylaxis were found to be significantly higher in the persistent group (p=0.031 and p=0.008, respectively). However, there were no differences in gender, age at symptom onset, mode of delivery, concomitant allergic disease and cow's milk allergy, family history of atopy, eosinophil count, and total IgE levels (p>0.005). The characteristics and comparison of patients with resolved and persistent hen's egg allergy are shown in Table III.

Table III: Comparison of patients with resolved and persistent hen's egg allergy.

	Resolved n=70	Persistent n=15	p
Sex: male, n (%)	41 (58.6)	11 (73.3)	0.440
Age at symptom onset, mo*	4 (1-30)	6 (1-22)	0.455
Age at diagnosis, mo*	10 (3-48)	14 (11-52)	0.031
Delivery mode, cesarean section, n (%)	48 (68.6)	7 (46.7)	0.189
Atopic dermatitis, n (%)	38 (54.3)	9 (60.0)	0.906
History of recurrent wheezing, n (%)	16 (22.9)	3 (20)	1.000
The presence of anaphylaxis, n (%)	2 (2.9)	4 (26.7)	0.008
Concomitant cow's milk allergy, n (%)	32 (45.70)	6 (40)	0.906
Family history of atopy, n (%)	40 (57.1)	6 (40)	0.356
Eosinophil count, /mm^3*	400 (100-3000)	700 (100-2100)	0.180
Total IgE, kU/L*	66.5 (3.6-2270)	100 (14-608)	0.268

*Median (min-max)

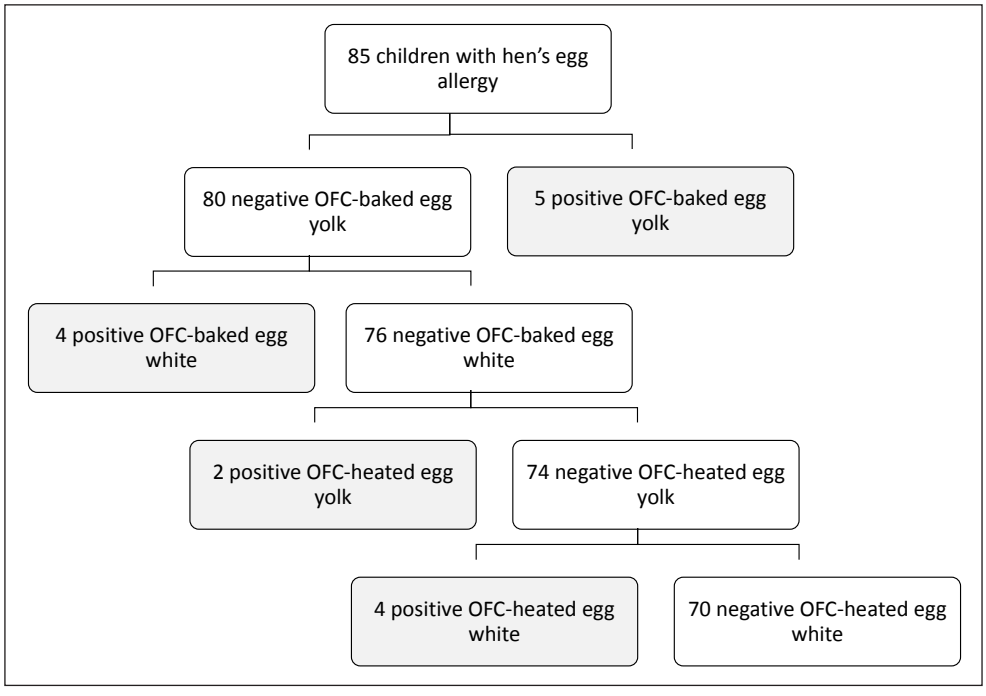

Figure 2. Outcomes of hen's egg ladder.

Table IV: Comparison of age at tolerance according to mode of delivery.

	Cesarean section (n=55)	Spontaneous vaginal (n=30)	p
Baked egg yolk, mo*	12 (6-36)	9.5 (5-18)	0.001
Baked hen's egg, mo*	15 (9-35)	12 (10-24)	0.040
Heated egg yolk, mo*	18 (6-42)	15 (12-28)	0.023
Heated hen's egg, mo*	24 (6-48)	18 (9-29)	0.037

*Median (min-max)

When the median age of tolerance was compared by mode of delivery, the age of tolerant patients for all forms of hen's egg was statistically higher in the Caesarean group ($p<0.05$) (Table IV). Caesarean section was found to be a factor delaying tolerance in all forms of hen's egg allergy.

DISCUSSION

In our study, we have shown that children with IgE-mediated hen's egg allergy develop tolerance at an average age of 20 months using a hen's egg ladder that prioritises egg yolk first and then whole egg including egg white. The presence of anaphylaxis was significantly higher in patients with persistent hen's egg allergy. Also, caesarean section was found to be a factor delaying tolerance in all forms of hen's egg allergy.

The natural history of HEA has been reported in many studies in different countries. Tolerance varies between reports from 12% to 73% at 6 years of age (1, 3, 4). In Japan, the proportions of patients who had acquired tolerance to HEA were 30% and 73% at ages 3 and 6 years, respectively (1). Recent studies have suggested that children with hen's egg allergy who tolerate baked eggs are more likely to outgrow their egg allergy than those who do not (18). The egg ladder, based on a gradual transition from baked eggs to raw eggs, is one of the disease-modifying interventions such as oral immunotherapy (19). Dietary modification therapy in the form of milk and egg ladders have been used as a method of primary, secondary, and tertiary prevention of allergy, particularly in Ireland, the UK, and Canada (20). A home approach can be used to escalate the diet after demonstrating tolerance to the baked forms, by introducing a less cooked form of egg after tolerating the baked egg. The egg ladder is essentially an oral immunotherapy, although it is not always labelled or recognised as such. Risk assessment and education are essential for patients who are candidates for home treatment (21, 22). Besides, the four major proteins in egg white are the more likely to cause egg allergy, as research has shown that egg yolk proteins are less allergenic (14, 23). In 2019, Dang et al. have confirmed that the majority of egg-allergic infants were sensitised to egg white but not to egg yolk (24). Therefore, in our study, the egg ladder was started with egg yolk, rather than whole egg as in other egg ladders, and tolerance was induced in 82.4% of patients.

Hen's egg allergy is often associated with urticaria and eczema in infancy. In some cases, it can also lead to life-threatening or fatal anaphylactic reactions (25). Clinical symptoms reported by parents to hen's egg are as follows; the most common are hives (75%) and angioedema (21%), and in more than 10% of patients consist of vomiting, lethargy, rhinitis, conjunctivitis, cough, and abdominal pain (12). In our study, eczema (53%), urticaria (15.2%), angioedema (10.5%), and vomiting (9.4%) were observed.

Chomyn et al. (12) have reported that 46.8% of patients had another food allergy, the most common being peanut allergy. In addition, atopic comorbidities were common, with eczema reported in 67.9%, asthma in 13.8%, and allergic rhinoconjunctivitis in 20.2% of the children. In our study, the most common co-allergens were cow's milk and peanuts and 55.3% of the patients had atopic dermatitis, 29.4% had food protein-induced allergic proctocolitis, and 22.3% had a history of recurrent wheezing. In studies of hen's egg allergy conducted in Türkiye, the rate of anaphylaxis varies between 3.3% and 11.4% (26, 27). In our study we found it to be 7%.

There are many studies investigating the natural history of egg allergy and the factors that influence tolerance. In the study by Peters et al. (2) followed-up 140 infants with challenge-confirmed egg allergy at 1 year of age. Egg allergy resolved by 2 years of age in 66 (47%) infants. However, resolution was lower in children with baked egg allergy compared with baked egg tolerance at 1 year of age (13% and 56%, respectively). In the subgroup of infants who were tolerant to baked egg at 1 year of age, frequent ingestion of baked egg (≥5 times per month) compared with infrequent ingestion (0-4 times per month) increased the likelihood of tolerance. In our study, tolerance to

whole egg was observed earlier in children who tolerated baked egg earlier. Other factors associated with earlier tolerance were younger age at diagnosis and low eosinophil count. On the other hand, older age at diagnosis, presence of anaphylaxis and caesarean section were the factors that delayed tolerance.

The main limitation of our study was that sIgE levels could not be measured at baseline and follow-up due to a physical problem at our centre. However, all patients with IgE-mediated egg allergy had a clear history of an immediate type reaction, a positive skin test, and/or positive OFCs.

The overall prognosis of egg allergy in children is generally favourable, with a relatively high likelihood of resolution. However, it can have a profound impact on the quality of life and diet of young children, and these ubiquitous foods are difficult to avoid, making accidental exposure common. Food ladders are tools designed to guide the gradual reintroduction of food allergens from extensively heated (i.e. baked) to less heated forms of protein. The benefits of using food ladders in the management of children with egg allergy are that they facilitate the expansion of the home diet and promote more rapid resolution of the food allergy. This study makes a valuable contribution to the existing literature on the safety and efficacy of the use of egg ladders in infants with IgE-mediated hen's egg allergy. It also paves the way for future research into the hen's egg ladder in the form of a large multi-center prospective study.

Conflict of Interest

Authors indicate no such interest.

Authorship Contributions

Concept: **Demet Can,** Design: **Demet Can,** Data collection or processing: **Gulce Baranli Aydinlioglu,** Analysis or Interpretation: **Gulce Baranli Aydinlioglu,** Literature search: **Melike Ocak,** Writing: **Melike Ocak,** Approval: **Demet Can.**

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