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EXPERIMENTAL ALLERGY AND IMMUNOLOGY

Tolerance to egg proteins in egg-sensitized infants without previous consumption

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Abstract

Background: Egg-sensitized infants who have never eaten egg may react at first ingestion. We sought to determine the association between skin prick test (SPT) and specific IgE (sIgE) to egg proteins (EP) and oral food challenge (OFC) outcomes to find cut-off points which can diagnose egg allergy.

Methods: One hundred and fifty-four infants up to 18 months, with cow's milk allergy (CMA) and/or atopic dermatitis (AD) without previous egg consumption, were recruited. SPT to EP were performed. If it was positive, sIgE was performed. If positive SPT and/or sIgE ($n = 94$), OFC was performed between 12 and 18 months. Receiver operating characteristic (ROC) curves were plotted, and the outcome of the OFC was related to SPT and sIgE. The cut-off points with the best diagnostic accuracy were found.

Results: Ninety-four patients were sensitized to egg (69%) and 60 nonsensitized (31%). Of the sensitized, 27 tolerated cooked (CE) and raw egg (RE) (28.7%). Sixty-seven were allergic (71.3%): 29 reacted to CE, seven to egg yolk (EY) and 22 to egg white (EW) and 38 reacted to RE. 69.2% tolerated CE. EW SPT and ovalbumin (OVA) sIgE have the best area under the curve (AUC). The higher positive predictive values (PPV) were obtained for EW SPT and EW sIgE.

Conclusions: In egg-sensitized infants with EW SPT ≥ 8 mm and/or EW sIgE ≥ 8.36 KU/l, egg diagnostic OFC can be avoided as there is 94% probability of becoming positive. In the other patients, OFC should be performed safely and early to avoid unnecessary diets.

Food allergy (FA) is an important health issue, and it affects 6–8% of children under the age of 3 years (1). In the first 2 years, there is an incidence of symptomatic egg allergy of 2.5% (2–4). Egg sensitization is frequent during the first year, specially associated with cow's milk allergy (CMA) (5) and atopic dermatitis (AD) (3, 6). It can occur from the passage of proteins during breastfeeding or by skin damage (7).

Many studies have addressed the frequency of sensitization to food allergens (6), but the likelihood of infants, sensitized to egg, of having reactions when they first receive egg and the possibility of prediction remains to be fully elucidated (7).

Better knowledge of the accuracy of skin prick test (SPT) and sIgE levels would help to identify egg-allergic between

sensitized infants (8, 9). The current gold standard for the diagnosis of food allergy remains the double-blind, placebo-controlled food challenge (DBPCFC) (10). As oral food challenges (OFC) are risky, objective diagnostic criteria to identify patients most likely to pass them are of great interest (11, 12). Moreover, as early weaning is becoming fashionable, the safe introduction of foods is important in high-risk infants (13).

The aim of this study was to determine the association between the level of SPT and sIgE to egg proteins (EP) and the OFC outcome in egg-sensitized infants who have never ingested egg to find cut-off points which can accurately diagnose egg allergy, avoiding unnecessary oral challenges.

Methods

Study population

We searched a population where there is high egg sensitization prevalence. One hundred and fifty-four infants under 18 months, with the diagnosis of IgE-mediated CMA and/or AD without previous egg consumption, were prospectively and consecutively recruited from Paediatric Allergy and Clinical Immunology Department, Sant Joan de Déu Hospital, Barcelona, between October 2010 and October 2011. All consented to participate. SPT to EP were performed and, if positive, sIgE. According to SPT, children were included in the 'egg-sensitized group' (positive SPT) or the 'non-egg-sensitized group' (negative SPT). The egg-sensitized group included 94 infants under 18 months, mean age 6.7 months (range 1–16 months), 57 boys (63.1%) and 37 girls (36.9%), 33 CMA (35.2%), 35 AD (37.2%) and 26 CMA + AD (27.6). The non-egg-sensitized group included 60 infants: mean age 6 months, (range 1–18 months), 34 boys (56.6%) and 26 girls (43.4%).

Study design and methods

The study was approved by the hospital's ethics committee, and informed consent was obtained. SPT to egg white (EW), egg yolk (EY), ovalbumin (OVA) and ovomucoid (OVM) were performed on the forearm, with 1 mm lancet and commercial extracts (Stallergenes Iberica, S.A.). A negative saline and a positive histamine control were used. A wheal of ≥ 3 mm (major diameter) was considered positive according to the EAACI (European Academy of Allergy and Clinical Immunology) position paper (14). SPT was performed at diagnosis in all children and during the 3 months previous to the OFC in

sensitized. Blood samples were taken, and serum EP sIgE concentrations were measured with the Thermo Fisher ImmunoCAP-System, in sensitized patients, at diagnosis and just before OFC. Above 0.35 KU/l, sIgE was considered positive.

Every infant in the egg-sensitized group underwent an OFC, between 12 and 18 months, in our hospital, in a medically supervised setting with emergency medications. A single-blind challenge (SBC) was performed with EY, EW and raw egg (RE), according to EAACI guidelines (15) and regardless of the results of the SPT and sIgE. This procedure started with 1/8 of masked boiled EY, followed 1 h later with 1/4 of an EY and ending, 1 h later, with 1/2 of an EY. If there was no reaction, 3 h later, the same procedure was used with boiled EW. If negative, on the next day, OFC was carried out with masked RE. A positive challenge was classified as immediate (≤ 2 h) or late reactions (>2 h). The development of one or more of the following objective criteria was used to define a positive OFC: persisting itching, noncontact urticaria persisting for at least 5 min, angioedema, eczema exacerbation, rhinoconjunctivitis, vomiting and circulatory or respiratory compromise. A paediatric allergy specialist scored the symptoms. Possible late reactions were checked by telephone call.

The infants who completed the OFC without reactions were named 'egg tolerant'. The ones who tolerated cooked egg (CE) but no RE, 'cooked egg tolerant'. The ones with immediate reactions during the OFC were classified as 'egg allergic'. Tolerant patients were checked 1 month later to confirm the introduction of egg without reactions. The non-egg-sensitized children were told to introduce egg in their diets at home (16). They were examined for reactions by telephone. If any symptoms had happened, an OFC was performed in our hospital to confirm egg allergy (Fig. 1).

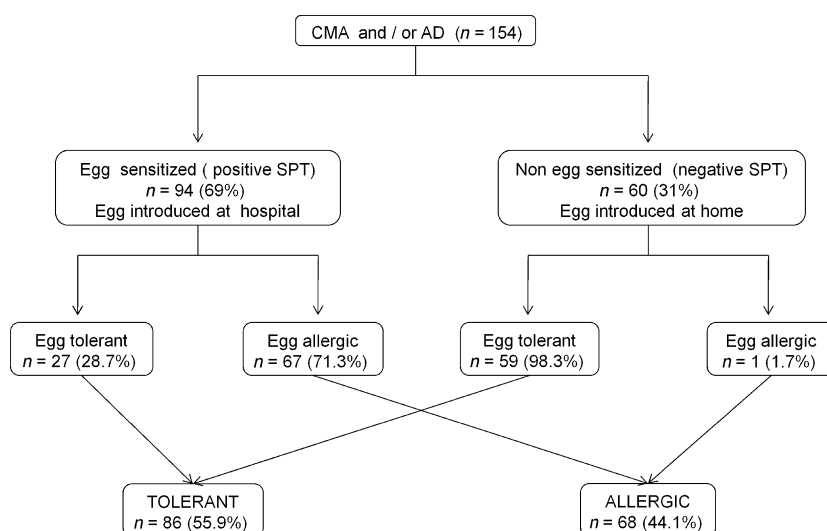


Figure 1 Patient classification relating SPT and outcomes after OFC. According to SPT results, children with CMA and/or AD were included in either the 'egg-sensitized group' (positive SPT, $n = 94$) or the 'non-egg-sensitized group' (negative SPT, $n = 60$). In the first group, egg OFC was undertaken at hospital, while, in the second,

it was introduced at home. A total of 28.7% of the egg-sensitized patients were tolerant at OFC; 71.3% were allergic. Among the non-egg-sensitized patients, only one elicited reaction, at home, with the introduction of RE (reaction which was verified with an OFC at hospital).

Statistical analysis

Mean, minimum and maximum values were used to describe continuous variables, and absolute and relative frequencies to describe categorical variables. SPT and sIgE sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV), and positive and negative likelihood ratios (LR) were calculated in egg-sensitized patients. The diagnostic accuracy of the SPT and sIgE to EP was evaluated with the area under the receiver operating characteristic (ROC) curve. Nonparametric test (Wilcoxon and Mann–Whitney *U*-test) was used to compare the allergic and tolerant groups. *P*-values <0.05 were considered significant.

Results

The egg-sensitized group included 94 infants, and egg was introduced at hospital. Twenty-seven infants were tolerant and 67 allergic. The non-egg-sensitized group included 60 infants. Egg was introduced at home. Fifty-nine were tolerant and one allergic (Fig. 1).

Egg-sensitized patients

Of the 94 sensitized patients, 27 tolerated CE and RE (28.7%). Sixty-seven were allergic (71.3%): 29 reacted to CE (30.8%), seven with EY and 22 with EW and 38 reacted to RE (40.5%). A total of 69.2% of the patients (65) tolerated CE (Fig. 2).

Forty (61.2%) of the 67 allergic patients suffered urticaria at OFC, 19 (28.3%) anaphylaxis (widespread urticaria + vomiting: 5, bronchospasm + urticaria: 4, rhinoconjunctivitis + vomiting + urticaria+angioedema: 2, vomiting + bronchospasm: 3, vomiting + bronchospasm + urticaria: 3, rhinoconjunctivitis + vomiting: 2), 3 (6.4%) vomiting, 3 (6.4%) rhinoconjunctivitis and 2 (3.3%) dermatitis worsening within the 3 h after OFC. No late reactions were recorded. Of the 67 patients who reacted, 24 had CMA (35.8%), 21 AD (31.3%) and 22 CMA + AD (32.8) without relevant differences between groups.

Skin prick test and sIgE at diagnosis were compared with the one before the OFC (mean time between both: 6 months). SPT had become negative in 14 of the 27 patients who tolerated egg (52%). In the other 13 (48%), there was a trend to maintain or decrease SPT size. Eighteen patients elicited negative sIgE before OFC (Table 1).

In allergic patients, there was a trend to increase SPT size ($P < 0.001$). All allergic patients elicited positive SPT before OFC (Table 1).

Patients allergic to CE elicited higher SPT and sIgE, mainly to OVM before OFC, than the ones only allergic to RE ($P < 0.001$) (Table 2).

Non-egg-sensitized patients

Only one patient nonsensitized to egg suffered urticaria after eating an omelette at home (1.6%). This reaction was confirmed after OFC at hospital. The symptoms observed were urticaria after having RE with tolerance to CE. The remaining 59 patients tolerated all kind of egg and egg-containing products at home (98.4%) (Fig. 1).

Test accuracy

Skin prick test and sIgE diagnostic accuracy for egg allergy and for CE allergy compared with RE allergy were evaluated with the ROC curves (Fig. 3). The results just before OFC were the ones considered (as far as these values had changed from the first results). The area under the curve (AUC) values were evaluated, and the optimal cut-off points obtained. They were calculated taking into account the highest positive likelihood ratios for egg allergy and the best sensitivity for cooked egg allergy.

For egg allergy, EW SPT and OVA sIgE had the best AUC (0.88 and 0.82, respectively). Sensitivity, specificity, PPV, NPV, positive LR and negative LR were calculated for the chosen cut-off points. The higher PPV were obtained for EW SPT and EW sIgE: 94.3% for 8 mm and 94% for 8.36 KU/l, respectively. For CE allergy, NPV of 92.8% for OVM SPT of 3.5 mm and NPV of 94.3% for OVM sIgE of 0.8 KU/l (Table 3).

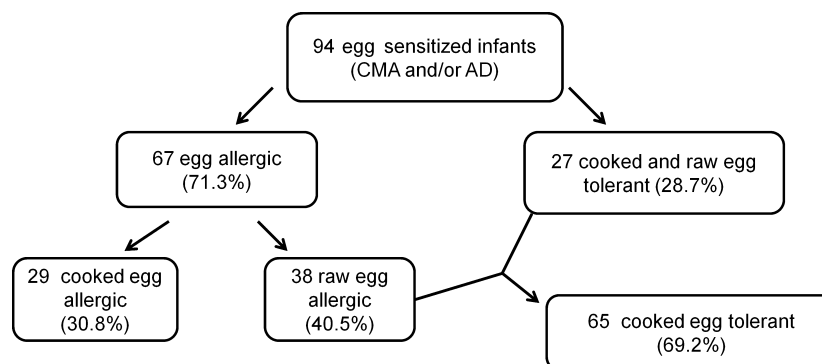


Figure 2 Sensitized infants. Of the 94 sensitized patients, 27 tolerated CE and RE (28.7%). Sixty seven infants were allergic (71.3%): 29

elicited reaction with CE (30.8%), seven with EY and 22 with EW and 38 reacted to RE (40.5%). 69.2% of the patients (65) tolerated CE.

Table 1 Skin prick test and sIgE in tolerant and allergic patients. In tolerant patients, there was a decrease in SPT if we compare the mean values at diagnosis (Initial) and just before OFC (Final), being *P*-value <0.05 only for EW (bold value). Allergic patients elicited positive SPT (>3 mm) before OFC (Final). In them, there was an increase in SPT values (*P* < 0.001) (bold values). This trend was not observed in sIgE values

Test	Initial mean (range)	Final mean (range)	<i>P</i>
Egg tolerant (<i>n</i> = 27)			
Yolk SPT(mm)	2.6 (0–5)	2.1 (0–10)	0.3095
White SPT (mm)	5.9 (2–11)	2.9 (0–11)	0.0030
OVA SPT (mm)	4.3 (0–14)	3 (0–15)	0.1338
OVM SPT(mm)	0.4 (0–4)	1.1 (0–7)	0.5588
Yolk sIgE (KU/l)	0.21 (0–1.46)	0.28 (0–1.99)	0.1371
White sIgE (KU/l)	1.68 (0–14.7)	1.72 (0–11.7)	0.0566
OVA sIgE (KU/l)	1.33 (0–15.8)	1.17 (0–11.7)	0.0585
OVM sIgE (KU/l)	0.07 (0–0.86)	0.77 (0–9.85)	0.8667
Egg allergy (<i>n</i> = 67)			
Yolk SPT (mm)	3.9 (0–11)	5.7 (0–14)	0.0007
White SPT (mm)	6.9 (0–15)	8.2 (2–15)	0.0019
OVA SPT (mm)	5.6 (0–16)	8 (0–17)	0.0000
OVM SPT (mm)	2.8 (0–14)	5.2 (0–17)	0.0003
Yolk sIgE (KU/l)	1.2 (0–6.78)	1.38 (0–7.56)	0.6908
White sIgE (KU/l)	7.36 (0–52.2)	7.70 (0–50.1)	0.0526
OVA sIgE (KU/l)	7.38 (0–55.7)	6.49 (0–65.6)	0.1711
OVM sIgE (KU/l)	1.48 (0–36.2)	3.68 (0–50.4)	0.2658

Discussion

Sensitized infants to any foods can display reactions at the first ingestion. Egg sensitization is the most prevalent especially in CMA and AD. It would be useful to determine whether these children would react at first egg ingestion. SPT and sIgE are the first determinations to take in account when food sensitization or FA is suspected. But, at present, only an OFC can lead us to the resolution of the quandary food sensitization vs FA.

We aimed to find the link between the level of SPT and sIgE to EP and the OFC outcome in egg-sensitized infants

who have never ingested egg. We found that EW SPT higher than 8 mm and EW sIgE higher than 8.36 KU/l have a high probability of eliciting a positive OFC.

As our research was on egg-sensitized infants, that is, children who had never ingested egg, SPT was first performed and sIgE performed only if the first was positive. Although both techniques are widely accepted in egg allergy diagnosis, some studies show a better sensitivity and NPV for SPT. A negative SPT, almost rules out egg allergy (4, 17, 18). Taking into account the characteristics of our study, we needed a high NPV test which allowed us to recommend the introduction of egg at home with the less possible risk. In fact, only one child reacted at home after eating raw egg. Although Mehl et al. (19) found, for hen's egg, in 27 of 268 (10%) children differing test results for SPT and sIgE in serum, their population was based on allergic children and not only sensitized as ours. Nevertheless, international guidelines advise SPT to be the first test to perform in the suspicion of allergy (4, 20, 21).

In a study by Monti et al. (7), 107 infants 1–19 months old with AD and sensitization to egg were evaluated, and the outcome of the OFC was related to SPT and sIgE. OFC was positive in 67.3% of the children. We have also included patients with CMA, finding a very similar percentage of egg allergy (71.3%). The cut-off point values they found as 100% predictive of egg allergy in this population were SPT to EY and OVA >5 mm and sIgE to OVA > 99 KU/l and to EY > 17.5 KU/l.

In another study by Dieguez et al. (5), 104 infants younger than 12 months with CMA and sensitization to egg were challenged, and it was related to SPT. The sensitization rate was 62.5%, very similar to ours (69%). OFC was positive in only 36.5% (71.3% in our study). These differences could be explained by the fact that they only performed an OFC with CE while we also tried RE where we found our higher allergic rate. Their optimal cut-off points (95% predictive of egg allergy) were EW SPT >6 mm and OVM SPT >5 mm. These differences with our cut-off points can be also justified by the fact that they only evaluated CE allergic infants as they more often show positive OVM.

Caffarelli et al. (22) studied 21 children, from 5 months to 4 years, sensitized to egg. The OFC resulted positive in 61%

Table 2 Skin prick test and sIgE comparison between CE and RE allergic patients. Patients allergic to CE elicited higher SPT and sIgE to OVM before OFC, than the ones only allergic to RE (*P* < 0.01)

Test	Cooked egg-allergic (<i>n</i> = 29) Mean (range)	Raw egg-allergic (<i>n</i> = 38) Mean (range)	<i>P</i>
Egg allergy (<i>n</i> = 67)			
Yolk SPT (mm)	6.3 (3–14)	5.3 (0–10)	0.3150
White SPT (mm)	8.6 (4–15)	8 (2–14)	0.3317
OVA SPT(mm)	8.7 (4–17)	7.4 (0–15)	0.1370
OVM SPT (mm)	8 (3–17)	2.9 (0–13)	0.0000
Yolks IgE (KU/l)	1.62 (0–7.34)	1.21 (0–7.56)	0.1099
White sIgE (KU/l)	10.1 (0.69–50.1)	5.95 (0–49.6)	0.0163
OVA sIgE (KU/l)	5.75 (0–22)	6.97 (0–65.6)	0.3524
OVM sIgE (KU/l)	8.01 (0–50.4)	0.79 (0–22.8)	0.0000

Bold values indicate statistically significative ones.

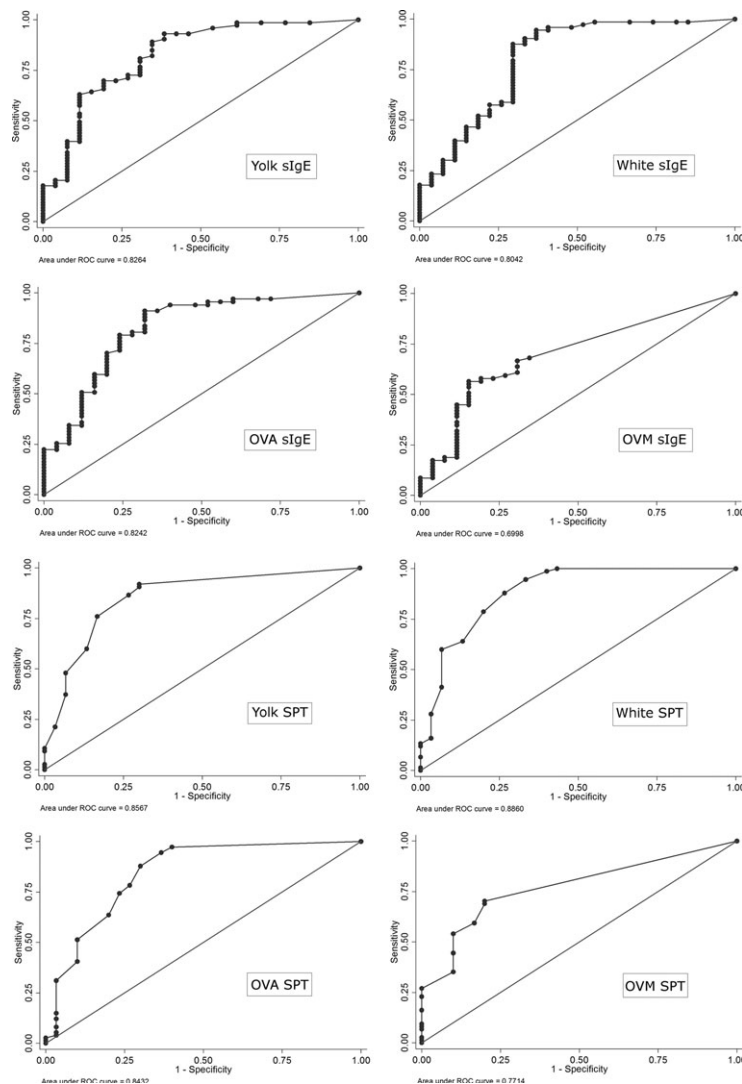


Figure 3 Receiver operating characteristic curves. EW SPT and OVA sIgE had the best AUC (0.88 and 0.82, respectively). OVM SPT and OVM sIgE had the worse (0.77 and 0.69, respectively).

of the cases and they found a good correlation of the OFC outcome and SPT with no advantages if sIgE was added. We found higher rates of allergic children probably because their patients' age was different to ours. Moreover, our OFC was performed between 12 and 18 months and, as known, tolerance increases with age.

Our study departs from a wider patient selection, as we recruited infants with CMA and/or AD, sensitized to egg. Our attempt was to represent all the egg-sensitized infant population.

The DBPCFC is the gold standard measure for FA. Although studies that rely on open food challenges (OpFC) in older children may be subjected to observer bias, this is not usually an issue in infants (23, 24). Although it could be considered as a weak point, the children in this study were 12–18 months old when challenged, not being able to report subjective symptoms. Nevertheless, a SBC was performed

with EY, EW and RE regardless of the results of the SPT and sIgE, according to EAACI guidelines (15). Diagnostic challenges are generally considered useful when the anticipated likelihood of passing a challenge without adverse reaction is around 50% (25). Another weak point in our study can be the fact that in nonsensitized infants, we did not perform any other test before introducing egg at home. But only one child reacted to RE.

We performed the ROC curve analysis to determine the optimal cut-off point of SPT and sIgE. Predictive values depend on prevalence; they cannot be applied to a population with a different frequency of the disease (7, 15). This is not a problem for LR_s. We chose the optimal cut-off points having in mind the best LR₊. In our study, EW SPT showed the best diagnostic accuracy. Whereas to evaluate OVM SPT and sIgE for CE allergy, we considered the highest sensitivity and NPV as prevalence lowers in this subtype of patients.

Table 3 Skin prick test and sIgE diagnostic accuracy for egg allergy in egg-sensitized infants. All values obtained acceptable AUC. The cut-off points with higher LR+ for each variable were chosen (bold values). The SPT value which obtained the best LR+, specificity and PPV was EW 8 mm (bold value). And the sIgE value with the best results was EW 8.36 KU/l (bold value). For CE allergy, the SPT and sIgE values which obtained better sensitivity and NPV were OVM 3.5 mm and OVM 0.8 KU/l, respectively

	Area under the curve (95% CI)	Optimal decision point	Sensitivity %	Specificity %	PPV %	NPV %	+LR	−LR
<i>Egg allergy</i>								
SPT (mm)								
Yolk	0.85 (0.77–0.91)	6	53.2	90.4	93	46	5.5	0.5
White	0.88 (0.8–0.93)	8	64.5	90.4	94.3	51	6.7	0.3
OVA	0.84 (0.76–0.90)	10	32.2	90.4	89.2	35.2	3.3	0.7
OVM	0.77 (0.67–0.84)	5	56.4	90.4	93.5	45.9	5.9	0.4
sIgE (KU/l)								
Yolk	0.82 (0.73–0.89)	1.84	23.8	95.6	93	33.8	5.4	0.7
White	0.80 (0.7–0.87)	8.36	26.9	95.8	94	34.8	6.4	0.7
OVA	0.82 (0.73–0.89)	6.86	29.3	95.4	94	35.5	6.4	0.7
OVM	0.69 (0.59–0.78)	5.59	16.6	95.6	90.3	31.9	3.8	0.8
<i>Cooked egg allergy</i>								
SPT OVM	0.83 (0.7–0.88)	3.5	89.2	59.4	48.1	92.8	2.17	0.18
sIgE OVM	0.93 (0.84–0.98)	0.8	87.5	92	82.2	94.3	10.8	0.14

Our major finding was to come to the conclusion that EW SPT higher than 8 mm and EW sIgE higher than 8.36 KU/l in egg-sensitized infants without previous consumption show LR+ of 6.7 and 6.4, respectively, 90% and 95% specificity, and a PPV of 94% for both in defining the positive OFC outcome.

For egg allergy, sensitivity and NPV are low (64% and 51%, respectively, for EW SPT, and 26% and 34% for EW sIgE). These data bring about that patients with lower EW SPT and sIgE can be symptomatic at OFC. Moreover, three of our patients with sIgE lower than 0.35 KU/l were allergic at OFC. Negative sIgE levels do not rule out allergy. OFC should be performed in hospital.

Most of our patients were reactive to RE. The only non-sensitized patient who became allergic was to RE, so it can be recommended to start egg in the diet of these patients as usual (8). Early diagnosis in sensitized infants will avoid elimination diets as most will tolerate CE.

As SPT and sIgE values at diagnosis and just before OFC change, it is advisable to perform egg SPT in infants with CMA and AD at first visit and, if positive, just before the age in which egg should be introduced in the diet to decide an OFC.

In conclusion, in children younger than 18 months, more than half of the patients with CMA and AD without previous egg consumption are sensitized to this food and more than 60% of them will be allergic. We find very useful to

perform egg SPT right before the introduction of the food. In sensitized infants with EW SPT ≥ 8 mm and/or EW sIgE ≥ 8.36 KU/l, egg diagnostic OFC can be avoided as there is 94% probability of becoming positive. In the other patients, OFC should be performed safely and early to avoid unnecessary restrictive diets. A high rate of sensitized infants tolerated cooked egg (69.2%). Nevertheless, in children with EW SPT and sIgE higher than mentioned and OVM SPT lower than 3.5 mm and sIgE lower than 0.8 KU/l, an OFC to CE can be performed as there is a high tolerability rate.

Author contributions

Montserrat Alvaro and M^a Teresa Giner conceived the study. M^a Beatriz García-Paba, Montserrat Alvaro and M^a Teresa Giner designed the study. M^a Beatriz García-Paba made significant contribution to the acquisition, analysis and interpretation of the data. Montserrat Alvaro and M^a Beatriz García-Paba wrote the manuscript. All authors made substantial contributions to the design, collection and interpretation of data; they all critically reviewed and approved the final manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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