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Original Article

Cross Reaction between Hen Eggs and Bird Eggs in Patients with Egg Allergy Based on Skin Prick Test, Specific IgE and Oral Food Challenge

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Abstract

Introduction: As some children have allergies to egg as an important food source, finding the right alternative is essential. To date, the interaction between other birds' eggs and hen eggs has not been investigated in Iran. Because of the common usage of eggs from birds other than hens in Iran, the present study aimed to compare hens' eggs with the eggs of other birds.

Method: In this case-control study, 70 children who had referred to our allergy clinic were evaluated. In patients who had a history of egg allergy, Skins Prick Test (SPT) and specific IgE Ab analyses were done, and then an Oral Food Challenge (OFC) was performed. Patients with egg allergy underwent SPT with eggs from birds such as turkey, goose, duck, quail, partridge, and pigeon.

Results: From among the 40 patients with egg allergy, 8 patients passed the OFC. The greatest cross-reactions were seen in turkey white egg and quail yolk egg extracts with 82.5% and 90% respectively. The least cross-reactions were reported in pigeon yolk egg and pigeon white egg with 30% and 37.5% respectively and partridge white egg and partridge yolk egg with 47.5% and 67.5% respectively. Among patients who had negative SPT with partridge egg (N=3), one patient passed and two failed the OFC. Three of the patients who had negative pigeon SPT (N=5) passed the OFC with pigeon egg.

Conclusion: In conclusion, turkey, goose, duck, and quail eggs cannot be used as an alternative to hen eggs. Therefore, only partridge or pigeon eggs can be considered as a suitable alternative to hen eggs.

Keywords: Hen Egg, Cross-Reaction, Egg Allergy

Introduction

Food allergy is defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food.[1] Food allergies can appear in the form of skin, respiratory tract, gastrointestinal tract, and/or cardiovascular manifestations, and people may develop food allergies at different ages.[2] Based on physiopathology, food allergies are divided into three categories: IgE mediated-response, IgE and cell-mediated response, and non-IgE-mediated response.[3,4]

Food allergies are diagnosed based on medical history and physical examinations. The results of these assessments guide physicians to choose the proper diagnostic tests. When the diagnosis remains unclear after such assessments, an oral food challenge can be performed.[5] Several methods can be used in food allergy testing, such as the allergy test, skin allergy test, patch test, radioallergosorbent test, elimination diet, and oral food challenge.[6]

Egg white comprises approximately 40 different proteins, 13 of which have been found to cause the production of specific IgE-antibodies in egg allergic individuals. Ovomucoid (Gal d 1), ovalbumin (Gal d 2), conalbumin (ovotransferrin) (Gal d 3), and lysozyme (Gal d 4) have been identified as major allergens in hen's eggs.[4,7] Alpha-livetin (Gal d 5) is thought to be a main egg yolk allergen responsible for bird-egg syndrome.[3,4,7]

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.[4] This may increase the risk for inadvertent allergen exposure.[8] The presence of cross-reacting proteins in various avian egg whites has been previously reported.[9,10] However, some investigations have shown no cross-reaction between hen egg and other birds' eggs.

Langeland et al. reported cross-reactions in the egg white proteins of various birds. Egg whites from different birds such as ducks, geese, and chickens contain proteins and allergens similar to hen eggs that cause cross-reactions.[11]

Añíbarro et al. reported an unusual case of food allergy after consumption of eggs from duck and goose in an adult patient without hen egg allergy. Ovalbumin seems to have been the responsible protein in this case. Skin tests were positive to egg whites from duck and goose, but skin tests and specific serum IgE were negative to hen egg proteins.[12]

The diagnosis of egg allergy is based on history taking, antigen-specific IgE measurements such as the skin prick test, in vitro antigen-specific blood IgE tests and histamine release tests, and oral food challenges.[13] Currently, the management of egg allergy is based on the correct identification of the causative allergen and minimal elimination of food products in diet.[14] Although oral immunotherapy is promising as a tolerance induction protocol, several questions and concerns still remain predominantly regarding safety.[14,15]

The importance of eating egg protein for children's growth is evident.[3,4] Several studies have investigated the cross-reaction between different birds' eggs.[11,12] but no such study has been performed in Iran. Given that the eggs of birds such as goose, duck, turkey, and quail are widely used in Iran, considering the genetic and racial differences in our population compared to other investigations, and because the interaction between the eggs of birds and hens egg has not yet been investigated in Iran, the present study aimed to compare hen egg with other birds' egg and chicken, if possible, to find an appropriate alternative.

However, some limitations should be noted. First, the number of children with egg allergy referring to the clinic is limited. Second, the costs of SPT, specific IgE Ab test, and oral food challenge are expensive, and the budget allocated to the study was limited.

Method

In the case group, 40 patients with a positive history for IgE-mediated hen egg allergy who had developed signs and symptoms including urticaria, angioedema, respiratory symptoms, and gastrointestinal tract symptoms were selected from among the patients referring to the studied clinic during the period between September 2016 and February 2019. All of them underwent SPT and determination of specific IgE Ab testing (egg white and egg yolk). The SPT was performed on the volar surface of the forearm by applying commercial extracts of hen egg white and yolk.

Histamine and saline were used as the negative control and positive control, respectively, and a wheal of 3 mm or more than the negative control was considered positive. Serum specific IgE levels for HE yolk and white were measured using ImmunoCap 100 (Thermo-Fisher Scientific, Waltham, Mass). The lower detection limit of the Cap-system was 0.35 KU/L for specific IgE.

Then, OFC was performed based on the standard guideline.[16] in the case group of patients with a history of egg allergy. The OFC test was not performed in children who had ever shown anaphylaxis to egg. The OFC was started with a dose of 0.24 gr egg white which was then doubled (0.48gr, 0.96gr, 1.9gr etc.) at hourly intervals until objective clinical manifestations appeared. The cumulative dose of egg white in the OFC test was 3.7gr (about one boiled egg).

All subjects in the case group underwent the skin prick-by-prick test with positive and negative controls. Then, 40 patients with egg allergies underwent the SPT with egg extracts from other known birds, including turkey, goose, duck, quail, partridge, and pigeon. All subjects were also exposed to chicken extract by the SPT.

The control group consisted of 30 children with no history of egg allergy who referred to the studied clinic. All subjects in the control group underwent the SPT with egg extract (mixed egg white and yolk). Children with a positive history of severe uncontrolled asthma or food allergy were excluded. The control group was enrolled to investigate the validity of the SPT.

In the total study population, the basic characteristics such as gender, history of prior reaction to egg, asthma, eczema, allergic rhinitis, family history of food allergy, and family history of any allergy were analyzed.

Ethical Considerations: The study was confirmed by the Ethics Committee of Shiraz University of Medical Sciences. Informed written consents were obtained from the parents.

Results

Among the case group subjects (N=40), 7 patients had a clear history of anaphylaxis to egg developing specific signs and symptoms including mucocutaneous reactions such as urticarial or angioedema; digestive reactions including vomiting, nausea, and abdominal pain; and respiratory reactions affecting the upper respiratory such as sneezing, nasal itching, and congestion or the lower respiratory tract such as coughing and wheezing. The criteria considered for anaphylaxis was multi-organ system involvement including cardiovascular, lower respiratory tract, or persistent gastrointestinal symptoms.[17] The results of SPT and specific IgE Ab tests in these patients were positive in six subjects to white egg and in one to egg yolk.

Other patients with a positive history of egg allergy (with positive SPT and specific IgE results) developed different symptoms, including urticaria, vomiting, nasal itching without congestion, angioedema, and cough without a history of anaphylactic reaction.

From among 33 patients, eight patients passed OFC. These patients had a mean of 8 mm wheal in SPT, but IgE was less than four. The most common cutaneous symptoms developed in patients who failed the OFC were urticaria, angioedema, erythema, and rash (seen in 25 patients). Gastrointestinal symptoms including nausea, vomiting, and abdominal pain were observed in 10 patients during the OFC. Upper respiratory symptoms such as congestion, sneezing, and rhinitis were reported in six patients because of the OFC. No patients had anaphylaxis or lower respiratory

symptoms due to the OFC test. Most of the patients developed clinical symptoms with 0.96 gr egg white in the OFC.

In the control group (which had no egg allergy), 10 healthy children without any food, egg, or respiratory allergies and 20 subjects with respiratory allergies including asthma or allergic rhinitis were selected and underwent SPT with egg extract. The results were negative in all of them. In the control group subjects with a positive history of allergy to respiratory allergens, two subjects had positive SPT results, but they passed the OFC. The baseline characteristics of the study population are shown in Table 1.

The statistical analysis showed that more than 82% of subjects in both groups had acceptable growth figures with no significant differences between the groups (*p*-value = 0.130).

The results of the skin prick-by-prick test with positive and negative controls and cross-reaction specific extraction of different eggs (quail, goose, duck, turkey, partridge and pigeon eggs) and chicken extraction are shown in Table 2.

The numbers of patients with positive skin prick tests to each mentioned extraction are demonstrated in Table 3.

In patients who had negative SPT with partridge egg (N=3), one patient passed and two failed the OFC. In patients with negative pigeon SPT (N=5), three patients passed the OFC.

Table 1. Baseline characteristics of study population compared in case and control groups

Title	Case Group N = 40	1st Control Group N = 10	2nd Control Group N = 20	P value
Sex				
Male	22 (55%)	6 (60%)	13 (65%)	1.00
Female	18 (45%)	4 (40%)	7 (35%)	
History of Atopic dermatitis				
Yes	33 (82.5%)	0	11 (55%)	0.000*
No	7 (17.5%)	10 (100%)	9 (45%)	
Parents were relatives				
Yes	18 (45%)	3 (30%)	6 (30%)	0.225
No	22 (55%)	7 (70%)	14 (70%)	
History of allergy in father				
Yes	19 (47.5%)	3 (30%)	10 (50%)	0.811
No	21 (52.5%)	7 (70%)	10 (50%)	
History of allergy in mother				
Yes	22 (55%)	6 (60%)	12 (60%)	0.808
No	18 (45%)	4 (40%)	8 (40%)	
Delivery				
Normal vaginal delivery	16 (40%)	5 (50%)	8 (40%)	0.810
Cesarean section	24 (60%)	5 (50%)	12 (60%)	
Birth age				
Term Neonate	33 (82.5%)	8 (80%)	18 (90%)	0.747
Preterm Neonate	7 (17.5%)	2 (20%)	2 (10%)	
History of dairy allergy				
Yes	24 (60%)	2 (20%)	2 (10%)	0.000*
No	14 (40%)	8 (80%)	18 (90%)	
Children' Nutrition				
Breastfeeding	12 (30%)	4 (40%)	10 (50%)	
Formula feeding	3 (7.5%)	2 (20%)	6 (30%)	0.007*
Both	25 (62.5%)	4 (40%)	4 (20%)	
Smoker parents				
Yes	2 (5%)	3 (33.3%)	4 (20%)	0.030*
No	38 (95%)	6 (66.7%)	16 (80%)	
Growth Figures				
Acceptable	33 (82.5%)	7 (77.8%)	17 (85%)	1.00
Not Acceptable	7 (17.5%)	2 (22.2%)	3 (15%)	

Table 2. Mean SPT results of specific extraction of different eggs in case group

Title	Mean ± STD	Min	Max
Histamine	3.05 ± 2.01	1	8
Normal Saline	1.26 ± 0.54	1	3
Yolk Egg	7.32 ± 5.68	3	30
White Egg	8.36 ± 4.58	2	25
Chicken	2.78 ± 2.45	1	10
Pigeon Yolk egg	4.16 ± 3.07	1	15
Pigeon White egg	4.06 ± 2.90	1	14
Duck Yolk egg	4.61 ± 1.72	1	8
Duck White egg	5.11 ± 1.44	3	9
Goose Yolk egg	6.30 ± 2.64	2	12
Goose White egg	7.19 ± 3.51	2	17
Turkey Yolk egg	7.36 ± 3.04	3	15
Turkey White egg	7.70 ± 2.92	3	15
Quail Yolk egg	7.37 ± 3.16	3	20
Quail White egg	7.62 ± 4.17	3	20
Partridge Yolk egg	4.94 ± 2.78	1	15
Partridge White egg	5.05 ± 3.35	1	13

Table 3. Frequency of positive skin prick test of specific extractions in case group

Title	Number of positive results N (%)	Title	Number of positive results N (%)
Pigeon Yolk egg	12 (30%)	Turkey Yolk egg	32 (80%)
Pigeon White egg	15 (37.5%)	Turkey White egg	33 (82.5%)
Duck Yolk egg	25 (62.5%)	Quail Yolk egg	36 (90%)
Duck White egg	29 (72.5%)	Quail White egg	32 (80%)
Goose Yolk egg	30 (75%)	Partridge Yolk egg	27 (67.5%)
Goose White egg	32 (80%)	Partridge White egg	19 (47.5%)

Discussion

Eggs are among the foods most commonly causing allergy, mainly in children.[3,6] Egg allergy is diagnosed based on clinical history and physical examination which indicates the essential laboratory tests such as SPT and Specific IgE Ab. When the diagnosis is unclear after these examinations, OFC should be performed.[13]

Hen eggs are the most important allergy among different egg allergies, given that hen eggs are more commonly used compared to other birds' eggs. Among food allergies to bird eggs, those to the eggs of other birds are of lesser significance.[4] The proteins in other birds' eggs differ from those in hen eggs, and some patients can tolerate other birds' eggs while being allergic to hen eggs. Therefore, this study compared hen egg allergy with allergies to other birds' eggs and chicken in order to find an appropriate alternative.

Based on the current results, two of the control subjects who had respiratory allergies had positive SPT results, but they passed the OFC. In the case group, proven by SPT and specific IgE Ab test, 17.5% patients had a positive history of anaphylaxis to egg and did not undergo the OFC. Therefore, the oral food challenge was done in 33 patients. In the case group, 24.2% of patients with a history of positive egg allergy passed the OFC with cooked egg. These patients had a mean of 8 mm wheal in SPT, but the specific IgE was less than four. Therefore, there was a significant relationship between IgE and OFC results in this population. In contrast, Cortot et al. examined egg white specific IgE levels, SPT results, and age as predictors of baked egg OFC outcomes. In their study, among the 52 challenges, 83% (n = 43) passed and 17% (n = 9) failed, including two who had anaphylaxis. Median SPT wheal size was 12 mm (range, 0-35 mm) for passed challenges and 17 mm (range, 10-30 mm) for failed challenges (p = 0.091).[18] The researchers concluded that based on their sample, SPT, egg white specific IgE, and age are not good predictors of passing a baked egg challenge. However, there was a trend for more predictability with SPT wheal size.[18] Therefore, future studies with larger and more diverse sample sizes are needed to determine more accurate indicators of OFC results and their relation to SPT and specific IgE levels.

In the current study, the most often reported signs and symptoms in the OFC were cutaneous reactions, gastrointestinal symptoms, and upper respiratory symptoms, respectively. None of the patients had anaphylaxis. Most patients developed clinical symptoms with 0.96 gr white egg in the OFC. Perry et al. analyzed the outcome of 584 OFC to milk, egg, peanut, soy, and wheat. They found that 253 (43%)

resulted in an allergic reaction. Among those who reacted, the most observed reactions were cutaneous, gastrointestinal, oral, lower respiratory, and upper respiratory reactions, respectively. No relationships were detected between specific IgE levels or the dose ingested and reaction severity.[19]

Also in a study by Boyano Martínez et al.,[20] the symptoms which occurred in the diagnostic challenge test were cutaneous in 37 (95%) subjects, this being the only clinical manifestation in 24 of them (62%). The cutaneous symptoms consisted of urticaria in 28 children, oral allergy syndrome in four, erythema in four, and angioedema in two. Vomiting was observed in 11 (28%) cases. Respiratory symptoms, which consisted only of rhinitis in many cases, were observed in eight (21%) children. Thirty-three percent of the children suffered cutaneous symptoms associated with digestive and/or respiratory ones.[20] Accordingly, similar to the current results, the most common clinical symptoms of egg allergy in the OFC were cutaneous reactions, followed in rank by gastrointestinal and respiratory symptoms.

In the current study, no significant difference was observed between children with egg allergy and control subjects regarding gender, history of allergy in mother or father, consanguineous relationship between parents, type of delivery, term or preterm pregnancy, and children's growth figures. However, there was a significant difference between the case and the control groups regarding history of atopic dermatitis, history of dairy allergy, children's nutrition type, and if one parent was a smoker or not (p-value < 0.05). More than 82% of the patients in the case group had a history of atopic dermatitis. Also, a history of allergy to dairy products was more commonly seen in children with egg allergy (60%). Most patients in the case group were fed with both formula and breastfeeding in their first two years of life. The number of smoker parents was higher in the control group (especially among children with respiratory allergy) than in the case group.

Similar to the current results, Robison et al. discussed the co-expression of Atopic Dermatitis (AD) and food allergy in their review article.[21] They concluded that the prevalence of food allergy in patients with AD varies with age and the severity of AD. In their birth-cohort study of 620 infants, Hill et al. demonstrated that as AD severity increased, adverse reactions to food increased as well.[22] More recently, Martin et al. conducted a population-based cohort study of more than 4000 infants (HealthNuts) and demonstrated that children with AD were 6 times more likely to have a food allergy to cow milk, egg, or peanut at the age of 12 months compared with infants without AD. In addition, children diagnosed at a younger age and requiring more medical therapy were more likely to have a food allergy.[23] Therefore, based on the current findings and the reviewed articles, it can be concluded that there is a strong relationship between food allergy, especially egg allergy, with AD and allergy to dairy products.

According to the results, none of the patients in the case group of the current study had an allergy to chicken in the SPT. The greatest cross-reaction based on severity was in turkey and quail eggs, and the least cross-reaction was observed in partridge and pigeon eggs. All patients had positive SPTs to turkey, goose, duck, and quail eggs. A large number of patients were allergic to quail egg yolk and white, turkey egg yolk and white, and goose egg yolk and white, respectively. In patients who had negative SPTs with partridge egg (N=3), one patient passed and two failed the OFC. In patients with a negative pigeon SPT (N=5), three patients passed the OFC.

In a similar study performed in Iran, the clinical cross-reactivity of different birds eggs in children with hen's egg allergy based on skin prick test results was assessed. They found that more than 96% of children with hen's egg allergy showed positive sensitization to at least one of the avian eggs.[24] The most frequent positive skin tests were related to quail's white (69.2%) followed by duck's white (65.5%), and sensitization was the least frequent in pigeon's yolk (44.2%). They concluded that we have to increase our knowledge in order to perform the necessary eliminations of avian eggs for children with hen's egg allergy, and also further research are essential investigating oral immunotherapy considering other birds' egg cross reaction.[24]

Given the results of Moghtaderi et al.'s study, specific IgE Ab testing and OFC have been applied in addition to SPT in this study (they used SPT as the only immunology test). Therefore, the results of the present study have explained more details about cross reaction between hen's egg allergy and avian eggs.

The current study determined a strong relationship between specific IgE Ab and OFC results. The most reported sign and symptoms during the oral food challenge were cutaneous reaction, gastrointestinal, and respiratory symptoms, respectively.

Based on the results that showed the greatest cross-reaction in turkey and quail eggs and the least cross-reaction in partridge and pigeon eggs, it is not possible to say that pigeon or quail eggs can be used by patients with egg allergies. An OFC should be performed to confirm the possibility of partridge and pigeon egg use.

Conclusion

In the current study, a severe cross-reaction was observed between turkey and quail eggs based on skin prick test results. However, partridge or pigeon eggs presented the least cross-reaction, and they could be considered as a suitable alternative to hen eggs. There was a strong relationship between specific IgE Ab and OFC results. The most reported

signs and symptoms in the OFC were cutaneous reactions, gastrointestinal symptoms, and upper respiratory symptoms, respectively. There were significant differences between the case and control groups regarding history of atopic dermatitis, history of dairy allergy, and children's nutrition type. Histories of atopic dermatitis and allergy to dairy products were more commonly seen in patients with egg allergy.

Ethical Approval

This dissertation was approved in the Faculty of Medicine of Shiraz University of Medical Sciences with the code of ethics IR.SUMS.MED.REC.1397.334. The ethics resolution can be viewed on the website of the National Ethics Committee website.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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