

Phenotypes of persistent hen's egg allergy in children and adolescents

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ABSTRACT

Background. Optimum management of food allergy (FA) includes consideration of co-allergies and multi-morbidities and tolerance assessment. Documentation of FA practices may pave the way for better practice.

Methods. Patients aged 3-18 years, with persistent IgE-mediated hen's egg allergy were reviewed.

Results. A total of 102 children with a median age of 59 months (IQR= 40-84) (72.2% males) were included. All were diagnosed during infancy and the initial symptoms were atopic dermatitis (65.6%), urticaria (18.6%), and anaphylaxis (5.9%). Of the total population, 21 (20.6%) experienced anaphylaxis with hen's eggs, and 79.4%, 89.2%, and 30.4% had multiple FAs (≥ 2 food categories), ever atopic dermatitis, and asthma, respectively. The most common co-allergies were tree nuts, cow's milk, and seeds, respectively. From 52 heated egg yolk and 47 baked egg oral food challenges, 48 (92.3%) and 41 (87.2%) were found as tolerant, respectively. The baked egg nontolerant group had a greater egg white skin prick test diameter [9 mm (IQR: 6-11.5) vs. 6 mm (IQR: 4.5-9); (p=0.009)] and specific IgE [12.6 kU/L (IQR: 4.11-45.4) vs. 6.2 kU/L (IQR: 1.9-12.4) (p=0.009)], respectively. In the multivariate analysis, baked egg tolerance was more likely in those with egg yolk-tolerant subgroup (OR: 6.480, 95% CI: 2.524-16.638; p<0.001) and heated egg tolerance in those with baked egg tolerance (OR: 6.943, 95% CI: 1.554-31.017; p=0.011).

Conclusions. Persistent hen's egg allergy is characterized by multiple food allergies and age-related multi-morbidities. Baked egg and heated egg yolk tolerance were more likely to be considered in a subgroup with a high expectation for finding a way to eliminate their allergy.

Key words: Hen's egg, allergy, atopic dermatitis, children, adolescents.

Hen's eggs are one of the most important basic foods of early childhood across many countries and cultures because of ease of access and affordability. However, it is also an important trigger of food allergies (FA) in early childhood. For example, in Turkey, it is the most common etiology of both immunoglobulin (Ig)-E-mediated food allergies¹ and food protein-induced enterocolitis syndrome² in early

childhood, as well as the third cause of food-induced anaphylaxis.³

Though it varies according to both culture and study design, the prevalence of IgE-mediated FA is estimated to be between 0.5-2.5%.^{4,5} However, egg sensitization rates are much higher than allergy prevalence; therefore, routine allergy testing is not recommended for those without a history of allergies and early-onset moderate-severe atopic dermatitis (AD)^{6,7} because this may lead to unnecessary avoidance. The gold standard of IgE-mediated hen's egg allergy diagnosis is oral food challenge (OFC); however, this carries inherent risks as it is labor-intensive and time-consuming.⁸ Half of those diagnosed as having IgE-mediated egg allergy

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have been reported to resolve itself by the age of 3 years and two-thirds by the age of 5 years.^{4,9,10} Therefore, empirically, the age of 3 years can be regarded as an age when egg sensitivities are excluded, mild allergies are resolved and more persistent allergies remain.

It is important to document allergy practices to observe shortcomings and examine practice differences between centers. In this study, we aimed to document the co-allergies and comorbidities of children with persistent hen's egg allergies, how they were managed, and how different parts of the egg and different processed forms were consumed.

Material and Methods

Study Design and Subjects

In this retrospective study; patients aged between 3 and 18 years who were followed up regularly due to persistent IgE-mediated hen's egg allergy between January 2014 and December 2020 were included and those who had a resolved egg allergy within this period were excluded.

To evaluate age-related characteristics, the study population was grouped as preschoolers (age 3-5 years), school-aged children (age 6-11 years) and adolescents (age 12-18 years). Allergy to more than one type of food group was stated as multiple food allergies (≥ 2 food categories). The diagnosis of AD, allergic rhinitis (AR), and asthma/recurrent wheezing was made according to international guidelines.¹¹⁻¹³ The age of asthma diagnosis was determined as the start of asthma control therapy. The age of onset of AR was considered to be the age at which the patient showed signs of rhinitis when exposed to the aero-allergen to which they were sensitive. The analyses were made according to "current" status (atopic diseases during the past year visits as "current asthma," "current AD" and "current AR" or "inactive"), the patients' resolved atopic diseases as "inactive asthma", "inactive AD," and "inactive AR," or "never" status (no history of atopic diseases).¹⁴

Diagnostic Procedures

For skin prick tests (SPTs), allergen extracts (ALK®, Horsholm, Denmark) were applied on the volar surface of the forearm or back along with negative and positive controls. The mean wheal diameter was measured after 15 minutes by calculating the mean value of the longest diameter and the diameter perpendicular to it. According to the routine practice of the clinic, SPTs were performed if the patient did not use any drug such as antihistamine that could interfere with the SPT within the last 5 days. Allergen-specific IgE levels were measured using the Immuno-CAP method in the sera of the patients (Thermo Fisher Scientific, Uppsala, Sweden). A positive SPT (3 mm or more above the negative control) and specific IgE (≥ 0.35 kU/L) was defined as usual. In the presence of positive SPT and/or sIgE, the diagnosis of hen egg allergy was based on either a positive OFC or a consistent and clear-cut history of IgE-mediated symptoms within 2 hours after the ingestion or in the presence of a positive SPT and/or sIgE suggesting clinical reactivity with $>95\%$ positive predictive value (PPV) (SPT ≥ 7 mm than the negative control and/or sIgE ≥ 7 kU/L).¹⁵

The local ethics committee of Hacettepe University approved the retrospective study (Number: GO-20/1115, Date: November 17th, 2020).

Statistical Analysis

IBM SPSS Statistics for Windows v.22.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Values are shown as the median and interquartile range for data not normally distributed. The Mann-Whitney U test or Kruskal-Wallis test was used for comparisons and, Pearson's Chi-square (χ^2) test or Fisher's exact test for between-group comparisons. Univariate and multivariate analyses were performed to predict persistence. Predictors that were significant based on univariate regression analysis ($P < 0.2$) were then included as covariates in multiple regression analysis. The odds ratio

(OR) with 95% confidence intervals (CI) was calculated via uni- and multivariate analyses. All statistical tests were two-sided, and the level of statistical significance was set at $p < 0.05$.

Results

Study Population

A total of 102 children with a median age of 59 months (IQR 40-84) (72.2% males) were enrolled into the study. The median follow-up period of the patients was 26 months (IQR:13.3-48.7). Of the study group, 53.9%, 42.2%, and 3.2% of the patients were preschool children, school-age children, and adolescents, respectively.

The median age at diagnosis was 6 months (IQR: 4-6). The initial symptoms were AD (65.6%), urticaria (18.6%), and anaphylaxis (5.9%) (Fig. 1). In 21 of these children (20.6%), there was a history of anaphylaxis after exposure to hen eggs. The rate of having experienced anaphylaxis with eggs was 10.9% (6/55) and 31.9% (15/47), in the preschool children and school age children- adolescent groups ($p=0.009$), respectively (Table I).

Food Co-Allergies

Multiple food allergies were diagnosed in 79.4% of the study population. (Table I) The most common co-allergies were tree nuts (60.8%), cow's milk (38.2%), sesame seeds (38.2%), peanut (23.5%), legumes (11.8%), and wheat (7.8%), respectively. The most common tree

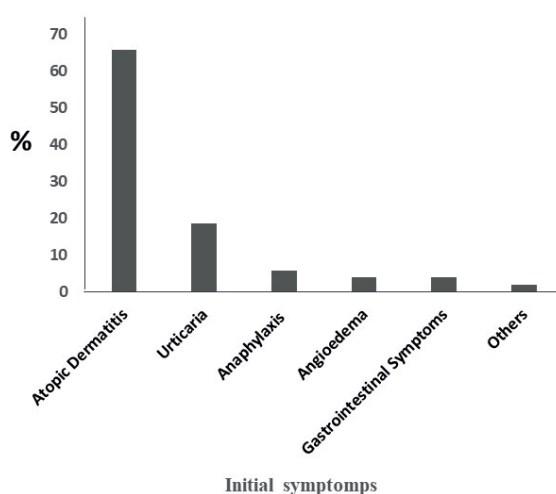


Fig. 1. The initial symptoms in egg allergy diagnosis

nut co-allergies were hazelnut [46.1% (47/62)], cashew [45.1% (46/62)], and walnut [43.1% (44/62)], respectively. Food allergies according to baked egg tolerance (Fig. 2a) and age groups (Fig. 2b) are shown in Fig. 2.

Multi-morbidities

When comorbidities were considered, 89.2% (n=91) and 30.4% (n=31) of the patients had a history of AD and asthma, whereas 34 (33.3%) and 29 (28.4%) of the 102 children had current AD and asthma, respectively. Three-quarters (75.8%) (22/29) of patients with asthma were school age children and adolescents group ($p < 0.001$). A total of 27 patients (26.4%) had aeroallergen sensitization and compatible rhinitis symptoms with exposure to these allergens and most (85.1%) were from the

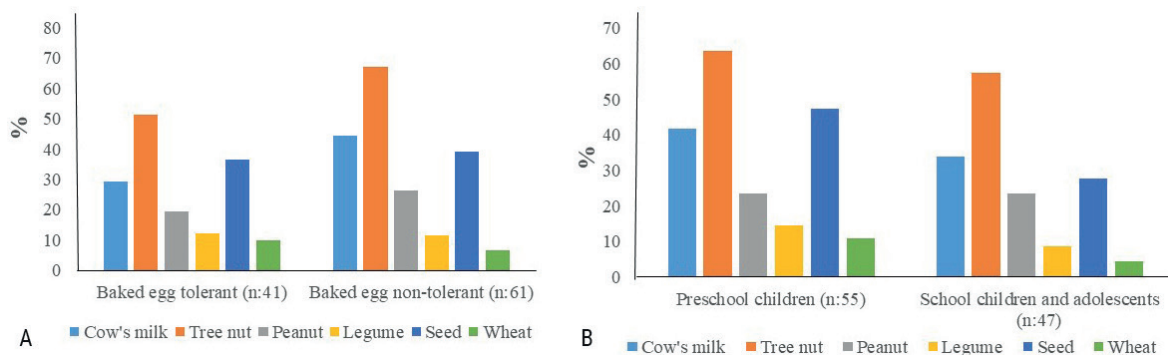


Fig. 2. Food allergies according to baked egg tolerance (Fig. 2a) and age groups (Fig. 2b)

Table I. The characteristics of the study group and its subgroups according to age and baked egg tolerance.

Patient characteristics	Baked egg tolerance			Child's age		
	All (N=102)	Tolerant (n=41)	Non-tolerant (n=61)	Preschool (n=55)	Older (n=47)	P
Age, month	59 (40-84)	49 (39-69)	61(41-94)	40 (36-48)	89 (72-108)	<0.001
Male gender, n (%)	74 (72.2)	32 (78)	42 (68.9)	41 (74.5)	33 (70.2)	
Total IgE, kU/L	421 (164-1018)	412 (126-688.3)	432 (175-1187)	369 (131.3-593)	517 (181-2010)	
Eosinophils, / μ L	400 (253-793)	300 (200-700)	450 (300-825)	400 (300-700)	500 (200-900)	
Eosinophils, %	5.4 (3.1-8.6)	4.2 (2.4-7.2)	6.1 (3.3-8.7)	5.2 (3.2-6.8)	6.8 (3.1-9.3)	
Egg white sIgE, kU/L	7.78 (2.93-25.2)	6.2 (1.9-12.4)	12.6 (4.11-45.4)	7.64 (3.13-20.4)	10.3 (2.53-38)	
Egg yolk sIgE, kU/L	3.17 (0.71-8.6) [n=52]	1.58 (0.57-4.47) [n=17]	4.5 (0.71-11.6) [n=35]	3.42 (0.66-10.2) [n=29]	3.06 (0.71-7) [n=23]	
Ovomucoid sIgE, kU/L	2.93 (0.82-10.3) [n=28]	0.86 (0.45-4.5) [n=9]	4.57 (0.97-39.2) [n=19]	0.92 (0.44-6.08) [n=16]	4.63 (2.01-23.5) [n=12]	
Egg white SPT, mm wheal	7.5 (5-11)	6 (4.5-9)	9 (6-11.5)	8 (5.13-10.4)	7 (4.9-11)	
Egg yolk SPT, mm wheal	5 (3-8) [n=79]	3 (0-5) [n=29]	6.8 (4.3-8.62) [n=50]	4.5 (2.3-7.8) [n=44]	5.5 (3.5-9) [n:35]	0.009
Egg anaphylaxis, n (%)	21 (20.6)	3 (7.3)	18 (29.5)	6 (10.9)	15 (31.9)	
Single FA, n (%)	21 (20.6)	12 (29.3)	9 (31.1)	11 (20)	10 (21.3)	
Multiple FA, n (%)						
2 FA	30 (29.4)	13 (31.7)	17 (27.9)	12 (21.8)	18 (38.3)	
3 FA	29 (28.4)	8 (19.5)	21 (34.4)	16 (29.1)	13 (27.7)	
\geq 4 FA	22 (21.6)	8 (19.5)	14 (23)	16 (29.1)	12 (12.8)	

Data are presented as median (interquartile range) unless indicated otherwise. FA: food allergy, SPT: skin prick test.

school-age children and adolescents group (p<0.001) (Table II).

Baked Egg and/or Egg Yolk Tolerance

Of the 102 children, 52 had heated egg yolk OFC and 48 (92.3%) were found to be tolerant. From 47 baked egg OFCs, 41 were found to be tolerant (87.2%). Overall, 47.1% (48/102) and 40.2% (41/102) were consuming egg yolk and baked egg regularly, respectively. There was no difference between the baked egg tolerant and nontolerant subgroups concerning current age, sex, presence of concomitant AD, eosinophil counts/percentages, and serum total IgE levels (Table I). However, in the baked egg nontolerant subgroup, there was higher egg white SPT [9 mm (6-11.5)] and specific IgE [12.6 kU/L (4.11-45.4)] compared with the tolerant subgroup (p=0.009). Ovomuroid-specific IgEs were evaluated in only 28 patients and there was a

tendency of higher ovomucoid sIgE [4.57 kU/L (IQR: 0.97-39.2)] in the baked egg nontolerant group compared with the tolerant subgroup [0.86 kU/L (IQR: 0.45-4.5)] (p=0.099). The rate of having experienced anaphylaxis with egg was 29.5% (18/61) and 7.3% (3/41) in the baked-egg nontolerant and tolerant subgroups (p=0.007), respectively. Remarkably, the presence of multiple food allergies (≥2) was more frequent in the baked egg nontolerant group compared with the tolerant subgroup (p=0.075), but the difference was not statistically significant.

Multivariate analysis revealed that baked egg tolerance was more likely in those with egg yolk tolerance (OR: 6.480, 95% CI: [2.524-16.638]; p<0.001) and heated egg yolk tolerance in those with baked egg tolerance (OR: 6.943, 95% CI: [1.554-31.017]; p=0.011) as detailed in Table IIIa-IIIb.

Table II. The comorbid allergic diseases.

Comorbidity	All (N=102)	Baked egg tolerance			Child's age		
		Tolerant (n=41)	Non-tolerant (n=61)	P	Preschool (n=55)	Older (n=47)	P
Asthma							
Never	71 (69.6)	31 (75.6)	40 (65.5)	NS	47 (85.5)	24 (51)	<0.001
Inactive	2 (2)	1 (2.4)	1 (1.6)	NS	1 (1.8)	1 (2.1)	
Current	29 (28.4)	9 (22)	20 (32.7)	NS	7 (12.7)	22 (46.8)	<0.001
Atopic dermatitis							
Never	11 (10.8)	6 (14.6)	5 (8.2)	NS	3 (5.5)	8 (17)	
Inactive	57 (55.9)	24 (58.5)	33 (54)	NS	32 (58.2)	25 (53)	
Current	34 (33.3)	11 (26.8)	23 (37.7)	NS	21 (38.2)	13 (27.6)	
Allergic rhinitis							
Never	75 (73.5)	33 (80)	42 (68.9)	NS	50 (90.9)	24 (51)	<0.001
Current	27 (26.4)	8 (19.5)	19 (31.1)	NS	4 (7.2)	23 (48.9)	<0.001
Aeroallergen sensitivity							
Grass pollen	11 (10.7)	4 (9.7)	7 (11.4)	NS	0	11 (23.4)	0.016
Mite	12 (11.7)	2 (4.8)	10 (16.3)	NS	4 (7.2)	8 (17)	
Alternaria	6 (5.8)	2 (4.8)	4 (6.5)	NS	0	6 (12.7)	
Pet	9 (8.8)	1 (2.4)	8 (13)	NS	0	9 (19)	
Others	2 (1.9)	0	2 (3.2)	NS	0	2 (4.2)	

Data are presented as number (percentage). NS: non-significant.

Table IIIa. Predictors in univariate and multivariate analysis for baked egg tolerance.

	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Age	0.991	0.979-1.004	0.172			
Gender	0.622	0.249-1.555	0.310			
Current AD	0.606	0.255-1.436	0.255			
Egg white SPT	0.880	0.785-0.985	0.027			
Egg white sIgE	0.980	0.962-0.997	0.025			
Egg yolk tolerance	5.342	2.252-12.673	<0.001	6.480	2.524-16.638	<0.001

Table IIIb. Predictors in univariate and multivariate analysis for egg yolk tolerance.

	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Age	0.996	0.985-1.007	0.479			
Gender	0.526	0.215-1.291	0.161			
Current AD	0.584	0.252-1.351	0.209			
Egg yolk SPT	0.803	0.693-0.931	0.004			
Egg yolk sIgE	0.890	0.772-1.027	0.110			
Baked egg tolerance	5.342	2.252-12.673	<0.001	6.943	1.554-31.017	0.011

AD: atopic dermatitis, CI: confidence interval, OR: odds ratio, SPT: skin prick test.

Discussion

The management of FA has different goals: to confirm the diagnosis; to look for underlying causes; to identify co-allergies; to check comorbidities; to identify the consequences; to assess the predictors of the course of the disease and tolerance of processed forms; and to monitor components of disease activity, impact, and control. Due to limited data about persistent egg allergies in children besides infancy in the literature, our study concerning the characteristics of patients aged over 2 years with egg allergies deserves further awareness.¹⁶⁻¹⁸

In our study, 79.4% of children had multiple FAs. This high rate may be related to the fact that only patients aged over 24 months and those with persistent hen's egg allergies during the follow-up period were included in the study, those with mild allergies had resolved by this time, and persistent allergies were more likely to have multiple FAs. This rate is similar to other studies¹⁷ and even higher than in some.^{16,19,20} The fact that our center is a reference center for the

country may have resulted in more referrals of patients with multiple and severe allergies and persistent cases. Multiple FAs is a critical problem because daily life restrictions can lead to many consequences in nutrition, growth, and mental health.

Nearly 90% of our patients had a history of AD, and more than one-third had current AD. Atopic dermatitis, beginning in the infantile period with a severe course, is commonly accompanied by FA, of which hen's egg allergy is the most common.¹ The most common FA is cow's milk allergy in patients diagnosed as having FA without AD.¹ This feature illustrates the importance of eczema in the clinical presentation and development of egg allergies. The rate of AD multi-morbidity in our study was higher than in previous studies.^{17,21} Consistent data show that the number of FAs increase as the severity of AD increases, as does the persistence of AD.²²

Egg white and egg yolk differ in their protein constituents and allergenicity. The main allergenic proteins identified in eggs have

different physicochemical characteristics and different allergenic potentials; therefore, thermal heat processing and digestibility have different impacts on the allergenic capacity of these proteins.²³ In this retrospective review, we showed that almost half of the patients were evaluated for the tolerance of baked egg and egg yolk. Potential reasons for these evaluations being performed only on half of the patients may include the reluctance of parents, a current or severe history of reactions in the past, avoiding hospital visits due to the COVID-19 outbreak²⁴, or the physician's or parent's desire not to take the risk of OFC due to high sensitivity.

In our study, we found that 92.3% of the patients who underwent OFC with egg yolk tolerated the egg yolk, and 47.1% of the entire group regularly consumed egg yolk. In fact, egg yolk is less allergenic than egg white, and more than 90% of patients with egg allergy can tolerate egg yolk, as shown in two recent studies.^{25,26} Although we know that it is not possible to safely separate the egg yolk and egg white parts other than in hard-boiled eggs, it may be desirable for patients and parents to feel that the yolk is tolerated because it can support the hope that they can recover from the allergy. However, the documentation of practice is important in terms of reflecting the expectations of families and physicians.

Similarly, it was observed that 87.2% of the patients who underwent OFC with baked eggs could tolerate them, and as a result, 40.2% of the study group could consume baked eggs. Considering that 50-85% of patients with egg allergies have been reported to tolerate baked egg products^{23,27-29}, our low rate may be a result of the desire of patients and/or physicians. However, the measurement of ovomucoid sIgE is the variable that best reflects the ability to consume baked eggs, and the low rate of this assessment in our study group is actually due to the limitations of the social security system in Turkey for component-based sIgE testing. In particular, considering that most patients have multiple allergies, it seems necessary to develop reliable multiplex assays instead of singleplex

measurements for both cost and blood sampling in these young patients. In addition, in the multivariate analysis, we found that patients who tolerated baked eggs were more likely to be from the egg yolk-consuming subgroup and vice versa, reflecting the presence of a subgroup of patients/parents with a high expectation of finding a way out of their allergy. Considering that patients who consume baked eggs can develop an earlier tolerance³⁰ and consumption of various egg products such as egg yolk and/or baked eggs increases the nutritional variety and quality of life of children, more efforts should be made in this regard.

Atopic dermatitis and subsequent egg allergy are considered the first steps of atopic march, and over time, these patients may develop asthma, aeroallergen sensitivity, and AR.³¹ Indeed, when we classified the patients by age groups, we found that AR, asthma, and aeroallergen sensitization were more frequent in school-age children and adolescents ($p < 0.001$), which is consistent with the predefined allergic march.³²⁻³⁴

Almost all egg allergies develop in the first year of life and generally have a better prognosis compared with many other food allergies. Although early studies report resolution rates of 52% and 66% at ages 3 and 5 years, respectively^{9,10}, more recent studies from tertiary referral centers show that the estimated tolerance rates are 4% at 4 years, 12% at 6 years, 37% at 10 years, and 68% at 16 years of age.^{4,35} In this study, we included patients aged over 24 months with persistent egg allergies and nearly half of the study group (46.1%) were aged over 5 years.

The limitations of our study were that both egg yolk and baked egg challenges were not performed in all patients, the most likely reasons included the concerns of families and physicians, the COVID-19 pandemic period, and a low rate of component-specific IgE measurements. However, the strengths of this study include real-life practice, the production of baseline data for improving practice, and

documentation of a subgroup of patients/parents seeking a way to eliminate the allergy.

In conclusion, this study evaluated children and adolescents with persistent hen egg allergies, characterized by multiple food allergies and ever/current atopic dermatitis at a national reference centre. We showed that in this group, the possibility of heated egg yolk tolerance, and more importantly, baked egg tolerance, might not have been adequately addressed by both ovomucoid-specific IgE measurements and the relevant OFCs. Considering the evidence that encouraging the consumption of baked eggs can support the resolution of hen's egg allergies, it may shed light on how centers can reach a better level of practice.

Ethical approval

The local ethics committee of Hacettepe University approved the retrospective study (Number: GO-20/1115, Date: November 17th 2020).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: BEŞ; data collection: HÜ, STD, AA; analysis and interpretation of results: HÜ, ÜMŞ, ÖS, BEŞ; draft manuscript preparation: HÜ, BEŞ. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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