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Original article

Hen's egg white hypersensitivity among a group of Egyptian atopic children

Background: Egg allergy is potentially life-threatening. The prevalence of egg allergy in Egypt is still unclear. This study is to evaluate the frequency of egg hypersensitivity in a group of Egyptian atopic children.

Methods: Eighty allergic children were enrolled, each is subjected to clinical evaluation, skin prick testing (SPT) using a commercial egg white extract, and serum egg white specific IgE (SpIgE) estimation. Six patients with suspected egg allergy consent to perform open oral egg challenge. **Results:** Twenty-eight patients had history of exacerbation of their allergic diseases upon exposure to egg white, of these patients, 8 had negative SPT and serum egg white SpIgE. SPT was positive in 25 (31.2%) patients, of these patients, 3 (4%) were +3, 22 (28%) were +2, of whom 5 patients tolerate eggs without adverse effects. Serum egg white SpIgE was positive in 19 (24%) patients with a mean of 0.81 IU/ml (range: 0.35-4.52 IU/ML). Egg white allergy based on positive history, positive SPT and/or egg white SpIgE was detected in 23 (28.8%) patients. Open oral egg challenge was positive in one patient with positive history but negative tests giving an overall frequency of egg allergy of 30 % (n=24). While egg white SpIgE did not correlate with the ages, positive SPT was significantly more frequent among younger patients ($t= 1.7, p=0.02$). Egg sensitization and allergy did not affect the severity of asthma ($p > 0.05$). **Conclusion:** Although positive SPT/ serum specific IgE to eggs are good tools for diagnosis, oral food challenge remains the gold standard in suspected cases. Further wide-scale studies are needed to outline the real prevalence of egg allergy in Egypt.

Keywords: Egg allergy – children – skin prick test.

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INTRODUCTION

Hen's eggs are a common food source in many cultures, and egg protein is found in a wide range of cooked or manufactured foods.¹ Egg white is one of the foods most frequently incriminated in food allergy below the age of 3 years. The estimated prevalence of egg allergy has been reported to vary, depending on the method of detection with self-reported prevalence values of up to 7% have been demonstrated, while double-blind, placebo-controlled food challenge-confirmed egg allergy has shown lower estimates, up to 1.7%.²

The development of egg specific IgE antibodies in infancy has been shown to be predictive of an increased risk for significant atopic disease, suggesting that immunologic reactivity to

egg antigens may be an early marker of atopic disorders³, and the development of asthma.⁴

Egg allergy can be divided into IgE-mediated and mixed IgE- and non-IgE-mediated reactions.⁵ IgE-mediated allergic reactions are the most common type of allergic reactions to egg.⁶ Egg allergy is potentially life-threatening. Anaphylaxis can occur with exposure to egg, and asthmatics, in particular, are at high risk for severe allergic reactions.⁷

The diagnosis of egg allergy can be suggested by a previous adverse reaction to egg-containing foods, usually before the age of 2 years and double-blind, placebo-controlled food challenge (DBPCFC) remains the definitive test that confirms the diagnosis. Since DBPCFC is considered not practical in the primary care setting, measurement of egg-specific serum IgE antibody levels, skin

prick testing (SPT) and atopy patch testing are the other main diagnostic tests available.⁸

Hen's egg is a main dish in Egypt especially for infants and children and is often introduced before the age of one year. This may offer an increased risk to egg allergy among Egyptian children. In fact, the prevalence of egg allergy in Egypt is still unclear; therefore, we sought to study the frequency of egg white hypersensitivity and allergy in a group of Egyptian atopic children.

METHODS

This cross-sectional study comprised 80 children with physician made diagnosis of allergic diseases. These patients were consecutively enrolled from the Pediatric Allergy and Immunology Unit, Children's Hospital, Ain Shams University. For every patient, an informed consent was obtained from parents or care-givers before enrolment. The study protocol was approved by the local ethical committee of the Pediatric Department, Ain Shams University.

Study population:

Inclusion criteria:

- Age at enrolment between one and 18 years.
- A physician made diagnosis of allergic diseases such as bronchial asthma, allergic rhinitis, urticaria and/or eczema.

Exclusion criteria:

- Patients who cannot stop antihistamine therapy.
- Extensive skin lesions and positive dermatographism.

The studied patients were subdivided according to the type of allergic disease into 3 subgroups (table 1). **Group 1** comprised 59 patients with bronchial asthma whose ages ranged between 1-11 years with a mean of 4.27 years. They were 42 males and 17 females. **Group 2** included 7 patients with *urticaria* whose ages ranged between 2-7 years with a mean of 4.36 years and were 3 females and 4 males. **Group 3** comprised 14 patients with *combined allergic diseases* of whom 12 had bronchial asthma with urticaria and 2 had urticaria with allergic rhinitis. Their ages ranged between 1-7 years with a mean of 2.8 years and were 8 males and 6 females.

Study Measurements

All patients in the study are subjected to the following:

1. Clinical evaluation: Detailed history was taken for the duration and severity of symptoms, possible precipitating factors, and family history of allergy. Twenty eight patients had history of exacerbation of

allergic symptoms upon egg intake. Of these patients, 18 had bronchial asthma, 4 had papular urticaria and 6 had papular urticaria with bronchial asthma and/or allergic rhinitis. Patients were subjected to general clinical examination to exclude other diseases. Examination of skin, ear, nose and throat and chest were conducted to verify the diagnosis and outline the severity of asthma exacerbation.

2. Skin prick testing for egg white

Skin prick test was performed by single person (E.A.M.) for each patient using egg white commercial allergen extract (Omega Lab Montr. Canada), positive histamine control and negative control. First generation short-acting antihistamines (sedating antihistamines) were avoided for at least 72 hours before testing. While second generation antihistamines were avoided for at least 5-days before the test.

The test sites on the volar aspect of forearm were marked and labelled at least 3 cm apart to avoid the overlapping of positive skin reaction. The marked site was dropped by the allergen and gently pricked by sterile skin test lancet. Positive and negative control solutions were similarly applied. The patient waited for fifteen minutes before interpretation of the results. The resultant wheal and flare was measured. Epinephrine ampoule was ready for any possible systemic reaction. The size of the skin wheal elicited by the egg white extract was compared with those of the histamine and the control solutions. The area of wheal elicited by the histamine was designated as + 3. A wheal of 3 mm or more above the negative control was considered a positive result.⁹

3. Serum egg white specific IgE

Serum egg white specific IgE assay was measured by ELISA (RIDASCREEN specific IgE, R-Biopharm AG, Darmstadt, Germany). According to the manufacturer's recommendations, egg white specific IgE was considered detectable at levels above 0.35 IU/ml, increased when ranged from 0.7 to 3.49 IU/ml, and significantly increased from 3.5 to 17.49 IU/ml. High level when more than 17.5 IU/ml and extremely high when ≥ 100 IU/ml.

4- Oral egg challenge test

Subjects with suspected egg allergy (positive history of exacerbation or positive SPT and/ or specific IgE) whose ages ranged between 2-5 years with a mean of 4 years underwent open oral egg challenge (OFC). Emulsified raw egg was put upon the inner border of the lower lip. If no reaction ensued, a further half-boiled egg was given after 30 minutes and repeated every 30 minutes until a reaction occurs or a maximum amount tolerated

without reaction (a whole egg white: the normal daily intake). After the last administration of egg white the children were watched for at least 4 hours and then discharged provided that no clinical reactions appeared. Parents were asked to report late onset reactions at home during the following three days.¹⁰

Statistical analysis:

Standard computer program SPSS for Windows, release 15.0 (SPSS Inc, USA) was used for data entry and analysis. All numeric variables were expressed as mean \pm standard deviation (SD). Comparison of continues variables between two groups was done using student t test for normally distributed variables. ANOVA test was used to assess the difference between more than two study group means. Chi-square (χ^2) and Fisher exact tests were used to compare frequency of qualitative variables among the different groups as appropriate. Spearman's correlation test was used for correlating non-parametric variables. Kappa test was used to assess the inter-observer agreement. Kappa greater than 0.70 (70%) considered as significant good agreement and Kappa more than 0.40 (40%) as fair but below 0.40 is to be considered poor. For all tests a probability (p) less than 0.05 was considered significant.

RESULTS

Results of SPT, specific IgE and open oral challenge to egg white in the study:

SPT to egg white was positive in 25 (31.2%) patients of whom 3 (4%) patients were +3, 22 (28%) patients were +2. Skin prick test was negative in 55 (68.7%) patients of whom 30 (37%) patients were +1 and 25 (31.2%) patients did not give any reaction.

Serum egg white specific IgE was positive in 19 (24%) patients with a mean of 0.81 IU/ml. Of whom, 13 (16.3%) patients had low level of specific IgE, five (6.3%) had slightly increased level and one (1.3%) patient had significantly increased level of egg white specific IgE = 4.52 IU/ml.

In the present study, 12 patients were suspected to have egg allergy based on positive history of exacerbation or positive results in one of the tests (SPT or serum specific IgE). Of these patients, 6 underwent open oral egg challenge test while the remaining 6 patients did not consent. Oral egg challenge was positive in only one patient with

positive history of egg allergy but negative tests (table 2). Urticaria developed in this patient one hour after ingestion of a whole egg white.

Variation of the results of SPT and specific IgE to egg white with history of egg allergy:

History of allergic exacerbation upon exposure to egg was significantly more recorded among the studied children with positive SPT to egg white and serum egg white specific IgE level than those with negative results (p = 0.001).

The effect of family history of allergy on the results of SPT and specific IgE to egg white:

No significant relationship between family history of allergy and results of SPT and serum specific IgE to egg white was observed among all the studied cases (p > 0.05).

The relationship between egg white specific IgE and the ages of the studied patients:

Patients with positive SPT were significantly younger than those with negative skin prick test (t= 1.67, p =0.02). On the other hand, among the 17 patients with positive specific IgE, no significant correlation was found between age and serum level of egg white specific IgE.

The agreement between the results of SPT and specific IgE to egg white:

Among studied patients, serum levels of specific IgE to egg white significantly increased as the grade of SPT increased (table 3). Kappa test showed that the degree of agreement between skin prick test and specific IgE was fair (0.5), this implied that each test could not be an absolute substitute for the other.

Variation of the results of SPT and specific IgE to egg white with the type of allergic diseases:

The results of SPT and serum specific IgE to egg white did not vary significantly among studied patients with different allergic diseases whether bronchial asthma, urticaria or combined allergic diseases (p > 0.05).

The relationship between asthma severity and results of SPT and specific IgE to egg white:

Both SPT and serum specific IgE level to egg white were not significantly influenced by the different grades of bronchial asthma severity (p > 0.05).

Table 1. Demographic and laboratory data of studied patients.

	BA n= 59 (73.8%)	Urticaria n=7 (8.7%)	Urticaria & BA/AR n=14 (17.5%)
Age (years)			
Mean \pm SD	4.27 \pm 2.33	4.36 \pm 2.38	2.80 \pm 1.61
Range	(1-11)	(2-7)	(1-7)
Sex			
Male	42 (71.2%)	4 (57.1%)	8 (57.1%)
Female	17 (28.8%)	3 (42.9%)	6 (42.9%)
History of exacerbation on exposure to egg			
Positive	18 (30.5%)	4 (57.1%)	6 (42.9%)
Negative	41 (69.5%)	3 (42.9%)	8 (57.1%)
Family history of allergy			
Positive	39 (66.1%)	6 (85.7%)	9 (64.3%)
Negative	20 (33.9%)	1 (14.3%)	5 (35.7%)
Treatment			
On demand	14 (23.7%)	7 (100%)	10 (71.4%)
Low dose ICs (fluticasone)	18 (30.5%)	0	1 (7.1%)
Medium dose ICs	21 (35.6%)	0	3 (21.4%)
High dose ICs	1 (1.7%)	0	0
Medium dose ICs + LABA	4 (6.7%)	0	0
High dose ICs + LABA	1 (1.7%)	0	0
SPT to egg			
Positive	17 (28.8%)	2 (28.6%)	6 (42.9%)
Negative	42 (71.2%)	5 (71.4%)	8 (57.1%)
Egg white Sp. IgE (IU/ml)			
Mean \pm SD	0.34 \pm 0.23	0.39 \pm 0.11	0.63 \pm 1.13
Range	(0.15-1.40)	(0.29-0.58)	(0.15-4.52)
Positive	11 (18.6%)	4 (57.1%)	4 (28.6%)
Negative	48 (81.4%)	3 (42.9%)	10 (71.4%)

SD: Standard deviation; Sp.IgE: Specific IgE; BA: Bronchial asthma; AR: Allergic rhinitis; ICs: Inhaled corticosteroids; LABA: Long acting beta2 agonist; %: Percentage of total.

Table 2. Disease characteristics of patients subjected to open oral egg challenge.

Diagnosis	Age (years)	Sex	History of exacerbation	Sp.IgE (IU/ML)	SPT	OOC
Bronchial asthma	4.5	M	Positive	0.32	Negative (+)	Negative
Bronchial asthma and allergic rhinitis	2	M	Positive	0.32	Negative (+)	Negative
Bronchial asthma	4.5	F	Positive	0.24	Negative	Positive
Bronchial asthma	4	F	Negative	0.25	Positive (++)	Negative
Bronchial asthma	2.5	M	Negative	0.37	Negative	Negative
Bronchial asthma	5	F	Negative	0.15	Positive (++)	Negative

M: Male; F: Female; Sp. IgE: Specific immunoglobulin E; SPT: Skin prick test; OOC: Open oral challenge; SPT (+) : < 3mm above negative control; SPT (++) : \geq half the size of histamine wheal reaction. Sp.IgE <0.35: Negative

Table 3. Variation of the serum egg white specific IgE in relation to the grade of the skin prick test.

Serum egg white sp. IgE level	Results of skin prick test			χ^2 /Exact Fischer	P
	(+) n (%) =30(37.5%)	(++) n (%) =22(27.5%)	(+++) n (%) =3(4%)		
Mean \pm SD	0.29 \pm 0.05	0.64 \pm 0.9	0.9 \pm 0.43	3.13	0.04

Sp. IgE: Specific immunoglobulin E; SD: Standard deviation; n: number; %: Percentage of total; SPT (+) : < 3mm above negative control; SPT (++) : \geq half the size of histamine wheal reaction; SPT (+++): equal histamine wheal reaction

DISCUSSION

Our study demonstrated a high frequency of egg white hypersensitivity (30%) among atopic Egyptian children by positive history, positive skin prick test and/or elevated serum egg IgE titre and open oral egg challenge test. Our findings are in agreement with other studies that showed higher prevalence of egg white allergy among children with bronchial asthma¹¹ and atopic dermatitis.¹² Meanwhile, the prevalence of egg allergy was found to be much lower among non-atopic children being 1.6% in Denmark¹³ and 1.3% in the United States.¹⁴ A meta-analysis of the prevalence of food allergy estimated that egg allergy affects 0.5 to 2.5 % of young children.² The majority of studies included in the meta-analysis were based upon self-reports of food allergy, which tend to overestimate the prevalence. This was found to be 0.0004% in Germany¹⁵, and 0.6% in Mexico¹⁶ when double blind placebo controlled food challenge was used for diagnosis of egg allergy.

Although the gold standard for diagnosis of food allergy is the standardised oral challenge test¹⁷, performing the oral challenge test is time-consuming (over 4–6 hours with an allergist) and it places the patient at risk for an allergic reaction during the testing.¹⁸ It has been claimed that performing an oral challenge test as a diagnostic tool can be unnecessary when there is an increase in serum specific IgE above certain levels.^{19, 20} A wide range of predictive levels of serum egg white specific IgE indicating a positive reaction to egg was reported in several studies being as high as 10 IU/ml (95%)¹⁹, 6 IU/ml (95%)²⁰, 1.5 IU/ml (95%)²¹, more than 0.35 IU/ml (92%).²² These variations in the predictive values are much more dependent upon the population prevalence of egg allergy rather than the sensitivity and specificity of the performed test. Thus, these results may not apply to other populations, such as adults. Although the measurement of specific IgE for egg could provide an indication of the likelihood of clinical reactivity to egg, yet it neither predicts the severity of allergic reactions that may develop in each individual nor the natural history of the allergy.²³

In our study, egg white allergy was significantly more frequent in younger patients which conforms with the natural history of egg allergy demonstrated in previous studies with variable ages of egg tolerance.²⁴⁻²⁶

In our series, all patients with both positive SPT and specific IgE to egg white had history of exacerbation of their allergic disorders upon exposure to egg white (within 2 hours). However, none of our patients experienced atopic dermatitis, GIT symptoms (vomiting, abdominal cramps or diarrhea) or anaphylaxis. A high risk (>70%) exists for developing the same atopic disorder as one's parents, given that both parents have the identical disorder.²⁷ Documented food allergy in a sibling or a parent also increases the likelihood for the development of food allergy in an offspring.²⁸ In our study, 75% of the patients with history of egg allergy had at least one parent with similar allergic symptoms, however, none of these parents reported allergy to any food denoting that the absence of parental history of food allergy should not rule out the possibility of food allergy in their offspring.

One limitation in our series was that the majority of cases were bronchial asthma which could offer a bias towards bronchial asthma than other allergic conditions. However, it has been reported that 31.9% of the studied atopic children with egg allergy had asthma, 16% had allergic rhinitis while 3.3% had urticaria.²⁹ Similarly, sensitization to egg protein during infancy was found to be associated with an increased risk of development of respiratory allergic disorders.^{30, 31} Meanwhile, atopic dermatitis and urticaria/angioedema represented the most often observed skin manifestations triggered by egg.^{32, 33}

In the current study, we found that positive SPT to egg and serum egg white specific IgE had no relationship with the severity of bronchial asthma. This may be attributed to the mild manifestation of egg allergy observed in those patients. In fact, there was no clear correlation between values of the specific IgE to egg and the severity of allergic reactions³⁴, although they are useful in predicting the likelihood of clinical reactivity. Likewise, the severity of past reactions is

not a good marker for the severity of future reactions.³⁵ Meanwhile, specific IgE titres was found to be correlated with the severity of the reaction during a standardized challenge to egg. Moreover, specific IgE titres may help to determine the potential risk of a reaction to eggs.³⁶

One out of 6 patients who underwent open oral egg challenge test had proven egg allergy. This denotes that the remaining five cases who had weakly positive skin prick test/ positive specific IgE had egg sensitization rather than egg allergy. Another study limitation is that oral challenge was not performed in the whole studied sample to validate the history with the results of SPT and specific IgE. It has been reported that positive specific IgE without symptoms must be carefully interpreted because it can be due to a low degree of sensitization, unable to express clinical symptoms at this moment, but useful in the future as a guide on the disease course.³⁷

Serologic and clinical cross-reactivity with other bird eggs (turkey, duck, goose, seagull, and quail) and a minority of patients with allergy to egg are reactive to chicken meat as well.³⁸ Also, it has been reported that infants presenting with likely milk/egg allergy without already known peanut allergy are at high risk of also having peanut sensitization and therefore possible peanut allergy.³⁹ In our series, none of our patients had history of peanuts or chicken meat allergy.

In conclusion, egg hypersensitivity in Egypt is not uncommon. The combination of history of allergy following egg ingestion, positive SPT/ specific IgE is a good tool for diagnosis. The sensitivity to egg white was not related to the type of atopy, the severity of asthma or family history of atopy. The diagnosis of egg allergy needs meticulous evaluation and oral food challenge remains the gold standard in suspected cases. Further wide-scale studies are needed to outline the real prevalence of egg allergy in Egypt.

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