

## Summary

### Introduction

There is limited data about the natural course of egg allergy in the literature. We aimed to analyze the factors that can affect the tolerance or persistence of egg allergy

**Material-Method:** A total number of 126 IgE- mediated egg allergic patient who had data about tolerance gaining were included in the study. Demographic and laboratory data were recorded retrospectively. Kaplan–Meier curves was used for estimation of resolution and the factors related to resolution by Cox regression model.

**Results:** Among 126 patients 81(64.2%) had gained tolerance with a median survival time of 48 months (min:12- max:121). Tolerance was gained in 22.2% (28) of these patients in the first 2 years of life, in 46.8% (49) 2-6 years, 3.1% (4) between 7-12 years. In univariate analysis, baseline sIgE level <8.2 (Hazard ratio: 2.193; (95% CI 1.309-3.674, p:0.003), no history of anaphylaxis (at initiation or during OFC) (Hazard ratio: 11.292; (95% CI 2.766-46.090, p:0.001) and baseline egg SPT<11 mm (Hazard ratio: 2.906; (95% CI 1.424-5.930, p:0.003) were found to be related to earlier resolution of egg allergy. In multivariate analysis only anaphylaxis was significantly related to later resolution (Hazard ratio: 6.547; 95%CI 1580-27.434, p:0.01).

**Conclusion:** Higher levels of egg sIgE, skin prick test induration and anaphylaxis at onset or during oral food challenge, can give hint about persistence of egg allergy

**Key-Words:** Egg Allergy, Egg specific IgE, Skin prick test induration, persistence, tolerance

**An Impact Statement:** Anaphylaxis as onset symptom or during oral food challenge could predict persistence of egg allergy.

## **FACTORS EFFECTING NATURAL COURSE OF EGG ALLERGY**

### **Introduction**

Hen's egg allergy is one of the most seen allergens during childhood. Its prevalence ranges between 1%-2% (1). Egg was reported to be the most seen allergen at children with anaphylaxis under one year old and 35% of children with atopic dermatitis especially boys with severe form of eczema (2,3).

Although most of the children gain tolerance until school age, recent studies showed that egg allergy may persist into adolescence. Savage et al (4), reported 12% of the children gained tolerance by age of 6 and 68% by age 16. In another study 49% of the children outgrow egg allergy by 6 years old (5). It is hard to predict whether the allergy persists or resolves naturally. History of severe reaction or anaphylaxis, reaction at low level of food ingestion, high specific IgE levels (by skin prick test or immunoassay), comorbidity of another allergic disease is reported to be predictors of persistence egg allergy (4,5).

Elimination diets are the gold standard management plan in all food allergic patients. As egg is an important source of protein and a common ingredient in many foods, questions about resolution of egg allergy are the point of interest. In this study it is aimed to identify the risk factors for persistence of egg allergy after 6 years by clinical and laboratory parameters.

### **Material-Method**

The records of a total number of 204 patients with a history of egg allergy, attending from January 2019 to January 2022 were analyzed retrospectively. Patients with no sensitization (9 patients), non-IgE reactions (23 patients) and patients with IgE reactions who had no data about tolerance were excluded from the study. Thus 126 patients' data was evaluated. The diagnosis of egg allergy was confirmed with skin prick tests prick by prick ( $\geq 3$  mm larger than negative control) and/or specific IgE positivity ( $>0.35$  kU/L) with a clear clinical history (early reactions as hives, angioedema, dyspnea, cough, vomiting, etc. within 2 hours of egg ingestion), or a positive oral food challenge to boiled egg. Negative oral food challenge to boiled egg in the follow-up or consumption of egg at home without any reaction for the last one month was accepted as resolution of egg allergy.

Clinical characteristics (age, age at diagnosis, symptoms, comorbid allergic diseases and food allergy, history of family atopy, prematurity) and laboratory data (Total IgE level, eosinophil

count and percentage, skin prick test and oral food challenge test results) were recorded from the patient file and hospital registry system.

The study was approved by the local ethics committee of Ege University (Ethics number: E-99166796-050.06.04- 291753) and informed consent was obtained from all parents/guardians.

#### Statistical Analyses

Data were evaluated using the Statistical Package for Social Sciences 25.0 (SPSS for Windows 25.0, Inc., Chicago, IL, USA). Analysis included descriptive statistics (means, standard deviation), comparison of the means of quantitative data for dual groups using the Student t-test, paired t-test, chi square test and Mann-Whitney-u test.  $P < 0.05$  was considered significant. Receiver operating characteristic curve analysis for sIgE and skin prick test induration was used for distinguishing patients with resolution or persistence of egg allergy. Kaplan–Meier curves was used for estimation of resolution and the factors related to resolution by Cox regression model.

## RESULTS

A total number of 126 patients were enrolled to the study. The median age at symptom onset was 4 months (IQR:4)(2-6). Forty-four (34.9%) of the patients were female. Among them 80(63.4%) had atopic dermatitis and 81(64.2%) had another food allergy, with cow's milk(n=72)(57.1%) being the most common. Nine (7.1%) of the patients had history of anaphylaxis with egg. The most common symptom at home was skin related (87.3%). Demographic data was shown in Table-1.

The median egg specific IgE level was 6.13(IQR:17.6)(min:0.48-max:280), median SPT induration was 9 mm(6.0)(3.0-45.0). A total of 88 oral food challenge (OFC) with boiled egg was performed. Sixteen (12.6%) patients experienced anaphylaxis during OFC. The most seen reaction was skin related (24.6%).

The number of the children who had outgrown egg allergy was 81(64.2%). The median survival time was 48 months (12-121). Tolerance was gained in 22.2% (28) of these patients in the first 2 years of life, in 46.8% (49) 2-6 years, 3.1% (4) between 7-12 years. Twenty-four months cumulative disease survival probability was 77.7%, %50 at 48 months, %42 at 60 months, % 38.8 at 72 months (Fig 1). Skin symptom and anaphylaxis at home was more common in patients who had not gained tolerance ( $p:0.01$ ,  $p:0.01$  respectively). Egg oral immunotherapy was applied to 9(7.1%) of the patients whose allergy persisted. Egg specific IgE and skin prick

test induration diameter were higher in the persistence group too ( $p < 0.01$ ,  $p < 0.01$  respectively). Table-2 shows the comparison of the patients who outgrown allergy or not.

ROC-Curve analysis for skin prick test induration and baseline specific IgE level was used for distinguishing patients who had persistence or outgrown egg allergy at the age of 2 and 6. For 2 years the highest sensitivity and specificity was 3.6 kU/L (AUC:0.629  $p$ : 0.024) for sIgE and 5.5 mm (AUC:0.671  $p$ : 0.002) for SPT; for patients with 6 years 8.2 kU/L (AUC:0.629  $p$ : 0.024) for sIgE and 11 mm (AUC:0.671  $p$ : 0.002) for SPT. In patients above the cut-of level of SPT ( $> 11$  mm) and sIgE level (8.2 kU/L), the tolerance developed over a longer period of time (median 48 (IQR:42) months for patients SPT  $< 11$  mm, and median 72 (IQR:66) months for patients SPT  $> 11$  mm) and sIgE (median 36 (IQR:48) months for patients whose sIgE  $< 8.2$  kU/L, and 72 (IQR:24) months for  $> 8.2$  kU/L) according to Kaplan-Meier Analysis ( $p < 0.01$ ,  $p < 0.01$ , respectively, Log-rank, Mantel-Cox regression) (Fig2a-2b).

Cox-regression analysis was used to determine the factors for resolution of egg allergy for a duration of 72 months. In univariate analysis, baseline sIgE level  $< 8.2$  (Hazard ratio: 2.193; (95% CI 1.309-3.674,  $p$ :0.003), no history of anaphylaxis (at initiation or during OFC) (Hazard ratio: 11.292; (95% CI 2.766-46.090,  $p$ :0.001) and baseline egg SPT  $< 11$  mm (Hazard ratio: 2.906; (95% CI 1.424-5.930,  $p$ :0.003) were found to be related to earlier resolution of egg allergy. In multivariate analysis only anaphylaxis was significantly related to later resolution (Hazard ratio: 6.547; 95%CI 1580-27.434,  $p$ :0.01).

## DISCUSSION

In this study 64.2% of the children achieved tolerance to boiled egg with a cumulative tolerance probability 50% at 48 months. Initial egg sIgE level  $< 8.2$  kU/L, skin prick test induration  $< 11$  mm and no history of anaphylaxis at home or during OFC were significantly associated with earlier resolution of egg allergy.

Ngai et al (6) reported egg allergy resolved at 71% of Chinese children with a median of 36 months. Boyana-Martinez et al (7) followed 58 patients prospectively until egg tolerance developed. Half of the children tolerated egg at 35 months of follow-up, and 66% after 5 years. A systematic review reported a resolution rate of 68% by the age 16 years (4). In contrast in HealthNuts population-based study, 5276 children had been followed prospectively and resolution occurred at 89% of the egg allergic children ( $n$ :471) by 6 years old (8). In our study 64.2% of 126 patients achieved tolerance (61.1 % by 6 years old), only four (3.1%) of the patients gained resolution after 6 years old.

Little is known about the prognostic factors that can show tolerance to any food. Presence of other food allergies and atopic diseases, high egg specific IgE/SPT wheal size levels, respiratory and multisystem symptoms are found to be associated with persistent egg allergy(7,9). Arikyilmaz et al(10) reported that initial egg sIgE level 6.2kU/L could distinguish tolerance or persistence at the age of 6. Another study also found baseline sIgE level and initial symptoms to be independent predictors for resolution(6). Schrier et al(5) also published elevated egg sIgE levels were related to persistent egg allergy. We found a cut of level of initial sIgE 3.6 for two years and 8.2 kU/L for six years to distinguish persistence and tolerance. It could be said that as the initial sIgE level is higher, the resolution time of allergy will be later. We found the same result for skin prick test induration as for 2 years 5.5 mm, for 6 years 11 mm. A recent study indicated the wheal size at SPT at one year old, was not a good predictor of egg allergy persistence at 6 years old (8). Ngai et al (6) reported skin prick test wheal size >6 mm was associated with later resolution.

In a recent study egg was found to be the most common allergen causing anaphylaxis <12 months of children(2). Nine of our patients had history of anaphylaxis and 16 had anaphylaxis during OFC. Three of the patients had anaphylaxis both at home and during OFC. In accordance with the literature the resolution was delayed in children with anaphylaxis in our study.

In a recent study presence of atopic dermatitis, peanut and wheat allergy were predictors for persistence (2). Peters et al(8) also found early-onset severe eczema was associated with persistence. We found no risk for persistence in patients with atopic dermatitis. This may be the reason of higher rate of atopic dermatitis among our patients (63.5%). The rate is lower in the literature. Samady et al(11) evaluated 38,408 children and found 0.9% had egg allergy. Among these patients with egg allergy 19.0% had atopic dermatitis.

One of limitation of our study is its retrospective design. We could not reach all the laboratory data. Second limitation is that we could only investigate standard serum egg-specific IgE levels. Recent developments in component resolved diagnosis technology can be more informative both for diagnosis and to predict development of tolerance. Dang et al(12) reported Gal-d 1 sensitization increased the risk of persistent egg allergy by 2.5-fold and all four egg allergens (Gal-d 1, 2, 3, 4) by 4-fold.

In conclusion this study showed that egg tolerance was achieved at 64.2% of the patients. Skin prick test induration <11 mm or sIgE<8.2 kU/L could predict achievement of tolerance at the

age of 6. Anaphylaxis at home or during OFC was the only associated factor with persistent egg allergy.

**Conflict of interest:** Authors have no conflict of interest

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Table-1 Demographic properties of the patients

	N=126(%)
Gender (F/M)	44/82
Age at symptom onset	
Median (IQR)(min-max)	4(4)(2-10)
Atopic Dermatitis	80(63.4)
Concomitant food allergy	81(64.2)
Family atopy history	39(31)
Initial symptom	
Anaphylaxis	9(7.1)
Skin	110(87.3)
Gastrointestinal	15(11.9)
Respiratory	9(7.1)

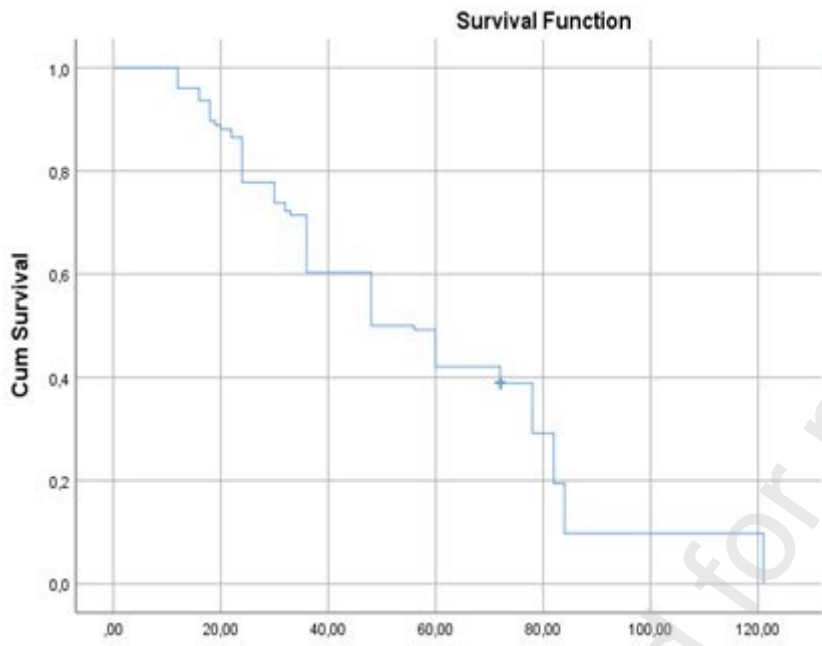
Table-2 Characteristics of patients who outgrown egg allergy and persistence

	Tolerance n:81(%)	Persistence n:45(%)	p
Sex(F/M)	28/53	16/29	0.91
Family history of atopy	28(37.3)	11(25.0)	0.16
Concomitant food allergy	52(64.1)	29(64.4)	0.74
Atopic dermatitis	56(69.1)	24(53.3)	0.07
Prematurity	5(7.2)	3(6.8)	0.93
Initial Symptom			
Skin	77(95.1)	33(73.3)	0.01
Respiratory	5(6.2)	4(8.9)	0.72
Gastrointestinal	8(9.9)	7(15.6)	0.34
Anaphylaxis	2(2.5)	7(15.6)	0.01
Age at symptom onset	4(3.25)(1.0-20.0)	5.5(4.0)(1.0-13.0)	0.91
Symptom onset before 6 months	11(14.9)	6(14.3)	0.93
Symptom during OFC	6(18.8)	46(82.1)	<0.01
Skin	10(17.9)	21(67.7)	<0.01
Respiratory	0(0.0)	14(43.8)	<0.01
Gastrointestinal	1(1.8)	8(25.0)	<0.01
Anaphylaxis	1(1.8)	15(46.9)	<0.01
Egg specific IgE(kU/L) Median(IQR)(min-max)	4.91(10.3)(0.58-280)	11.0(37.5)(0.48-100)	0.01
Skin prick test induration mm	8.0(5.0)(3.0-45.0)	10(7.25)(4.0-35.0)	0.01
Total IgE	199.0(433.9)(8.0-3963.0)	304.0(531.1)(17.4-3321.0)	0.37
Eosinophil count %	4.46(5.14)(0.0-21.0)	6.18(7.46)(0.8-19.6)	0.14

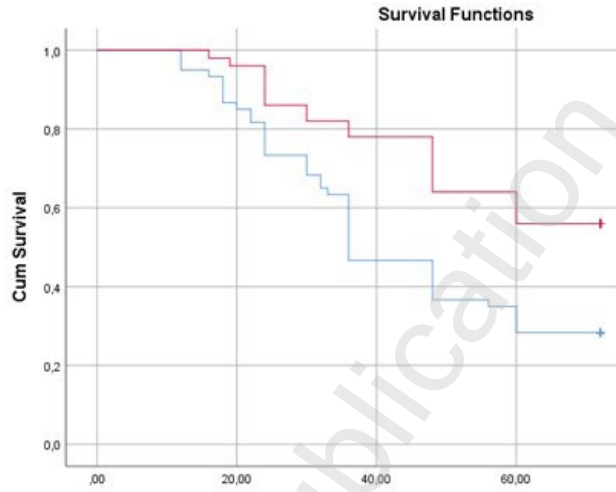
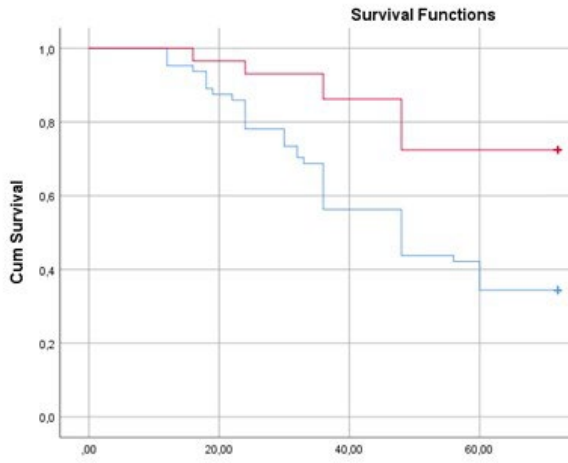


Table-3 Factors with earlier resolution of egg allergy before 6 years

	Hazard Ratio(%95 CI)	p
Gender	0.938(0.578-1.521)	0.794
IgE	1.000(0.999-1.000)	0.297
Eosinophil %	0.967(0.915-1.022)	0.240
Egg sIgE	0.999 (0.985-1.005)	0.293
F1<8.2 Ku/L	2.193(1.309-3.674)	0.003
Concomitant food allergy	0.880(0.529-1.464)	0.623
SPT induration <11 mm	2.906(1.424-5.930)	0.003
SPT induration	0.927(0.870-0.987)	0.018
Atopic dermatitis	0.520(0.308-0.879)	0.015
Anaphylaxis at initiation or during OFC	11.292(2.766-46.090)	0.001



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