

LETTER TO THE EDITOR

Skin prick test and development of tolerance in egg allergy

To the Editor,

IgE-mediated egg allergy is one of the most common food allergies in childhood (1). Most children with egg allergy develop tolerance over time (2). Children with egg allergy periodically undergo oral food challenge (OFC) that is the gold standard for determining tolerance acquisition (3) and for preventing unnecessary allergens avoidance. However, OFC is expensive, time-consuming, and may cause anxiety and severe reaction. Therefore, interest in simple markers to predict the development of egg tolerance in children is growing. Current data do not identify definitive associations between achievement of egg tolerance and laboratory or clinical parameters, such as decrease in egg-specific IgE concentration over time (4), baseline lower levels of egg-specific IgE (5), or milder symptoms at initial exposure (6). Little is known about the usefulness of skin prick tests (SPTs) in predicting the loss of clinical egg hypersensitivity. Case reports have sparsely documented that children outgrew clinical hypersensitivity when positive SPT reactions to egg became negative (6). To our knowledge, this is the first report analyzing whether the loss of positive SPTs to egg white or egg yolk may help to predict the development of spontaneous clinical tolerance.

We conducted a study in children with egg allergy, followed at a hospital-based outpatient allergy clinic. Egg allergy was defined as egg-positive OFC and associated positive SPTs to egg or a clear-cut history of egg reaction associated with egg sensitization. During periodical visits, children with hen's egg allergy, who did not experience anaphylaxis with egg or symptoms after ingesting a small amount of egg or baked egg in the past 2 years, were consecutively enrolled in the study. At recruitment, a careful history was obtained from parents and SPTs to egg were performed. Children with negative SPTs to both egg white and egg yolk were assigned to group 1, those with positive SPTs to egg white and/or egg yolk to group 2. Participants in each study group performed OFC to assess the acquisition of egg tolerance. When allergic symptoms to foods or aeroallergens were reported, children underwent SPTs to foods or inhalants and, when necessary, OFC to the suspected food.

All patients underwent SPTs with egg white and yolk extracts (ALK Abello, Milan, Italy), 1 mg/ml histamine, and control solution within 3–6 month prior to OFC. Patients were tested by a trained nurse using a standard one-prick lancet (Allergopharma, Milan, Italy) technique on the volar side of the forearm. Wheal reactions were read after 15 min. SPT was regarded as positive when the diameter of the wheal was greater than 3 mm after subtracting the diameter of the wheal elicited by the diluent, and it was graded as follows: ++++ if wheal was greater than twice the area of histamine standard, +++ if it was twice, ++ if it was equal, + if it was half, negative if it was less than half.

To assess resolution or persistence of egg allergy, all children underwent open OFC to egg (3) with material and personnel

immediately available for the control of adverse reactions. Before OFC, an intravenous access was obtained. Challenge consisted of increasing doses every 20 min of 1, 5, 20 mg lyophilized white egg protein, and then a boiled egg divided as follows: 1/48, 1/24, 1/16, 1/8, 1/4, and 1/2 that corresponds to 125, 250, 375, 750 mg, 1.5, and 3.1 g of egg protein. Patients were observed for at least 2 h. Blood pressure was monitored (7). Adverse reactions were considered immediate when they appeared within 2 h and late after 2 h. OFC outcome was graded according to Niggemann et al. (8).

When challenge was negative, children received egg at home for 4 days, and they were checked for adverse reactions. When OFC resulted in subjective or unclear symptoms, a double-blind placebo-controlled OFC was performed using the same above titration steps. Local Ethical Committee approved the study.

Student's *t*-test or analysis of variance was used to analyze differences in continuous variables and chi-square test or Fisher exact test in categorical variables. Sensitivity, specificity, negative and positive predictive accuracy for egg SPTs were calculated at rechallenge. Odd ratio (OR) and its 95% confidence interval (95% CI) were calculated. The frequency of positive OFC has been reported about 30% (3). A power calculation was performed, based on the assumption that the frequency of positive OFC in children with loss of SPT positivity was 10%. Estimating 50 children in group 1, we would need at least 15 children in group 2 to provide an 80% power at the 5% level of significance to detect a threefold decrease in positive challenge. Taking into account possible dropouts, the first 52 voluntary subjects were included in group 1 and 23 in group 2. Statistical analyses were performed with SPSS software (v.19).

Seventy-five children with egg allergy (44 males), aged 3–78 months (mean age 14 months), were divided in two groups. Group 1 consisted of 23 children with negative SPTs to both egg white and egg yolk at recruitment (Table 1). At first reported egg reaction, 19 (82.6%) children presented skin symptoms, 5 (21.7%) gastrointestinal symptoms, and 1 (4.3%) respiratory symptoms. Group 2 included 52 children who still have positive SPTs to egg white and/or egg yolk. At first reported egg reaction, skin symptoms occurred in 48 (92%) patients, gastrointestinal in 8 (15%), and respiratory in 1 (1%). Table 1 shows that there was no association between persistence of SPT positivity to egg and several variables. Persistence of egg SPT positivity was significantly associated with at least one atopic symptom ($p = 0.004$), especially atopic dermatitis (4 vs. 25; OR (CI 95%) = 4.39 (1.31–14.71); $p = 0.01$), rhinoconjunctivitis (4 vs. 26; OR (CI 95%) = 4.75 (1.42–15.88); $p = 0.007$), rash (2 vs. 0; $p = 0.03$). Clinical hypersensitivity reactions to foods other than hen's egg were experienced by four children (2 to cow's milk, 1 to walnut, 1 to fish, 1 to vanilla) in group 1 and 18 (7 to cow's milk, 4 to hazelnut, 2 to walnut, 2 to kiwi, 2 to wheat, 1 to fish, pea, and

Table 1 Baseline characteristics of children with negative skin prick test to egg (group 1) and positive skin prick test to egg (group 2)

	Group 1 n = 23	Group 2 N = 52	OR (95% CI)*	p value
Positive OFC‡	1 (4)	13 (25)	7.33 (0.89–59.88)	0.03
Age, months†	62 (18–195)	66.5 (24–184)		0.82
Male‡	12 (52)	32 (61)	1.46 (0.54–3.95)	0.44
Age at first reported egg reaction, months†	5 (0–27)	7 (0–39)		0.56
Age at last reported egg reaction, months†	17 (4–150)	25 (6–179)		0.24
Interval time last egg reaction and challenge, months†	17 (0–183)	25 (0–84)		0.24
Interval time first SPTs and last SPTs, months†	26 (7–181)	26 (0–168)		0.33
Isolated skin symptoms at first egg reaction‡	19 (82)	48 (92)	2.52 (0.57–11.14)	0.80
At least one atopic symptom‡	13 (56)	45 (86)	4.94 (1.57–15.55)	0.004
At least allergic reaction to one food‡	4 (17)	18 (35)	7.0 (0.27–178.5)	0.67

*OR, odds ratio; CI, confidence interval.

†Mean (range).

‡Number (%).

peanut) in group 2 ($p > 0.05$). There was no difference between groups in numbers of SPT positive reactions to foods or aeroallergens.

In group 1, 1 (4.3%) of 23 children failed OFC to egg, and in group 2, 13 (25%) of 52 children ($p = 0.03$). Positive challenges elicited in all cases immediate manifestations within 1 h from egg intake. The most frequent manifestations were cutaneous (11 of 14 cases, 78%). Rash, urticaria, and angioedema were isolated in 10 (71%) of 14 cases. Gastrointestinal symptoms developed in three children. Anaphylaxis occurred in two children.

In group 1, one patient did not pass OFC and developed urticaria following ingestion of 5 mg lyophilized white egg protein (total ingested dose 6 mg of lyophilized white egg). In group 2, two children had positive OFC after 1 mg lyophilized white egg intake, six patients after 5 mg (total dose, 6 mg of lyophilized white egg), three patients after 20 mg (total dose, 26 mg of lyophilized white egg), one patient after 125 mg egg protein intake (total dose, 151 mg), and one patient after ingesting half egg (total dose, 6.2 g). One patient had a grade I reaction, 10 children presented mild-to-moderate systemic reactions (grade IIA), and two had severe systemic reactions (IIIA and IIIC) (8).

There was no difference in negative outcome of OFC between children under 6 years of age and those over 6, both in group 1 and group 2.

Table 2 shows diagnostic accuracy calculated for egg SPTs at OFC in all 75 children. Sensitivity and negative predictive value to egg gave the best results, whereas positive predictive value and specificity were poor.

Children with clinical reactions to other foods were more common in the group with positive OFC to egg, than in those with negative OFC (Table 3). At challenge, all children with positive egg OFC and 48 (78%) children with negative OFC had atopic symptoms. Urticaria and rhinoconjunctivitis were significantly more common in children with persistent egg allergy (Table 3).

The results of our study give support to the hypothesis that children are more likely to outgrow egg allergy when SPT to

Table 2 Diagnostic accuracy of egg SPT in the whole population

	Egg white plus egg yolk	Egg white	Egg yolk
Sensitivity	0.92	0.90	0.88
Specificity	0.36	0.33	0.42
Positive predictive value	0.25	0.38	0.42
Negative predictive value	0.95	0.88	0.88

egg become negative over time, compared with subjects with persistent positive SPTs. Therefore, the conversion of a positive egg SPT may provide useful information to identify children who acquire tolerance to egg and it may reduce the need of OFC. However, 1 of 23 children with negative SPT had urticaria upon challenge with egg (4%). So, until further data on frequency of mild reactions in large subject sets become available, OFC remains the gold standard for diagnosing food allergy.

Prior observations showing that SPT reactions to egg decreased in size or became negative when children achieved tolerance corroborate our results (6). We extended previous findings by including a larger group of patients and a control group, by performing SPT with egg white and egg yolk, and supervised OFC. The predictive value of SPTs in the diagnosis of egg allergy widely varied among studies (5, 9). Our data suggest that a negative egg SPT should be considered useful to rule out clinical hypersensitivity reactions on the exposure. On the other hand, a positive egg SPT was a poor predictor of clinically relevant food allergy because of the high false-positive rate (5, 9). Moreover, our results confirm earlier findings by showing that egg white extract has a slightly higher predictive accuracy.

Several factors have been associated with the development of tolerance in egg allergy. We were unable to confirm that occurrence of milder cutaneous symptoms at first egg clinical reaction was associated with increased likelihood of passing egg OFC at follow-up (6). In agreement with previous studies (2, 5), we found that allergy to other foods was significantly

Table 3 Characteristics of children with positive and negative outcome of OFC to egg

	Positive OFC n (%)	Negative OFC n (%)	OR (95%CI)	p value
Patients	14 (19)	61 (81)		
Males	8 (57)	36 (59)	1.08 (0.33–3.49)	0.89
Isolated skin symptoms at first egg reaction	10 (71)	50 (81)	1.81 (0.48–6.87)	0.37
At least one positive SPT to food	7 (50)	19 (31)	0.45 (0.13–1.47)	0.14
Clinical reactions to other foods	6 (42)	10 (16)	0.26 (0.07–0.91)	0.02
Children under 6 years of age	5 (35)	39 (65)	3.19 (0.95–10.71)	0.05
Atopic symptoms				
Rhinoconjunctivitis	9 (64)	21 (34)	0.29 (0.08–0.98)	0.03
Asthma	8 (57)	23 (37)	0.45 (0.14–1.47)	0.18
Urticaria	7 (50)	8 (13)	0.15 (0.04–0.54)	0.001
Atopic dermatitis	6 (42)	21 (34)	0.70 (0.21–2.28)	0.55
Anaphylaxis	0	1 (1)	–	0.62
Diarrhea	0	2 (3)	–	0.49
Angioedema	1 (7)	3 (4)	0.67 (0.06–6.99)	0.73
Rash	1 (7)	1 (1)	0.21 (0.01–3.69)	0.24
Vomiting	2 (14)	3 (4)	0.31 (0.04–2.06)	0.20
At least one atopic symptom	14 (100)	48 (78)	1.27 (1.11–1.44)	0.14

OFC, oral food challenge; CI, confidence interval; OR, odds ratio.

related to persistent egg allergy. This is in contrast with findings by Shek et al. (4). Sample size in this study has not been calculated to investigate such prognostic factors. Therefore, it is not surprising that our results are only partly in agreement with those of earlier reports.

This study has several strengths. SPTs were performed by trained technical staff. OFCs have been performed by standardized procedures and supervised by a single trained physician to minimize interoperator variability. The range of data allowed investigation for the effects of potential factors influencing the achievement of egg tolerance.

Our study might be influenced by some limitations. First, we should have studied each child by SPT and OFC to egg in a large unselected cohort to avoid selection bias. This is ethically and economically unfeasible. Second, tolerance development was not based on outcome of double-blind-controlled OFC that is considered the 'gold standard' (3). We performed open OFC that is the most common test used for identifying children with food allergy, to relate our findings to real-life situations. Third, SPT results may depend upon type of commercial extract used. Therefore, our data should be cautiously generalized in allergy practice. Four, SPT results are often reported as wheal diameter. We used a semiquantitative + system that

relates the egg wheal response to that of histamine. This reduces differences due to test procedures between personnel and among patients over time. However, it is not possible to compare our findings with studies using the measure of wheal diameter. Five, SPT to egg is unhelpful in predicting baked egg tolerance (10).

In conclusion, we think that our findings have several implications for both clinical practice and research. At follow-up visits, children with egg allergy should undergo SPTs to white egg and yolk before OFC. Clinicians should not wait for a negative skin test result to perform OFC, the gold standard for diagnosing food allergy. However, when SPT become negative, egg ingestion elicits only mild reactions. So, such children might reintroduce egg at home. Larger studies are required to definitively clarify this issue.

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