Corrélation entre le taux d'IgE spécifiques et la sévérité de la réaction chez les patients allergiques à l'oeuf

BENHAMOU, Avigael Hanna

Abstract

Les taux d'IgE spécifiques sont utiles au diagnostic de l'allergie à l'oeuf. Cependant, le rapport de ces taux avec la sévérité de la réaction n'a pas été étudié. Cette étude a pour but de déterminer si les taux d'IgE peuvent être prédicifs de la sévérité de la réaction allergique. Nous avons revu les tests de provocation orale à l'oeuf entre 2003 et 2005 à l'Unité d'Allergologie Pédiatrique. Nous avons analysé 51 tests dont 69% étaient positifs. Les IgE spécifiques au blanc d'oeuf variaient statistiquement significativement entre les patients avec réaction absente, modérée ou sévère. Les patients avec tests négatifs avaient un taux médian d'IgE spécifiques à 1.17, ceux avec réaction modérée à 2.47 et ceux avec réaction sévère à 3.70 kU/1 (p=0.006). Nos résultats montrent donc une corrélation entre le taux d'IgE spécifiques et la sévérité de la réaction clinique à l'oeuf.

Reference

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Correlation between specific immunoglobulin E levels and the severity of reactions in egg allergic patients


Different studies proposed specific immunoglobulin E (IgE) cut-off levels for the diagnosis of egg allergy. Little is known if IgE titres could be helpful for prediction of the severity of the reaction. The aim of this study was to determine whether IgE titres are associated with the severity of the reaction during a standardized egg challenge. We reviewed data obtained during oral challenge tests to egg performed between 2003 and 2005, and attributed a clinical score to the positive reactions. Serum specific IgE levels were analysed in relation with the severity of the reaction. We analysed data from 51 oral food challenges to egg, raw or cooked. Sixteen challenges (31%) were negative and 35 (69%) were positive of which 13 challenges (37% of positive reactions) elicited a severe reaction. IgE levels in our patients ranged from undetectable to 14.90 kU/l. We could determine a cut-off level of 8.20 kU/l for a 90% probability of clinical reactivity. IgE titres were statistically significantly different between the patients with absent, mild and moderate or severe reaction. Patients with negative challenge had IgE levels between 0.33 and 6.41 kU/l (median 1.17), those with mild and moderate reaction had IgE levels ranging from 0.35 to 14.90 (median 2.47) and patients with severe reactions had IgE between 1.18 and 11.00 (median 3.70) (p = 0.006). Our results show a correlation between IgE titres and the severity of the clinical reaction to egg. IgE titres may help to determine the potential risk of a reaction to eggs.

Food allergy is a frequent problem in the paediatric population, affecting about 6–8% of children less than 3 yr of age (1, 2). The most common offending foods are milk, followed by hen’s egg, peanut, wheat and soy (3). Hen’s egg allergy affects as much as 1.6% of children before their third birthday (4), with almost all children suffering from IgE–mediated reactions. Anaphylaxis to egg can be severe, as fatal reactions have been reported (5). Egg is ubiquitous in most type of cuisines as well as in processed foods making complete avoidance difficult (6). Consequently, the risk of accidental exposure is important when compared with other foods such as fish.

Accurate diagnosis of food allergies is warranted by a proper history correlated to immunoglobulin (Ig)E tests (skin prick tests and/or antigen-specific IgE in the serum) completed in unclear cases by standardized food challenge. In order to reduce the need for food challenges, Sampson et al. (1) proposed cut-off levels of allergen-specific IgE for predicting clinical allergic reactivity to egg, milk, peanut and fish. These initial studies were followed by others, with a large variety of cut-off levels identified (7–9,10). It became apparent that cut-off levels were most dependent on the age and the type of food-induced reactions the patients were having.
However, the studies cited above did mostly set cut-off levels for the diagnosis, but did not validate IgE titres for the prediction of the severity of the reaction. Recently, Hourihane et al. developed a scoring system for the severity of a food-induced allergic reaction and correlated symptoms elicited by peanut challenges with peanut specific IgE titers (11). They found an association between IgE levels and the clinical reactivity. However, clinical reactivity can vary for specific foods and these data to peanuts cannot be generalized to all foods. This issue has practical implications, as a frequent question asked by the parents is whether lower levels of IgE are indicative of a lower risk of a severe reaction after accidental ingestion of a given food (12, 13). The aim of our study was to determine whether IgE titres were associated to the severity of the reaction during a standardized egg challenge.

Patients and methods

Patients

We reviewed clinical data obtained during all oral challenge tests performed in our clinic between 2003 and 2005 for the diagnosis or follow-up of immediate, IgE-mediated allergy to egg. We analysed data from 35 children (11 females and 24 males) on 51 oral food challenges to egg, raw or cooked, performed between January 2003 and December 2005. Thirty-three challenges were to raw egg and 18 to cooked egg. The median age of the patients was 3.9 yr (range 16 month–11.9 yr). Ten additional challenges were not analysed because of incomplete data or a time interval above 6 month between the IgE measurement and the oral challenge. Thirty-six patients had a history of past or current allergy to other foods, mostly to various nuts, milk and peanuts. Serum was obtained for quantification of egg white-specific IgE antibody titres on the day of the food challenge, or within a time range of <6 month before. Serum samples were analysed using the UniCAP System™ (Phadia, Uppsala, Sweden) according to the manufacturer’s instructions.

All data were treated confidentially and consulted only by the investigating physicians. The study was reviewed and approved by the ethics committee of the Department of Paediatrics.

Oral food challenges

Oral food challenges were performed according to previously published guidelines (14) when the diagnosis of IgE-mediated egg allergy was suspected. Children < 3 yr of age and children with immediate-type reactions were tested by an open food challenge. Children with atopic dermatitis or potentially presenting with equivocal reactions such as oral pruritus were tested by double-blind, placebo-controlled food challenges (DBPCFC). Food challenges were not performed in children with a convincing history of a severe reaction <2 yr ago and/or a high level of specific IgE according to previously published cut-off numbers (7). Children taking anti-histamines were asked to avoid them at least 24 h before provocation but topical steroids were authorized. Children were admitted to our day-clinic in the morning in a fasting state. Challenge material was either pasteurized raw egg, or cooked egg boiled for 10 min for open challenges or egg hidden in a chocolate tasting preparation for DBPCFC. The initial challenge dose and the following doses were set according to the history of the last reaction, but were similar in most patients (raw egg: 2.5, 5, 7.5, 15 and 15 g; cooked egg 3, 6, 10, 15 and 16 g). When the patient tolerated the first dose, the following ones were given every 15 min. When a reaction to a very low dose was suspected, the first challenge dose was 0.5 or 1 g. According to symptoms observed during the challenges, the doses and the time interval between two doses were adapted. The challenge was interrupted when children demonstrated unambiguous clinical reactivity (14) or after the administration of 45 g of egg. All children were then observed for at least 2 more hours after the end of the feeding.

Scoring of the reactions elicited by the food challenge

The food challenge was considered as positive if the patient presented objective clinical signs such as urticaria, angio-oedema, wheezing, cough, rhinorrhea, conjunctival redness, diarrhoea, vomiting, agitation and tachycardia. Abdominal pain, although a subjective sign, was also taken in account but only if present with at least one of the objective sign. The food challenge results were scored as negative, mild to moderate or severe using a clinical reference table adapted from a previous publication (15) (Table 1).

Statistical analysis

Demographic characteristics of the study population were described using proportions or median and ranges. Contingency tables were analysed using the Fisher’s exact test. IgE levels between groups were compared using the Mann–Whitney test for two groups or the Kruskal–
Wallis test for multiple groups. Correlation between IgE and threshold dose was analysed using Spearman rank correlation. A probability (p) value <0.05 was considered significant. A logistic regression model was obtained using the p value of a positive challenge test result as the dependant variable and the natural logarithm of IgE levels as the independent variable: \( \ln(1/p) = a + b \ln(\text{IgE}) \), where \( a \) is the constant of the model and \( b \) the model coefficient associated with the independent variable. From this model was derived a receiver operating characteristic curve (ROC) plotting sensitivity vs. 1-specificity (likelihood ratio) for each cut-off value of \( \ln(\text{IgE}) \) and reflecting the discriminant capacity of the model. The probability of a positive challenge test giving a specific \( \ln(\text{IgE}) \) level was determined using the following formula derived from the logistic regression model:

\[
p = \frac{1}{1 + e^{-a-b \ln(\text{IgE})}}
\]

Results

Challenge results

Sixteen challenges (31%) were negative and 35 (69%) were positive of which 13 challenges (37% of positive reactions) elicited a severe reaction. Table 2 lists the symptoms provoked during food challenges. Symptoms started within minutes to 2 h after giving the first dose.

IgE cut-off levels for prediction of clinical reactivity

Immunoglobulin E levels in our patients ranged between undetectable (<0.35 kU/l) and 14.90 kU/l. The parameters of the logistic regression model for a positive challenge test result from our population were \( a = 0.3583385 \) (95% CI: 0.3241864–1.040863) and \( b = 0.9239563 \) (95% CI: 0.2260884–1.621824). The ROC showed an area under the curve of 0.741 indicating poor discriminant diagnostic capacity. Using different IgE titres, we calculated the sensitivity, specificity as well as the predictive positive values (PPV) and predictive negative values (NPV) of the test (Table 3). The PPV and NPV were calculated for the general population with an estimated rate of 1.6% of egg allergy (4), with the rate of allergy in our study population (69%), as well as by considering a prevalence of 10% in a ‘hypothetical, normalized’ population as suggested earlier (9). No optimal IgE cut-off level associating a high sensitivity and specificity could be determined. We then calculated the predicted probabilities of having a positive challenge to eggs at a given

<table>
<thead>
<tr>
<th>Grade</th>
<th>Skin</th>
<th>Gastro-intestinal tract</th>
<th>Respiratory tract</th>
<th>Cardio-vascular</th>
<th>Behavioural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate</td>
<td>Localized or generalized</td>
<td>Oral tingling, pruritus,</td>
<td>Nasal congestion</td>
<td>Change in</td>
<td>Change in</td>
</tr>
<tr>
<td></td>
<td>pruritus, flushing,</td>
<td>oral “tingling,” mouth</td>
<td>and/or sneezing</td>
<td>activity level</td>
<td>activity level</td>
</tr>
<tr>
<td></td>
<td>urticaria and angioedema</td>
<td>swelling, nausea and/or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>Any of the above</td>
<td>Any of the above</td>
<td>Rhinorrhea, marked</td>
<td>Tachycardia</td>
<td>Change in</td>
</tr>
<tr>
<td></td>
<td>plus repetitive vomiting and/or</td>
<td>plus repetitive</td>
<td>congestion,</td>
<td>dysrhythmia</td>
<td>activity level</td>
</tr>
<tr>
<td></td>
<td>diarrhoea</td>
<td>vomiting and/or</td>
<td>sensation of</td>
<td>and/or mild</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>diarrhoea</td>
<td>throat pruritus</td>
<td>hypotension</td>
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<td></td>
<td></td>
<td></td>
<td>or tightness</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>hoarseness,</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>‘barky’ cough,</td>
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<td></td>
<td></td>
<td></td>
<td>difficulty</td>
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<td></td>
<td></td>
<td></td>
<td>swallowing,</td>
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<td></td>
<td></td>
<td>dyspnea,</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>wheezing,</td>
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<td></td>
<td></td>
<td></td>
<td>cyanosis</td>
<td></td>
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</tbody>
</table>

The grading is based on the organ system most affected, e.g. if severe respiratory symptoms are present but only mild gastro-intestinal symptoms, then the anaphylaxis severity score would be ‘severe’. Adapted from Sampson (15).

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Behavioural n (%)</th>
<th>Gastro-intestinal tract n (%)</th>
<th>Skin n (%)</th>
<th>Respiratory tract n (%)</th>
<th>Cardio-vascular n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mild and moderate</td>
<td>22</td>
<td>8 (36)</td>
<td>18 (82)</td>
<td>15 (68)</td>
<td>7 (32)</td>
</tr>
<tr>
<td>Severe</td>
<td>13</td>
<td>4 (30)</td>
<td>12 (92)</td>
<td>4 (30)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Total positive</td>
<td>35</td>
<td>13 (37)</td>
<td>31 (88)</td>
<td>20 (57)</td>
<td>12 (34)</td>
</tr>
</tbody>
</table>

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specific IgE value. We determined that this value with a 95% predicted probability was 17.40 kU/l, which is outside the range of our data, and with a 90% predicted value at 8.20 kU/l (Fig. 1).

IgE titres according to the severity of the challenge

We then analysed IgE titres according to the severity of the reaction during the food challenge. The group with a negative challenge had IgE levels between 0.35 and 6.41 kU/l (median 1.17). The patients with mild reaction had IgE levels ranging from 0.35 to 14.9 (median 2.47). The patients with severe reactions had IgE between 1.18 and 11.00 (median 3.70) (Fig. 2). Data analysis by the Kruskal–Wallis test showed a statistically significantly difference between the three groups (p = 0.006).

Severity of food challenge reactions and IgE titres in raw egg vs. cooked egg challenges

Immunoglobulin E titres were analysed comparing the two groups of patients (raw vs. cooked egg with positive challenges) (Fig. 3). Statistical analysis revealed that the IgE titres were significantly higher in patients challenged positive to cooked egg than to raw egg (p = 0.016 by Mann–Whitney test). Of the 33 challenges with raw eggs, seven were negative, 16 were rated as mild or moderate and 10 as severe. Nine of the 18 challenges with cooked egg were negative, six

![Fig. 1. Probability of reacting to egg at a given immunoglobulin E value (ln scale).](image1)

![Fig. 2. Whisker’s box plots for immunoglobulin E titres to egg white in patients with no clinical reaction, mild and moderate reactions, or severe reactions during a food challenge.](image2)

![Fig. 3. Whisker’s box plots for immunoglobulin E titres to raw or cooked egg white in patients with a positive food challenge.](image3)
mild to moderate, and three severe. No statistically significant difference was observed for the severity of the reaction between patients challenged with raw or with cooked eggs ($p = 0.1$ by Fisher's exact test).

Threshold dose eliciting a reaction and severity of the reaction

Next, we determined if severe reactions were starting with lower doses, when compared with mild and moderate reactions. In challenges with a mild and moderate reaction, the median threshold dose was 6 g (range: 2.5–20 g), and in challenges with severe reactions the median threshold dose was identical (6 g, range: 0.5–15 g; $p = 0.78$ by Mann–Whitney test). These results were obtained by pooling data from challenges with raw and cooked egg, as statistical analysis showed no difference of threshold dose between both groups.

We then correlated IgE values to the threshold dose and found no statistically significant relation by Spearman’s correlation (Fig. 4).

**Discussion**

Measuring specific serum IgE titres has shown to be helpful in the prediction of allergy or tolerance in children with a possible diagnosis of IgE-mediated food allergy. In this study, we could demonstrate that serum IgE to egg white is predictive of the severity of the reaction to egg during a food challenge. We also confirm that IgE titres are highly dependant of the study population for the diagnosis of egg allergy.

For the last 30 yr, clinicians have largely relied on standardized food challenges such as DBPCFC for diagnosis of unclear cases of food allergy (16, 17). More recently, various studies have proposed ‘cut-off’ value of antigen-specific serum IgE or weal diameter sizes for the diagnosis of food allergy, to reduce the number of food challenges (8, 18). Sampson and Ho identified PPV and NPV values of different food-specific IgE antibodies such as milk, egg and peanut using the CAP-FEIA system (9). They found that, in their population mainly referred for severe atopic dermatitis, an egg-specific IgE cut-off level for a >95% of PPV was 6 kU/l, >90% of PPV was 2 kU/l and >90% of NPV was 0.6. These initial studies were followed by a publication by Boyano et al. showing that the cut-off point for a 90% probability of allergy to egg was above 0.35 kU/l, i.e. the level of detection for this method (19). Osterballe and Bindslev-Jensen determined a similar level (1.5 kU/l) for a 95% accuracy (20). However, Celik-Bilgili et al. found a much higher value (10 kU/l with a 95% accuracy in their population of young children (median of 13 month) with predominantly atopic dermatitis (21). These studies clearly show that IgE values have to be considered according to the symptoms and the age of the patients (22).

We could determine a cut-off level of 8.20 kU/l for a 90% reaction probability. This level is above the levels published previously and emphasizes the importance of considering titres in a specific population for the prediction of clinical reactivity. When considering the 95% PPV determined by Sampson (9), we had 10 challenges with IgE levels above 6 kU/l and all but one reacted. When using the 90% PPV, we had 29 challenges with IgE levels above 2 kU/ml of which four challenges were negative. In our study, IgE levels were significantly higher in allergic patients but the absence of measurable egg-specific IgE did not exclude a reaction. This convinced us that we need to consider a food challenge in patients with a history compatible with an egg allergy but low or negative specific IgE.

Our results confirm that egg-specific IgE titres have to be interpreted specifically to a given population, and that they might provide a help in deciding the indication for a food challenge, according to the risk of reaction to the test, or of unnecessary diet acceptable to the patient and the family.

We next looked at the type of reactions our patients had during food challenges. Unlike previous studies (9, 20, 21), skin symptoms were not the most frequent complain of our patients but 86% of them had gastro-intestinal reactions. This difference of presentation can be attributed to the fact that our patients where not referred for evaluation of atopic dermatitis but mainly because of a suspected immediate reaction to egg. The severity of the reaction correlated with the IgE
level, as none of the patients with very low levels (<1.10 kU/l) had a severe reaction. We could also show that IgE titres were discriminatory of the severity of the reaction at the food challenge. Previously, Sampson and Ho failed to show a correlation between IgE values to egg and the severity of the reaction (9), but Hourihane et al. have shown a clear association between peanut-specific IgE titres and challenge scores (11). Most importantly, they have also shown that there is a poor correlation between the severity of the reported reactions in the community and those elicited by low-dose DBPCFC. We emphasize that the results presented here only predict the severity of an allergic reaction to egg during a food challenge, but that it was not our aim to study IgE titres and the prediction of the severity of a reaction in the community, which is most often related to the dose ingested by accident.

An issue often neglected when studying egg allergy is the reactivity to cooked or raw egg. Indeed, egg proteins have different allergenic properties and some are partially inactivated by cooking (23, 24). As in egg allergic patients, tolerance to cooked egg usually develop before tolerance to raw egg, we considered initially challenging older patients with prolonged egg allergy to cooked eggs. In our studies, patients with higher IgE levels were in general challenged to cooked eggs whereas patients with lower levels were challenged to raw egg but tolerated cooked eggs. Nevertheless, the primary aim was to examine IgE levels and the severity of the reaction, and we could show that there was no difference between patients challenged to cooked eggs or to raw eggs. However, we have a clear bias of selection that must be considered when interpreting IgE cut-off levels for clinical reactivity. We partially relied on previously published cut-off levels and did not challenge patients with very high levels of IgE. This might not have influenced our data as the comparison of the retrospective and the prospective study done by Sampson showed little difference (7, 9).

In conclusion, the results presented here show a clear correlation between IgE titres and the severity of the reaction during a standardized challenge to egg. IgE titres may help to determine the potential risk of an egg challenge and if the challenge is indicated at a given time, or may suggest starting a food challenge with a low initial dose.

References


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