Accidental Allergic Reactions in Children Allergic to Hen’s Egg

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Abstract

Background: Hen’s egg is one of the main causes of food allergy in children. Accidental exposure is common in food-allergic patients. However, the few studies that analyze this problem focus mainly on peanut allergy. We sought to calculate the frequency of accidental exposure reactions in children allergic to hen’s egg during a 12-month period, to analyze the clinical characteristics and circumstances surrounding the reactions, and to identify risk factors for the most severe reactions.

Methods: Ninety-two egg-allergic children (55 boys; median age, 52 months) were included in the study. A systematic questionnaire about accidental exposure was administered. Reactions were classified as mild, moderate, and severe. Egg white–specific immunoglobulin (Ig) E antibody titers were determined.

Results: Nineteen (21%) children had 24 reactions in the previous year (42% mild, 50% moderate, and 8% severe). Most reactions took place at home (50%) under routine circumstances (83%). Children with severe or moderate reactions had higher specific IgE levels to egg white (adjusted odds ratio for every 0.1-unit increase in the decimal logarithm, 1.15; 95% CI, 1.03-1.28; \( P = .008 \)) and lower serum total IgE (adjusted odds ratio for every 1-unit increase in the decimal logarithm, 0.16; 95% CI, 0.05-0.54; \( P = .001 \)) than those children with mild or no reactions.

Conclusions: Reactions to accidental exposure are frequent in children with egg allergy. The proportion of severe or moderate reactions was 58%. The risk factors for such reactions included high titers of specific IgE to egg white and low titers of serum total IgE.

Key words: Egg allergy. Accidental exposure. Accidental ingestion.
Introduction

Hen’s egg is one of the most frequently implicated foods in pediatric food allergy. Egg allergy affects 1.6% of children aged between 2 and 3 years [1]. It usually appears at the age of 1 year, coinciding with the first eggs consumed. Around 50% of allergic children achieve tolerance by the age of 4, and 66% do so by the age of 6 [2].

Ovomucoid, ovalbumin, lysozyme, and conalbumin, all of which are present in egg white, are the major allergens in egg. Recent studies have revealed 2 subpopulations in egg-allergic children: those who react to raw and heated egg white and those who react only to raw white, with tolerance to heated white [3,4]. This feature, which is an evolutionary phenomenon in many egg-allergic children, is due to the high heat resistance of ovomucoid [5]. Ando et al [3] showed that ovomucoid-specific immunoglobulin (Ig) E (sIgE) titers are more discriminatory than those of sIgE to egg white or ovalbumin.

Egg, both raw and cooked, is a widely consumed food containing proteins of high biological quality. Egg is used in pastry products, cookies, ice cream, and many sauces. Hen’s egg is also used as a food additive. Albumin is used as a clarifying agent in the production of wine and beer, and lysozyme is added to cheese and wine because of its antibacterial properties, thus making it useful for the pharmaceutical and cosmetic industries.

Allergic reactions caused by accidental intake are a major concern, and the quality of life of children, parents, and caretakers is affected because of potential life-threatening reactions [6,7].

The few studies that analyze accidental allergic reactions (AARs) in food-allergic children focus mainly on nuts, because of the severity of nut allergy [7-14].

The objectives of this study were to ascertain the frequency of AARs in children with egg allergy, to analyze the severity and circumstances of these reactions and the products causing them, and to identify possible risk factors for the most severe reactions.

Methods

Patients

We performed a cross-sectional study of all children aged 18 months or older who were diagnosed with IgE-mediated allergy to hen’s egg in our department. All the children were on a diet free of eggs and egg derivatives and attended the department regularly.

Diagnosis was based on previously established criteria [15]. Each child was evaluated because of immediate hypersensitivity reactions after intake of hen’s egg and had a positive skin prick test result to egg white proteins (ovalbumin, ovomucoid, or both). An oral challenge test was positive in 22 children (24%), and the other 70 were younger than 24 months and had egg white sIgE levels greater than the cutoff point (0.35 kU/L) with a 90% positive predictive value. Consequently, a challenge test was not necessary [15].

The physician administered a questionnaire about possible AARs in the previous year in order to record clinical characteristics, places, circumstances surrounding the reaction, treatment administered, and progression. All parents of children who participated in the study signed a written informed consent form that was previously approved by the local ethics committee.

AARs were defined as symptoms suggesting immediate hypersensitivity. Symptoms were classified as follows: cutaneous-mucosal (urticaria/angioedema, rash, and conjunctivitis); gastrointestinal (vomiting, abdominal pain, and diarrhea); respiratory (dyspnea, wheezing, cough, cyanosis, stridor, aphony, dysphagia, and rhinitis); and systemic (loss of consciousness, weakness, and dizziness). Onset was acute and subsided in less than 24 hours.

Reactions not classified as AARs in this study included those caused by intentional intake of egg or derivatives or by skin contact with egg (except those exceeding the contact region or requiring treatment for their control), urticaria lasting more than 24 hours, and reactions definitely related to other foods in children with several food allergies.

Severity was classified based on symptoms as mild, moderate, and severe, according to investigator-defined criteria. Mild reactions comprised those with cutaneous symptoms (angioedema excluded), rhinitis, or conjunctivitis. Moderate reactions included angioedema or gastrointestinal symptoms, which may or may not have been associated with mild reactions. Severe reactions were those involving the lower respiratory tract (aphonia, dysphagia, dyspnea, wheezing, stridor, and/or cyanosis) or systemic symptoms (loss of consciousness, weakness, or dizziness).

Serum Specific IgE Determination

Serum sIgE to egg white (ImmunoCAP Specific IgE; Phadia AB) was determined at the regular follow-up visits as clinically indicated.

Statistical Analysis

The χ² test was used to calculate the association between qualitative variables; the Fisher exact test was used when the number of cases was less than 5 in any category. The Mann-Whitney test was used to compare nonnormally distributed numerical variables (age and serum total and sIgE levels). Univariate and multivariate logistic regression analysis were performed to evaluate the association between the children’s characteristics (demographic, clinical, and laboratory) and the risk of suffering AARs. Two types of analyses were carried out. In the first, the dependent variable was AAR vs non-AAR; in the second, it was moderate or severe AAR vs mild or non-AAR. The principal variable was the level of sIgE to egg white, and those factors with a P value <.25 in the univariate analysis were introduced as covariates. Decimal logarithmic transformations of serum total IgE and egg white sIgE were necessary to confirm the linearity of numerical variables, which the age variable fulfills. Odds ratios (OR) and 95% CI were calculated for each potential independent variable. Statistical calculations were carried out using SPSS 12.0 (SPSS Inc, USA).
Results

We included 92 children (55 boys) over a 16-month period. At the time of the study, median age was 52.2 months (range, 27-176 months). Fifty-five children (60%) had atopic dermatitis, 42 (46%) had asthma, and 24 (26%) had seasonal allergic rhinoconjunctivitis. Forty-eight children (52%) had other food allergies (fish, 21; seeds, 17; fruits, 15; legumes, 10; cow’s milk, 6; and shellfish, 6).

Nineteen children (21%) reported AARs during the year before the visit. Sixteen children experienced only 1 AAR, 2 experienced 2 AARs, and 1 experienced 4 AARs (total, 24 reactions).

The clinical histories revealed that 39 of the 73 children who did not report reactions within the previous year had had reactions associated with a food at some time. This means that 58 children (63%) allergic to hen’s egg had had food-related AARs in the past.

Place and Circumstances

Reactions took place at home in 12 cases (50%), at day care in 4 cases (17%), at a restaurant in 3 cases (13%), at school in 1 case (4%), at a neighbor’s home in 1 case (4%), and at other places in 2 cases (8%). Place was not recorded in 1 case.

On 3 occasions (13%), children were at a birthday party or other family celebration. Twenty reactions (83%) took place under routine circumstances. This information was not recorded in 1 case.

Products Causing the Reaction and Exposure

Twenty AARs (83%) were attributable to foods. On 4 occasions, no suspected product was identified. Fifteen of the 20 identified products (75%) were sold without wrapping, and 5 (25%) were packaged. Exposure was due to ingestion in 18 AARs (75%) and skin contact in 4 AARs (17%). This information was not known in 2 cases.

Causative Foods

Hen’s egg in its original form caused 7 AARs. In 13 reactions the causative foods were candies (4 cases), cakes or cookies (4 cases), fried foods coated in egg (2 cases), ice cream (1 case), mayonnaise (1 case), and frozen potatoes (1 case). In 2 of these products, egg was specified on the labeling.

In summary, egg content was easily identified in 9 of the 20 products causing AARs, and 7 were highly suspected of

<table>
<thead>
<tr>
<th>Table 1. Univariate Analysis of Association Between Accidental Allergic Reaction (AAR) and Risk Factors</th>
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<tbody>
<tr>
<td><strong>AAR Severity (Group B)</strong></td>
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<tr>
<td>No AAR (Group A)</td>
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<tr>
<td>Sex, No. (%)</td>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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<tr>
<td>Age at study, No. (%)</td>
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<tr>
<td>&lt;Median</td>
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<td>&gt;Median</td>
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<tr>
<td>Asthma, No. (%)</td>
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<tr>
<td>No</td>
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<tr>
<td>Yes</td>
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<tr>
<td>Atopic dermatitis, No. (%)</td>
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<tr>
<td>No</td>
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<tr>
<td>Yes</td>
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<tr>
<td>Severity, first reaction, No. (%)</td>
</tr>
<tr>
<td>Mild</td>
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<td>Moderate</td>
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<tr>
<td>Severe</td>
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<tr>
<td>Total IgE, No. (%)</td>
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<tr>
<td>&lt;Median</td>
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<td>&gt;Median</td>
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<tr>
<td>Egg white sIgE, No. (%)</td>
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<tr>
<td>&lt;Median</td>
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<td>&gt;Median</td>
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</tbody>
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Abbreviations: Ig, immunoglobulin.

*χ2 test.

Fisher exact test.
containing egg. As for the other 4, only 1 was sold packaged, and its labeling was not consulted.

Symptoms of AARs

Mucocutaneous symptoms were reported in 21 AARs (88%), as follows: urticaria 15 (perioral 5, other locations 10), angioedema 7, rash 5, and conjunctivitis 2. Seven reactions (29%) involved the gastrointestinal system (vomiting 6, abdominal pain 2) and 4 the respiratory system (cough 3, dyspnea 1, wheezing 1, dysphagia 1). None of the patients presented with systemic reaction. When all symptoms were considered together, 1 organ was involved in 16 AARs (67%) and 2 or more in 8 AARs (33%).

With regard to severity, 10 reactions (42%) were mild, 12 (50%) were moderate, and 2 (8%) were severe. Distribution was as follows: 7 children (37%) experienced mild reactions, 10 (53%) experienced moderate reactions, and 2 (10%) experienced severe reactions. Time from intake to onset of symptoms was less than 15 minutes in 11 reactions (46%), 15 to 30 minutes in 3 (13%), and 30 to 60 minutes in 1 (4%). In 9 cases this information was not known.

Treatment

Nine AARs (37%) required pharmacologic treatment (antihistamines in 8 [33%] and systemic corticosteroids in 4 [17%]). Three reactions required treatment with both drugs. Fourteen AARs (58%) subsided spontaneously without treatment. In 1 case this information was not known.

Place of Treatment

Four AARs (44%) were treated at home. Four required emergency assistance (3 at a general pediatrician’s office and 1 at the emergency department of a hospital). In 1 case this information was not recorded.

### Table 2. Egg White–Specific Immunoglobulin (Ig) E and Total IgE Levels in Children With No Accidental Allergic Reactions (AARs), Mild AARs, and Moderate or Severe AARs

<table>
<thead>
<tr>
<th></th>
<th>No AAR</th>
<th>Mild AAR</th>
<th>Moderate or Severe AAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg white sIgE, kU/L</td>
<td>Median</td>
<td>1.23</td>
<td>1.89</td>
</tr>
<tr>
<td></td>
<td>IQR</td>
<td>0.42-4.79</td>
<td>0.39-4.98</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>&lt;0.35-100</td>
<td>0.35-10.00</td>
</tr>
<tr>
<td>Total IgE, kU/L</td>
<td>Median</td>
<td>267</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>IQR</td>
<td>107-637</td>
<td>39-524</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>5-2815</td>
<td>18-1675</td>
</tr>
</tbody>
</table>

### Progression

Most of the reactions resolved either spontaneously or with treatment within a few hours. Fourteen (58%) reactions resolved in less than 1 hour, and 8 (33%) resolved in 1 to 6 hours. Only 1 reaction lasted between 7 and 24 hours. This information was not known in 1 case.

### Analysis of the Association Between AAR and Risk Factors

Table 1 summarizes the distribution of the AARs and the risk factors analyzed. Univariate analysis showed that AARs were more frequent in younger children and in those with a lower total serum IgE titer \((P<.05)\). Children with higher egg white sIgE titers and those complaining of atopic dermatitis also had more frequent reactions (statistical significance near \(P<.05\)). No differences were found regarding gender, severity of the first reaction with egg, or having asthma. On the other hand,
the risk of moderate or severe reactions was higher in children with lower total IgE titers (<.05), children with higher titers of egg white sIgE, and younger children (differences near statistical significance). No differences were found for the remaining factors analyzed.

Levels of total IgE and sIgE to egg white (Table 2) showed a reverse tendency. Titors of sIgE to egg white were higher in those patients who had moderate or severe reactions than in those with mild or no AARs. Nevertheless, total IgE titers were lower in patients who had AARs, regardless of severity, than in those who did not. Statistical comparisons are shown as crude OR in Table 3.

The results of multivariate analyses (Table 3) showed that the frequency of AARs was higher in children with higher titers of egg white sIgE (adjusted OR, 1.15; 95% CI, 1.03-1.28; P=.008) and in children with lower total serum IgE titers (adjusted OR, 0.16; 95% CI, 0.05-0.54; P=.001). These results were similar when the risk of suffering moderate or severe reactions was compared with that of suffering mild or no reactions.

Discussion

AARs are frequent in allergic children, although few studies analyze this problem. In our group of 92 egg-allergic children, the frequency of AARs was 21% during the previous 12 months. Although this figure could be underestimated because of recall bias, mainly in mild reactions, we do not think it is overestimated because of reactions caused by ingestion of other foods to which the patient may be sensitized or because reactions elicited by egg intake before the previous 12 months might have been included. The first possibility can reasonably be ruled out, because, in most of the reactions, egg or egg-containing foods were identified as the trigger and because the frequency of AARs in children allergic to egg and other foods was slightly lower (19%) than in those allergic to egg only (23%). In the second case, the possible inclusion of AARs occurring before the last 12 months is unlikely, because this information is systematically collected at every annual visit. When the date of the reaction was unknown, we checked that the reaction had not been registered at previous visits.

Accidental intake of foods depends on many factors. One is accessibility, which is higher for widely consumed foods, such as cow’s milk or egg. In a study of 88 children allergic to cow’s milk performed simultaneously with this study, our group found a frequency of AARs of 40%, that is, double that found in egg-allergic children [16]. This difference could be due to several factors: consumption of milk is higher than that of egg in Spanish households; milk and its proteins are found in many more foods; and the egg present in many of these foods could have lost its allergenicity after being heated during processing. Yu et al [7] calculated an annual incidence of 14.3% for accidental ingestion in a group of 252 Canadian children allergic to peanuts. Other studies carried out in North American children allergic to peanuts found annual rates of 33% to 50%, and the rate at 5 years varied from 55% to 75% [8,11,12]. In England, data on the annual rate of AARs in children allergic to peanuts, nuts, or both, decreased from 55% to 7% after implementation of an allergy management plan [13]. The low rate of AARs in Canadian children might be due to strict legislation in the labeling of food products and higher awareness in schools [7,17].

Spanish regulations on food labeling follow the recommendations of the European Union. When this study was performed (2004-2005), every ingredient had to be indicated; however, compound ingredients present in less than 25% of the manufactured product were excluded (this regulation does not apply for additives). Current legislation demands that manufacturers indicate the most allergenic foods, such as cow’s milk or egg, regardless of the amount present in the final product. This measure will undoubtedly contribute to the decreased risk of accidental exposure to foods in allergic children.

Moderate reactions were the most frequent (50%), followed by mild reactions (42%). Only 2 reactions (8%) were considered severe. Children allergic to cow’s milk more frequently presented mild (53%) and severe reactions (15%) [16]. In studies of children allergic to peanuts, the proportion of mild reactions was lower (22% to 43%), but other kinds of reactions were more frequent, possibly because of the nature of the allergen [7,18]. Nonetheless, differences in the criteria for classifying the severity of reactions makes comparison between studies difficult.

The most frequent route of exposure was oral. Four AARs were due to skin contact with egg, and all 4 cases were mild (urticaria): 1 was treated with antihistamines at the patient’s home, and the other 3 resolved without treatment. Reactions due to skin contact are well documented, especially in children highly sensitized to cow’s milk and peanuts [19,20], and in some cases, minimal amounts of the food can trigger these reactions, for example, through a contaminated object [21] or a kiss [22]. It is important that parents and caretakers are aware of this possibility in order to diminish the risk of AARs.

One of the objectives of the study was to identify risk factors in order to avoid AARs, especially the most severe ones. Of all the factors analyzed, higher egg white–specific sIgE and lower total IgE titers were associated with higher risk and more severe AARs. Previous studies of AARs in children allergic to cow’s milk [16] and to peanut [8] demonstrated that more severe AARs were associated with higher sIgE titers against the implicated foods. In addition, sIgE titers against an allergen indicate the intensity of sensitization. Higher titers are associated with a higher probability of reaction after intake of milk, egg, and other foods [15,23-25], with lower doses of food to trigger symptoms [26], with worse prognosis of the clinical course in patients with cow’s milk and egg allergy [2,27,28], and with more severe reactions in double-blind placebo-controlled food challenges in children allergic to egg or peanut [29,30]. However, other authors did not find an association between serum sIgE concentrations and severity of the reaction in patients allergic to peanuts and tree nuts [31,32]. Furthermore, anaphylactic reactions can occur with a low sIgE level, and no sIgE level can predict the severity of a reaction.

Lower concentrations of total IgE were also associated with a higher risk of AARs. Children with AARs had a higher titer of sIgE against egg white (see above) and a lower total IgE titer, thus accounting for the higher sIgE to total IgE ratio.
than the group of patients who did not present AARs. This ratio has been used elsewhere. Mehl et al [33] compared its ability to predict symptomatic food allergy with that of sIgE alone and found no differences between the two. Di Lorenzo et al [34] used the ratio to predict the clinical outcome of specific immunotherapy and found an advantage of the ratio over sIgE or total IgE alone. The relative effect of sIgE and total IgE on the risk of AARs is consistent with the idea that the intensity of the response of effector cells, basophils, and mast cells to a specific allergen depends on the fraction of the cell membrane occupied by sIgE against this allergen. In other words, the effect depends on the proportion of allergen sIgE/cell compared with total IgE. This feature would be of special interest in sensitization to multiple allergens [35]. Other factors related to the intensity of the basophil response include the density of high-affinity IgE receptors in the cell membrane, the number of IgE-binding epitopes of a single molecule, and the nature of antigen-antibody complex aggregates.

Our study showed that the frequency of AARs in a group of egg-allergic children was considerably lower than that of children allergic to cow’s milk. Severe reactions were scarce (8%) and in no cases needed hospitalization. In this group of children, higher egg white sIgE titers and lower total IgE titers were risk factors for AARs and more severe reactions.

A collaborative effort to decrease the number and severity of AARs must be made by health care professionals, allergists, and pediatricians who are aware of the extent the problem. Parents and caretakers should attempt to prevent accidental intake. The health authorities must improve and enforce regulations on food labeling and encourage public awareness of them. Finally, food manufacturers should provide precise information about the contents of their products, and professionals such as restaurateurs, pastry chefs, and bakers who use egg in the production of foods to be sold without wrapping should also alert customers to allergen content.

References


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