

High incidence of adverse reactions to egg challenge on first known exposure in young atopic dermatitis children: predictive value of skin prick test and radioallergosorbent test to egg proteins

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Summary

Background Egg skin prick test (SPT) and/or radioallergosorbent test (RAST) positivity has been described in infants and children with a food allergy, or in infants at high risk of atopy who have never eaten eggs. Clinical reactions are also observed when some of these children or infants eat eggs for the first time.

Objective and method A prospective study was made of 107 atopic dermatitis (AD) children (66 boys, 41 girls) aged 1–19 months (median 5 months) who had never ingested egg, to compare the outcome of a first oral egg challenge and the results of albumen and yolk SPTs and RASTs.

Results The egg challenge (conducted at age 12–24 months: mean 16 months, median 15 months) was positive in 72/107 children (67.3%). The reactions were immediate or early (first 6 h) in 56/72 (77.8%). The most severe (all within the first 6 h) were one case of anaphylactic shock (1.4%), three cases of laryngeal oedema (4.1%) and one serious attack of asthma (1.4%). The skin weal diameter at and above which reactions always occurred was 5 mm for both albumen and yolk. They were, however, also observed in the complete absence of a weal. The outcome of the challenge was always positive when the specific IgEs (sIgE) for albumen and yolk were > 99 KU/L and ≥ 17.5 KU/L, respectively. Here, too, reactions were noted even when sIgE levels were < 0.35 KU/L.

Conclusion AD children who have never eaten eggs may be sensitized and display reactions at the first ingestion. The percentage of reactions in this series was by no means negligible. These findings were observed in children with mild as well as moderate–severe AD when first examined. SPT for albumen and yolk diameter ≥ 5 mm, and sIgE for albumen > 99 KU/L and for yolk ≥ 17.5 KU/L were 100% specific in predicting the outcome of the challenge. It may thus be concluded that children with AD whose SPT and/or RAST for albumen and/or yolk are equal to or higher than these cut-off values should not be subjected to the oral challenge when consideration is given to the introduction of egg in their diet. Even when these cut-offs are not reached, however, clinical reactions to the challenge cannot be ruled out *a priori*, and it should be preferably performed in a protected environment, such as a hospital.

Keywords atopic dermatitis, egg oral challenge, food allergy, never-ingested egg

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Introduction

Double-blind, placebo-controlled food challenges show that about one-third of children with atopic dermatitis (AD) have a clinically significant food allergy (FA) [1]. It would thus be advisable to omit highly allergenic foods such as eggs from their diet until they are at least 1 year old to avoid the risk of sensitization [2].

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Egg skin prick test (SPT) and/or radioallergosorbent test (RAST) positivity, however, has been described in infants and children with FA [3, 4] or in infants at high risk of atopy [4–7] who have never eaten eggs. Clinical reactions are also observed when some of these infants or children eat eggs for the first time [3, 4].

It would be useful to determine whether, and to what extent, AD children who have never eaten eggs are sensitized and how many of them display a clinical reaction when first exposed. A prospective study has therefore been made of children with AD to compare the outcome of an oral challenge with never-ingested egg and the results of albumen and yolk SPTs and RASTs.

Materials and methods

Patients

Between 1 January and 31 December 1999, 250 children were referred to the AD service of our paediatric clinic by a general practitioner, or brought by their parents for diagnosis. AD rather than FA was primarily suspected. AD was diagnosed according to Hanifin and Rajka [8]. The atopic dermatitis area and severity index (ADASI) scores were used to classify AD as mild (1–6 points), moderate (7–12 points) and severe (13–18 points) [9].

One hundred and nine children who had never eaten egg directly or indirectly were chosen for the study. The final series, however, comprised 107 subjects (66 boys, 41 girls; age 1–19 months, mean 6 months, median 5 months), because the parents of two children refused their consent.

All the children were followed monthly until the first egg intake. A careful check was made to ensure that their previous diet had not included eggs or egg-containing foods.

Skin prick tests

The albumen and yolk SPTs were performed in the month prior to the egg challenge. Commercial food extracts (Neo-Abellò Diagnostics, Madrid, Spain) were diluted 1:10 w/v and a lancet with a 1-mm tip was pricked into the volar surface of the forearm through a drop of extract suspension. Histamine (10 mg/mL histamine base) and a negative control solution (50% glycerosaline solution) were also used. The skin weal diameter (mm) in response to histamine was measured after 15 min and to albumen and yolk after 20 min.

Determination of specific IgE

Serum levels of albumen and yolk sIgE were determined by CAP RAST (Pharmacia Diagnostics, Uppsala, Sweden) on blood samples taken during the SPTs. Results were interpreted according to the manufacturers' directions as: negative, 0, < 0.35 KU/L; borderline, 1, 0.35–0.69 KU/L; positive, 2, 0.70–3.49 KU/L; strong positive, 3, 3.5–17.49 KU/L; highly positive, 4, 17.5–49 KU/L; very highly positive, 5, 50–99 KU/L; extremely highly positive, 6, > 99 KU/L.

Challenge procedures

The challenge was performed when the subjects were 12–24 months old (mean 16 months, median 15 months). Anti-histamine and cortisone management was suspended during the 15 days prior to the challenge and at admission the children were in symptomatic remission. The test period consisted of 32 h in hospital followed by 8 days' controlled observation at home provided no reactions had appeared.

Egg

As a test dose, one whole raw egg mixed in with 200 mL of hot cow's milk or formula usually drunk and tolerated by the patient was administered when tepid. The challenge was scored as positive if objective clinical reactions were observed: skin (erythematous or macular rash, urticaria, angio-oedema, eczema), gastrointestinal (GI: vomiting, diarrhoea, abdominal pain, oral allergy syndrome), respiratory (asthma, laryngeal oedema, sneezing, repetitive coughing, nasal congestion, rhinorrhoea, nasal itching), ocular (conjunctival injection, itching,

eye-watering, periorbital oedema) and cardiovascular (hypotension, shock). These reactions were classed as immediate when they appeared within 1 h after the challenge, early (after 1–6 h) and late (after the 6th hour). If no reactions appeared within 32 h, the child was discharged. Parents were required to ensure that their child continued to ingest at least 50 mL of the milk and egg mixture per day. They were also told how to recognize FA reactions and to call an AD service doctor and return the child to hospital if a reaction occurred in the following 8 days. All children were re-examined at the end of the total challenge period.

Statistics

The sensitivity, specificity and positive and negative predictive values (PPV and NPV) of the albumen and yolk SPTs and RASTs were determined by comparison with the challenge results.

Results

AD was mild in 41/107 children (38.3%), moderate in 36 (33.6%) and severe in 30 (28%).

Challenge

Positive reactions were observed in 72/107 (67.3%) children: 20/41 with mild AD (48.8%), 28/36 with moderate AD (77.7%) and 24/30 with severe AD (80%).

Skin reactions (mostly urticaria, erythematous or macular rash) were the most frequent: 61/72 (84.7%), followed by GI reactions (usually immediate-to-early vomiting): 27/72 (37.5%). Respiratory, ocular and cardiovascular reactions occurred in 13/72 (18%), 4/72 (5.5%) and 1/72 (1.4%) cases, respectively. There were no nasal symptoms. Re-exacerbation of eczema was observed in 12 (16.6%).

Severe reactions were elicited in 5/72 children (7%): three cases of laryngeal oedema, with or without GI and/or skin symptoms; one serious attack of asthma accompanied by GI and skin symptoms; one case of anaphylactic shock: this last child and two of the three with laryngeal oedema were among the initially severe AD patients.

Only one organ or apparatus (usually the skin) was involved in 46/72 cases (63.9%), two (usually skin plus GI) in 17/72 (23.6%) and three (usually skin, GI and respiratory) in 9/72 (12.5%).

Reactions were immediate in 41/72 cases (57%), early in 15/72 (20.8%) and late in 12/72 (16.7%). They occurred in two stages in four cases (5.5%): three immediate plus early, one immediate plus late. The late reactions were nearly always re-exacerbation of eczema. In three cases, this was accompanied by diarrhoea. In one case, late AD followed an immediate erythematous rash and in eight it was present as an isolated symptom.

Skin prick tests

The albumen and yolk weal diameters and the results of the oral challenge are set out in Tables 1 and 2. When either diameter was ≥ 5 mm, the result was always positive. A 5-mm diameter was thus 100% specific for the result of a challenge. The specificity of a 4-mm diameter was 91.4% for albumen and 94.3% for yolk, and that of a 3-mm diameter was 85.7% and 88.6%,

Table 1. Albumen weal diameters and egg challenge outcome

Weal (mm)	Positive challenge (n)	Negative challenge (n)
0	4	26
1	2	3
2	3	1
3	18	2
4	32	3
5	4	0
6	3	0
7	2	0
8	2	0
9	0	0
10	2	0
Total	72	35

Table 2. Yolk weal diameters and egg challenge outcome

Weal (mm)	Positive challenge (n)	Negative challenge (n)
0	21	29
1	2	1
2	1	1
3	29	2
4	16	2
5	1	0
6	1	0
7	0	0
8	0	0
9	1	0
10	0	0
Total	72	35

Table 3. Sensitivity, specificity, PPV and NPV percentages in function of albumen and yolk weal diameters (mm)

Weal diameter (mm)	SPT albumen			SPT yolk		
	≥ 3	≥ 4	≥ 5	≥ 3	≥ 4	≥ 5
Sensitivity (%)	87.5	62.5	18	66.6	26.4	4.2
Specificity (%)	85.7	91.4	100	88.6	94.3	100
PPV (%)	92.6	93.7	100	92.3	90.5	100
NPV (%)	77	54.2	37.2	56.3	38.4	33.6

PPV, positive predictive value; NPV, negative predictive value.

respectively. By contrast, the sensitivity of both SPTs was highest for a 3-mm diameter and progressively lower for a 4-mm and a 5-mm diameter (Table 3). Positive challenges were, however, observed even in the absence of a weal (see Tables 1 and 2). When ≥ 5 mm was taken as the positivity cut-off for the albumen and yolk SPT, there were 14 SPT positives: two for both albumen and yolk, 11 for albumen only and one for yolk only. Of the five children with severe challenge reactions, three (two with laryngeal oedema and one anaphylactic shock) had a ≥ 5 mm weal diameter for albumen, whereas none of their yolk diameters was equal to or greater than the 5-mm cut-off.

Table 4. Relations between albumen and yolk sIgE levels and egg challenge outcome

CAP (KU/L)		Egg challenge			
		Albumen		Yolk	
Score	Value	Positive (n)	Negative (n)	Positive (n)	Negative (n)
0	< 0.35	17	27	33	29
1	0.35–0.69	0	1	6	0
2	0.70–3.49	6	1	6	3
3	3.5–17.49	8	2	10	3
4	17.5–49	6	2	5	0
5	50–99	23	2	12	0
6	> 99	12	0	0	0
Total		72	35	72	35

Radioallergosorbent test

Table 4 illustrates the relationship between the albumen and yolk sIgE levels and the outcome of the challenge. This, in fact, was always positive when the albumen IgE level was > 99 KU/L (CAP class 6) and the yolk level was ≥ 17.5 KU/L (CAP class 4). If the CAP results for albumen are divided into 'positive' for class 6 and 'negative' for classes 0–5, the specificity of the albumen CAP in predicting the outcome of the challenge is 100%, its sensitivity 16.6%, its PPV 100% and its NPV 36.8%. If the CAP results for yolk are divided into 'positive' for classes 4–6 and 'negative' for classes 0–3, the specificity of the yolk CAP in predicting the outcome of the challenge is 100%, its sensitivity 23.6%, its PPV 100% and its NPV 39.0%. Positive reactions, however, were also observed when the albumen or yolk values were less than 0.35 KU/L (Table 4). When albumen and yolk sIgEs of > 99 KU/L and ≥ 17.5 KU/L were classed as 'positive', therefore, 24 children were RAST-positive: five for both albumen and yolk, seven for albumen only and 12 for yolk only. The five children with severe reactions were RAST-negative. Their albumen and yolk sIgE levels, in fact, were from 1.93 to 44.8 and from < 0.35 –9.8 KU/L, respectively.

SPT and RAST

Combination of these SPT- and RAST-positives gives a total of 29 allergometrically positive children: nine SPT/RAST-positives, five SPT-positives and 15 RAST-positives.

Discussion

These findings show that AD children may be sensitized to eggs even if they have never eaten one and thus display clinical hypersensitivity reactions when first exposed. Oral egg challenge positivity was noted (at increasing percentages) in all ADASI grades. Similar findings have been described in children and infants with FA [3, 4] and in infants at high risk of atopy [4]. Because great care was taken to ensure that eggs and egg-containing foods had not been ingested prior to the SPTs/RASTs and the challenge, sensitization must have occurred *in utero* or during lactation. It has, in fact, been shown that food antigens such as egg proteins can both cross the placenta and elicit a specific immune response in the fetus [10–12], and be conveyed via the milk to a breast-fed infant [7, 13, 14].

The challenge was positive in 67.3% of our patients (72/107). This prevalence is much higher than the 42% found by Caffarelli et al. [3] in a study of 33 children with FA, aged from 5 months (1 subject only) to 57 months (mean 24 months), challenged with previously never-ingested egg. The difference could be ascribable to both age (our patients were challenged when aged 12–24 months, mean 16 months) and our longer observation period (hospitalization for 32 h, followed by controlled repetition of the challenge at home for 8 days on the part of non-responders) compared with only 5 h and 4 days in the other study.

The predictivity of the albumen and yolk SPTs was a function of weal diameter. Employment of the ≥ 3 mm diameter commonly used for grading SPTs [15] as the 'positive' cut-off gave an 87.5% sensitivity and an 85.7% specificity for albumen and an 88.6% specificity for yolk. Sporik et al.'s [16] study of 467 children with a suspected FA showed that a 3-mm weal had a 84% sensitivity in identifying children with egg allergy and a specificity of 70% (75% for children aged less than 2 years). Sampson [17], however, found that in patients with a median age of 7.9 years, a 3-mm weal had a 98% sensitivity but only 53% specificity in identifying children with egg allergy. Caffarelli et al. [3] too, reported a 92% sensitivity, but a specificity of only 57%. Eingenmann and Sampson [18] observed 100% sensitivity and 61% specificity in AD children with a median age of 4.6 years. These three lower specificities are presumably attributable to patient age (greater than our median 15 months at challenge and Sporik et al.'s 3.0 years). The prevalence of egg allergy, in fact, decreases with age [19, 20] and clinical tolerance of egg proteins appears within 3 years in about one-third of children with a prior egg allergy, although SPT positivity may persist and increase the number of false positives [20].

Our most significant finding, however, is that an albumen- or yolk-induced weal with a diameter ≥ 5 mm is 100% specific in defining the outcome of an egg challenge. Sporik et al. also found that positive challenges were always associated with this cut-off in children < 2 years old [16].

The sensitivity and NPV values observed in our patients were very low (18% and 37.2%, respectively, for albumen; 4.2% and 33.6%, respectively, for yolk), indicating that many children with a < 5 mm diameter (SPT 'negatives') displayed clinical reactions. Absence of a weal (especially for yolk) was also accompanied by positive reactions.

A RAST sIgE for yolk ≥ 17.5 KU/L was 100% specific in defining the challenge outcome, as in Roehr et al.'s study of 42 AD children [21], whereas its sensitivity was only 23.6% and its NPV 39%. Albumen sIgE levels > 99 KU/L were 100% specific, but only 16.6% sensitive, with an NPV of 36.8%. RAST sIgE levels < 0.35 KU/L (especially for yolk) were also accompanied by positive reactions. These results suggest that the > 99 KU/L albumen and ≥ 17.5 KU/L yolk cut-offs should only be used to confirm a symptomatic egg allergy and not to rule out an allergy, as already observed for the ≥ 5 mm weal diameter.

In their retrospective assessment of the predictivity capacities of allergen-sIgE levels in 196 children and adolescents with FA (median age 5.2 years), Sampson and Ho found that the IgE level indicating a 95% probability of a positive reaction to an egg challenge (95% predictive decision point) was 6 KU/L [22]. This has since been confirmed by Sampson in a prospective study of 100 children and adolescents with suspected FA (median age 3.8 years), in which 6 KU/L as the diagnostic decision point

correctly predicted egg reactivity in 96% of patients [15]. This cut-off is lower than ours for yolk, and even more so for albumen, perhaps because our children were much younger (median 15 months) when challenged. Comparison between the two series is also rendered less realistic by the fact that our children had never ingested egg, whereas Sampson's subjects were egg allergy suspects. Severe reactions were observed in our study in five (7%) patients. None of their clinical or laboratory features were predictive in this respect. Only three were initially classed as severe AD (and other severe AD patients had a non-severe and even a negative challenge result). In addition, only three displayed an albumen SPT equal or higher than the cut-off (as also displayed by non-severe responders) and all five displayed both a yolk SPT and sIgE levels below the cut-offs.

The appearance of these severe reactions was presumably a consequence of the fact that our challenge protocol required the administration of high allergen doses. We now employ a labial food challenge [23]; non-responders receive an initially small and then gradually increasing allergen doses at regular intervals. The preparation of the challenge meal, however, has been retained to keep as close as possible to the habits of North Italian mothers when they first introduce egg into their children's diet. Raw yolk and then the whole egg is added to a warm soup. Introduction of a soft-boiled egg (in which the albumen is no more than slightly coagulated) is a later step.

The conclusion to be drawn from these findings is that the first direct introduction of eggs in AD children requires caution. A high percentage of our children were sensitized even though they had never eaten eggs, and 67.3% displayed clinical reactions when challenged. Furthermore, this was true across all three grades of AD severity. As to the predictivity of the allergometric tests with regard to the outcome of the oral challenge, a cut-off at and above which the challenge was always positive was identified for both SPT and RAST. Confirmation of our results would suggest that AD children aged less than 24 months should not undergo the oral challenge when consideration is given to the introduction of egg in their diet if any one of their SPT and/or RAST for albumen and/or yolk levels is equal to or exceeds the cut-off value. It is obviously desirable to identify children who will very likely react to their first exposure to egg and hence should not be subjected to challenges that are potentially hazardous, costly and time-consuming for both physicians and families [15, 16, 21, 22, 24]. Twenty-nine of the 72 children (40.3%) who reacted, in fact, displayed values equal to or higher than the cut-off in one or more of the four tests and hence could have been exempted from the oral challenge.

Values lower than the cut-offs, however, cannot be used as *a priori* evidence that reactions will not occur. The challenge should be preferably performed in a protected environment, such as a hospital.

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