

Skin prick test predictive value on the outcome of a first known egg exposure in milk-allergic children

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Children with milk allergy have higher incidence of other food allergies, especially egg allergy. The objective of this study was to ascertain the accuracy of the prick test in children with IgE-mediated milk allergy for diagnosing egg allergy. Children under the age of 1 yr who came consecutively to Allergy Department 2003–05, and were diagnosed with IgE-mediated milk allergy were selected for this study. Egg introduction was completely avoided until the age of 14 months when clinical history, skin prick tests (SPT), specific-IgE antibodies determination and egg challenge test were performed. One hundred and four milk-allergic children were included. At least one positive prick test to any egg allergen was found in 65 out of the 104 (62.5%). Thirty-eight (36.5%) were allergic to egg proteins as well. Prick tests with egg white and ovomucoid (OVM) had the best diagnostic performances showing the largest areas under the receiver operating characteristic curve. The optimal diagnosis cut-off point was 6 mm for egg white and 5 mm for OVM. The positive likelihood ratios for these cut-off points were: 2.95 (95% CI: 1.74–4.99) for egg white prick test, and 20 (95% CI: 2.9–143.7) for OVM prick test. Children with specific IgE-mediated cow's milk allergy must be closely followed as a risk group for egg allergy. Early diagnosis is necessary and the SPT has shown itself to be a very useful tool for diagnosing immediate IgE reactions to egg on first known exposure.

MC Diéguez¹, I. Cerecedo¹, A. Muriel², J. Zamora², M. Sánchez-Cano¹ and B. De la Hoz¹

¹Servicio de Alergología, ²Unidad de Bioestadística Clínica, Hospital Universitario Ramón y Cajal, Madrid, Spain

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MCarmen D. Pastor, Hospital Universitario Ramón y Cajal Laboratorio de Alergia, planta 2 derecha Carretera de Colmenar Km. 9.100, Madrid, CP 28034, Spain

Tel.: +34 91 336 8341

Fax: +34 91 336 8693

E-mail: cdiéguez.hrc@salud.madrid.org

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Food allergy is the most frequent allergic pathology in early childhood, and milk is the most frequent food allergen. Two to three percent of the children have IgE-mediated milk allergy (1, 2). Previous studies have concluded that IgE-mediated milk-allergic children have a higher incidence of inhalant sensitization. Large groups of milk-allergic children have been followed up and inhalant sensitization with rhinitis or asthma symptoms has been found in 50% of the patients (3).

In Odense University Hospital, 39 milk-allergic children were followed over the course of 3 yr, recruited from a birth cohort. Forty-eight percent developed respiratory allergy with inhalant sensitization (4).

Similarly, it has been shown that IgE-mediated milk-allergic children have a higher incidence of other food allergies. Bishop et al. followed 100 milk-allergic children over a 5-yr period and found that 50% had adverse reactions to egg intake (5). In the above-mentioned Odense study, 38% of the patients developed adverse reactions to other foods, with egg white being responsible of 29% of the reactions (4). Higher prevalence of egg allergy in milk-allergic children has been described, with percentages ranging from 41% to 67% (6, 7).

All these studies point out milk-allergic children have a higher incidence of other food allergies including egg proteins. To prevent future adverse reactions when introducing new

foods, it would be clinically sound to identify those milk-allergic children who are more likely to develop egg allergy. The accuracy of the skin prick test (SPT) and specific-IgE antibodies in children with clinical history of adverse reactions after egg intake has been demonstrated in previous studies (8–16). The accuracy of these tests in children with atopic eczema who had not yet introduced egg proteins into their diets has been explored (17), but their accuracy in first known egg exposure in children without atopic dermatitis is still unknown.

The aim of this study was to estimate the diagnostic accuracy of the SPT with egg allergens in children with IgE-mediated cow milk allergy in first known egg exposure.

Materials and methods

Children who came consecutively to the Allergy Department at Ramón y Cajal Hospital in Madrid, 2003–05 and were diagnosed with cow's milk allergy (history of adverse reaction after milk intake with positive SPT with milk allergens and/or specific-IgE antibodies, and oral challenge test when necessary) were prospectively recruited. Those children with an anaphylactic reaction after milk intake, as well as patients with clinical history suggestive of a recent IgE-mediated milk-allergic reaction (< 6 months from last reaction), both with positive SPT and/or positive specific-IgE determination, were considered milk-allergic patients and were included in the study, although milk oral challenge test was not performed (18, 19).

So inclusion criteria were as follows:

- 1 IgE-mediated cow's milk allergy.
- 2 Children whose diets did not yet include egg proteins.

Following diagnosis, we gave the parents oral and written egg-avoidance instructions. All patients received the egg challenge test regardless of the result of the prick test, and vice versa. All of them were evaluated once in the time interval 12–15 months of age, and the following study was made:

- 1 Clinical history: To confirm a strict egg-avoidance diet.
- 2 Skin prick tests: Prick tests with egg white, yolk, ovalbumin (OVA), ovomucoid (OVM), ovo-transferrin (OVT) and lysozyme commercial extracts (Bial-Aristegui laboratories, Bilbao, Spain). Prick tests with other food commercial extracts of popular foods in Spanish

Mediterranean 1-yr-old children's diet were performed (fish mixture, nuts mixture, apple, peach, melon and lentil). Histamine (10 mg/ml) and physiological saline served as positive and negative controls respectively. A wheal of 3 mm or larger was regarded as positive, according to EAACI guidelines (20). SPTs were always performed by the same experienced nurses. The reader of the prick test result was blind to the results of the challenge test.

- 3 Egg challenge test: egg was introduced into the diet over a 2-day period. The first dosage was always one-fourth cooked egg yolk, gradually increasing to an entire cooked egg yolk. Cooked egg white was introduced next, gradually increasing the intake from one-fourth to one whole cooked egg white. This dietary change took place at the hospital for those children with a positive prick test to any egg fraction. Those patients with all negative egg allergen prick tests were introduced to egg at home, following the protocol described. Oral and written information was given to the parents about the treatment in the event of reaction after egg intake at home as well as an allergologist contact phone number. In case of reaction, a challenge oral test with egg was performed at the hospital to confirm the egg-allergy diagnosis and to rule out an incorrect classification because of doubtful reactions. Allergologist supervising egg oral challenge was blind to the results of the SPTs.

Egg challenge test classified children as follows:

- 1 Egg-allergic children: patient with cutaneous symptoms (urticaria and angioedema), digestive symptoms and/or respiratory symptoms within the 2 h following their first intake of egg.
- 2 Tolerant or non-allergic children: patients without any reaction after their first egg intake.

Tolerant patients were checked 1 month later to confirm that they had not had any reaction at home once egg proteins had been introduced into their daily diet.

Statistics

Median, minimum and maximum values were used to describe continuous variables, and absolute and relative frequencies to describe categorical variables. Sensitivity, specificity, positive (PPV) and negative predictive values (NPV), and positive and negative likelihood ratios of the prick test were calculated. The diagnostic accuracy of the prick test with egg

allergens was evaluated with the area under the receiver operating characteristic (ROC) curve. Chi-squared test or Fisher's exact test was used to compare the allergic and tolerant groups. p -values < 0.05 were considered significant. The SPSS program (version 10.0) was used.

Results

One hundred and four patients were included in the cohort, 57 of whom (54.8%) were male, 31 (30.4%) had at least one atopic parent, 60 (59.4%) had atopic dermatitis [diagnosed according to Hanifin and Rajka (21)], 17 (16.3%) had asthma and 52 (50%) had positive prick test to other tested foods (fish, nuts, apple, peach, melon or lentils).

Between the age of 12 and 15-month old, SPTs with egg allergens were given to all participating patients. Sixty-five out of the 104 (62.5%) had at least one positive prick test (Fig. 1). Thirty-eight patients (36.5%) out of the 104 milk-allergic children were also allergic to egg proteins. Thirty-seven were diagnosed during the egg oral challenge test. Only one patient from this group had every prick test with egg allergens negative. This child had had a slight cutaneous reaction after his first egg intake at home. An oral challenge test with egg had been performed on

this child at the hospital and the reaction had been confirmed. Sixty-six children out of the 104 (63.5%) tolerated the egg intake without any reaction (38 children with negative SPTs, at home and 28 with positive prick tests, at the hospital).

Prick test accuracy in the diagnosis of egg allergy

The diagnostic accuracy of the prick test was evaluated by ROC curve analysis. Areas under the curves (AUC) and optimal cut-off points [calculated as the maximum sum of sensitivity and specificity (22)] to every egg allergen are shown in Fig. 2. The largest AUC correspond to egg white and OVM prick tests and the smallest ones to the OVT and lysozyme prick tests. Sensitivity, specificity, PPV and NPV, and positive and negative likelihood ratios were calculated for the traditional 3 mm decision point and the optimal cut-off points calculated in our study (Table 1). In general, complete white egg prick test had higher sensitivity and OVM fraction had higher specificity.

Comparison of the egg-allergic group and the tolerant group

A significantly higher proportion of patients with atopic dermatitis and cutaneous hypersensitivity to other foods were found in the group of egg-

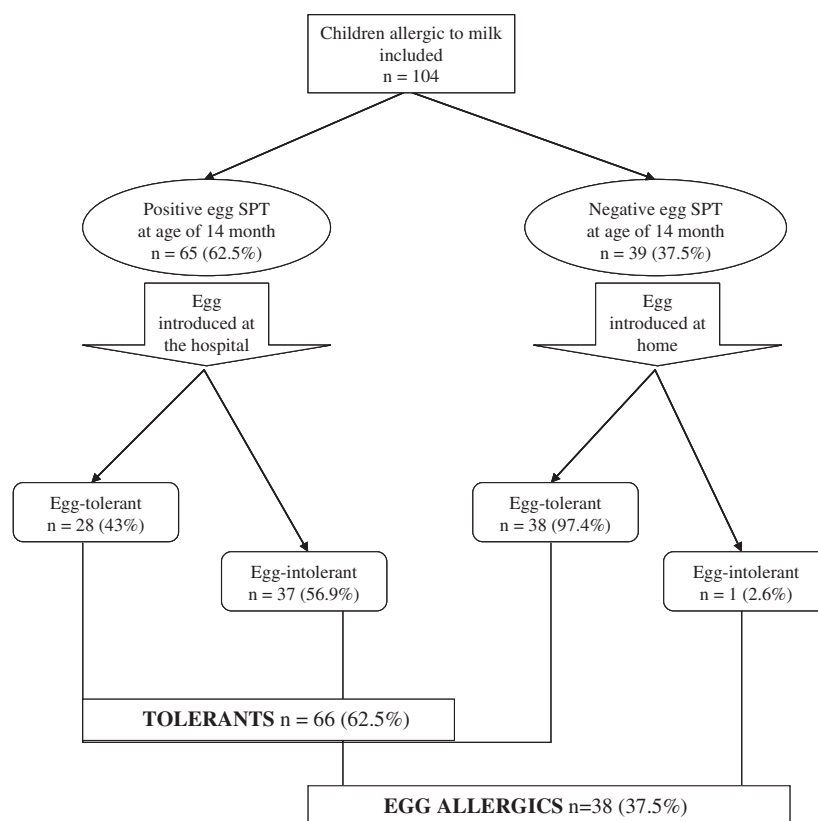
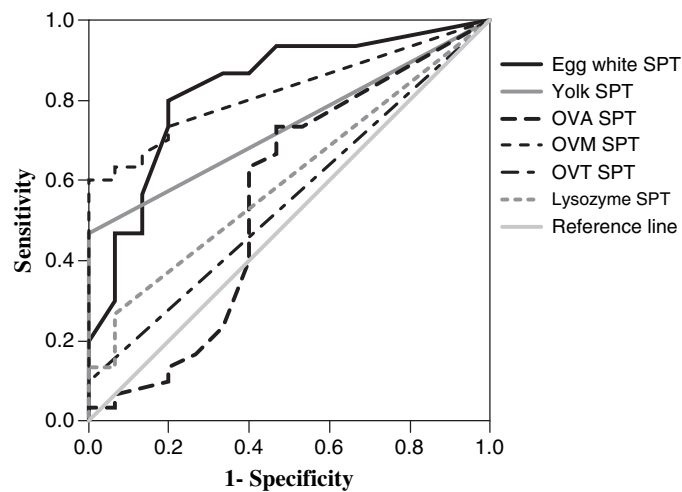


Fig. 1. Classification of patients skin prick test (SPT).



Allergen	Area under the curve (95% confidence interval)	Optimal decision point (mm)
EGG WHITE	0.83 (0.70–0.96)	6 mm
YOLK	0.73 (0.59–0.88)	3 mm
OVA	0.55 (0.36–0.75)	3 mm
OVM	0.82 (0.70–0.94)	5 mm
OVT	0.55 (0.37–0.72)	
LISOZIME	0.60 (0.43–0.96)	

Fig. 2. Diagnostic accuracy of the skin prick test (SPT) in egg allergy.

Table 1. Performance characteristics of egg white and OVM skin prick test at two different cut-off levels

	Egg white		OVM	
Cut-off level	3 mm	6 mm	3 mm	5 mm
Sn (95% CI)	94.6 (87.3–100)	81.1 (68.5–93.7)	66.7 (51.3–82)	58.3 (42.2–74.4)
Sp (95% CI)	40 (24.8–55.2)	72.5 (58.6–86.3)	85.3 (73.4–97.2)	97.1 (91.6–100)
PPV (95% CI)	59.3 (46.8–71.8)	73.2 (59.6–86.7)	82.7 (69–96.5)	95.4 (86.7–100)
NPV (95% CI)	88.9 (74.4–100)	80.6 (67.6–93.5)	70.7 (56.8–84.6)	69.4 (56.5–82.3)
+LR (95% CI)	1.58 (1.21–2)	2.95 (1.74–4.99)	4.53 (1.95–10.5)	20.42 (2.9–143.7)
–LR (95% CI)	0.14 (0.03–0.55)	0.26 (0.13–0.52)	0.39 (0.24–0.63)	0.43 (0.29–0.63)

Sn, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio, –LR, negative likelihood ratio; CI, confidence interval; OVM, ovomucoid.

allergic patients. No differences were found as to sex, atopic parents or asthma between the allergic and tolerant groups (Table 2).

Discussion

The present study has demonstrated that SPT performed with egg allergens are useful diagnostic tests in egg allergy even in children who did not introduce egg into their diet. Accuracy of white egg and OVM SPTs was very good in the diagnosis of those egg allergic children without history of adverse reactions after egg intake. In a similar study (17), Monti et al. (17) concluded

that children with atopic dermatitis may be sensitized to egg even if they have never eaten them, and display clinical hypersensitivity reactions when first exposed (67.3% positive challenges). As a difference, we have included a different risk group for egg allergy: milk-allergic children, including children with and without atopic eczema. The incidence of reactions to egg challenge on the first known exposure in our series was lower (36.5%). This fact may be explained because Monti's study included immediate (57%) and late reactions (atopic eczema exacerbations), while our study only included immediate IgE-mediated reactions.

Table 2. Clinical characteristics of egg-allergic patients and tolerant patients

		Allergic (n = 38)	Tolerants (n = 66)	p-value
Sex	Male	19 (50%)	38 (57.6%)	NS
	Female	19 (50%)	28 (42.4%)	
AD*	Yes	28 (75.7%)	33 (50%)	0.01
	No	10 (24.3%)	33 (50%)	
Other food allergies*	Yes	30 (81%)	22 (34%)	0.0004
	No	8 (19%)	43 (66.2%)	
Atopic parents	Yes	7 (18.4%)	25 (37.5%)	NS
	No	31 (81.6%)	41 (62.5%)	
BHR	Yes	8 (19%)	11 (15.6%)	NS
	No	30 (81%)	55 (84.4%)	

AD, atopic dermatitis; other food allergies: patients with at least one positive skin prick test to fish, fruits, nuts or legumes; BHR, bronchial hyper-responsiveness; NS, not statistically significant differences. *Statistically significant differences.

Receiver operating characteristic curve analysis may be used for three purposes: to determine the discriminative ability of a diagnostic test, to compare the discriminative abilities among several different diagnostic tests, and to determine the optimal cut-off point of a diagnostic test. Investigators use one of several different methods to determine a cut-off point: an arbitrary point was selected without any justification, the point on the ROC curve that was closest to the upper-left corner of the ROC plot, the point with a desired level of sensitivity or specificity, the point which maximizes the sum of sensitivity and specificity, or the point at which sensitivity equals specificity (22).

In previous diagnostic studies, there has been a tremendous variability in proposed cut-off points (23–28). Sources of variability were the inclusion of children with clinical history of previous reactions after egg intake, with very different ages, variations in prevalence of atopic dermatitis, immediate and delayed reactions, and different methods to determine this cut-off point. The goal in Monti et al. study was to obtain a 100% PPV. To achieve this objective they selected 5 mm cut-off point for egg white and yolk SPT, 99 KU/l for egg white IgE and 17.5 KU/l for yolk IgE. In our study, egg white and OVM allergens showed the best diagnostic accuracy. As long as sensitivity and specificity are counter balanced we decided to look for the cut-off point which maximized the sum of sensitivity and specificity (22). An OVM prick test of 5 mm or higher predicted a reaction to egg intake in 95% of the cases, the same 5 mm level for egg white SPT on Monti et al. with a 100% PPV. The usefulness, simplicity, low cost and low invasiveness of the prick test make it the preferred screening test in this risk group.

In Monti's study only white egg and yolk fractions were evaluated. We included an original approach, performing SPTs with white egg, yolk, OVA, OVM, OVT and lysozyme to all included patients. OVA, OVT and lysozyme SPTs were useless predicting egg tolerance milk-allergic population, while OVM prick test was as useful as complete egg white SPT.

As described in Materials and methods section, the tolerance test took place at the hospital for those children with a positive prick test to any egg fraction, whereas those patients with all negative egg allergen prick tests were introduced to egg at home. This difference in the performance of the egg challenge test could be a limitation for this study. To minimize the impact of this differential Reference Standard on study results we ensured both groups to follow exactly the same protocol of increasing doses. Negative tolerance test performed at home did not involve any risk of a wrong diagnosis. To avoid any misclassification of tiny reactions after egg intake at home, a challenge oral test with egg was performed at the hospital to confirm the diagnosis. Actually only one patient from the 'home-introducing' group had had a slight cutaneous reaction after his first egg intake. After oral challenge at the hospital this reaction was confirmed.

There is a need of change in milk-allergic children management in current clinical practice. Almost 40% of milk-allergic children likely to be also egg allergic. Given the diagnostic accuracy of egg allergens SPT we proposed these tests must be performed before egg proteins were introduced in their diet. Ninety-seven percent of patients (38 out of 39%) with all negative egg allergen prick tests have been introduced egg at home successfully.

Finally, the source of sensitization in those allergic patients who have not yet exposed to egg is an interesting discussion point and must be aim of future research, focusing on three main hypothesis:

- First one is intrauterine exposure. Some authors have detected food-specific IgE antibodies in umbilical cord blood, concluding that foetus may have become sensitized during pregnancy (29).
- Secondly, breast-feeding might also be a vector of exposure leading to sensitization, as egg proteins have been found in human milk (30, 31).
- Lastly, there may have been unnoticed intake of small pieces of egg without allergic reaction.

In conclusion, those children with specific IgE-mediated cow's milk allergy must be closely followed as a risk group for egg allergy. Early diagnosis is necessary and the SPT has shown itself to be a very useful tool for diagnosing immediate IgE reactions to egg on first known exposure.

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