

ORIGINAL ARTICLE

Safety of food challenges to extensively heated egg in egg-allergic children: a prospective cohort study

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To cite this article: Turner PJ, Mehr S, Joshi P, Tan J, Wong M, Kakakios A, Campbell DE. Safety of food challenges to extensively heated egg in egg-allergic children: a prospective cohort study. *Pediatr Allergy Immunol* 2013; **00**.

Keywords

children; baked egg; egg; food allergy; quality of life

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Accepted for publication 8 May 2013

DOI:10.1111/pai.12093

Abstract

Background: Many children with IgE-mediated allergy to egg can tolerate egg in baked foods. However, the clinical characteristics and severity of reactions of egg-allergic children who react to baked egg at open food challenge (OFC) are not well defined.

Methods: Children presenting to our tertiary referral clinic with a diagnosis of egg allergy and following complete egg avoidance in their diet were offered OFC to baked egg. Challenges were performed with incremental dosages to a total of one baked muffin containing 1/6 egg (equivalent to 1 g egg protein) following a standardized protocol. Data were collected prospectively from 2009–2012.

Results: Open food challenge to baked egg were carried out on 236 egg-allergic children who had been strictly avoiding egg in their diet. A total of 150 children (64%) passed and successfully incorporated baked egg into their diet. Eighty-six children (36%) reacted to their challenge. Of these, 12 (14%) experienced anaphylaxis (according to WAO criteria), including four to <100 mg extensively heated egg protein. Intramuscular adrenaline was administered to 5 of the 12 children, one of whom required a second dose due to persistent hypotension. Skin prick testing, asthma, or prior egg anaphylaxis were not predictive of challenge outcome.

Conclusion: The majority of children with IgE-mediated allergy to egg were able to tolerate 1 g of baked egg protein, but the outcome of OFC remained unpredictable, and 14% of children who failed OFC reacted with anaphylaxis. We recommend that OFC to baked egg should take place under medical supervision.

Allergy to hen's egg is increasing in prevalence, with a recent birth cohort reporting an incidence on 9% in infants (1). Until recently, most allergy guidelines recommended strict avoidance of all forms and amounts of allergen from the diets of allergic children. This was partly on the basis of safety but also on the belief that accidental allergen exposure may delay the onset of tolerance (2). However, a number of publications have since demonstrated that many egg-allergic children can tolerate extensively heated egg in serving size quantities (1, 3–5). The ability to incorporate extensively heated egg (in baked products such as cakes) significantly liberalizes the diet and may help to reduce anxiety over accidental ingestions. There is also the potential for altering the natural history of the disease and accelerating acquisition of tolerance to egg (3), contrary to initial concerns (2).

Tolerance to extensively heated egg is usually demonstrated at formal open food challenge (OFC) under medical

supervision, given the potential for anaphylaxis (3, 5). However, some guidelines support a home introduction protocol for selected egg-allergic children without a prior history of asthma (6). We therefore sought to assess the safety of OFC to extensively heated egg in children with high probability of clinical egg allergy and to identify factors that might predict clinical reaction and anaphylaxis at OFC.

Methods

Children presenting consecutively to our tertiary referral clinic with a clinical diagnosis of allergy to hen's egg and who were completely avoiding all forms of egg in their diet were offered OFC to extensively heated egg in a muffin ('baked egg') at the Children's Hospital at Westmead, Sydney. Egg allergy was defined as children with a previous convincing clinical reaction to egg within the past 12 months (and evidence of current

sensitization on the basis of positive skin prick test (SPT) to egg white or serum-specific IgE (ssIgE) to egg white) OR evidence of current sensitization consistent with a >95% likelihood of clinical reactivity (ssIgE $\geq$ 6 kUa/l in children over 2 yr, $\geq$ 2 KUa/l in those under 2 yr; SPT to egg white >7 mm in children over 2 yr, >5 mm in those under 2 yr) (7, 8). Exclusion criteria were recent allergic reaction to extensively heated egg within the past 12 months or refusal of consent; children with prior anaphylaxis to egg were not excluded. Recruitment and challenges were conducted over a 3-year period from April 2009 to December 2012. Data from some children in the current cohort (Jan 2010–Dec 2011) have been used in a separate study to identify test performance characteristics of SPT to ovomucoid and fresh baked muffin in predicting baked egg OFC (manuscript submitted).

Children were assessed and examined prior to challenge to ensure suitability, as well as to confirm coexisting atopy (physician-diagnosed asthma and receiving preventer therapy, allergic rhinitis, and/or eczema). Allergy to foods other than egg proteins was confirmed on the basis of prior history of clinical reaction with confirmatory positive testing (SPT or ssIgE) to the allergen implicated. Skin prick test was performed on the day of OFC according to standard guidelines, using commercial extract to egg white (ALK-Abello, Spain) and histamine 10 mg/ml (Hollister Stier Laboratories, WA, USA) as a positive control (9). A positive SPT was defined as a wheal size of at least 3 mm greater than a negative control read at 15 min. Open food challenge to baked egg followed a national protocol for baked egg OFC using incremental doses of baked muffin (10). A standard recipe was used for the muffin (appendix 1) baked at 180°C for 20 min, with one muffin containing 1/6th of a whole egg (approximately 1 gm of egg protein). The protocol used for OFC was as follows: Children were fed increments of the muffin starting from 1/16 muffin, 1/8 muffin, 1/4 muffin, 1/2 muffin, and then the remainder at 20-min intervals. The challenge was halted at onset of objective clinical symptoms, in line with PRACTALL criteria (11). Children were observed for a further 2 h following last muffin dose. Anaphylaxis was defined as per WAO criteria (12). Children with reactions involving skin and/or gastrointestinal symptoms alone were classified as mild-moderate reactors. Patients were instructed to avoid all egg for 48 h to detect possible delayed symptoms, and then to introduce baked egg (using cake containing a similar amount of egg) two to three times per week. Patients were subsequently followed-up by telephone one week later to confirm tolerance.

Data analysis was performed using GraphPad Prism 6 software (GraphPad Software Inc, La Jolla, CA, USA). Statistical analysis was performed using nonparametric tests: SPT data were compared using Mann–Whitney U test, while categorical data were analyzed using chi-squared test. A *p* value of <0.05 was considered significant. The study was approved by the Ethics Committee at the Children's Hospital at Westmead (HREC/10/CHW/3).

Results

A total of 236 children with a diagnosis of egg allergy and following strict dietary avoidance of egg were recruited to the

study (Fig 1). A total of 143 children (61%) were enrolled on the basis of recent clinical reaction to egg with evidence of sensitization on SPT or ssIgE testing, the remainder on the basis of sensitization consistent with a >95% likelihood of clinical reactivity (7). There were no statistical differences between the baseline demographics of these groups (Table 1). Thirty one (13%) of children had a previous history of anaphylaxis to egg, four had previously experienced non-anaphylactic reactions to egg in baked foods (cake). Eight children had experienced anaphylaxis to egg and at least one other food. Eighty-five children had food allergies to at least two other food groups (excluding egg). Thirty-six (15% of total cohort) had a history of prior anaphylaxis to these other food allergens, the most common triggers being cow's milk protein (18 children); peanut/tree nuts (13); fish/seafood (4). Thirteen children had experienced anaphylaxis to more than one food group.

Challenge outcome

Eighty-six children (36%) reacted to their challenge. Thirteen children (15%) reacted to 60 mg protein (1/16 muffin) or less, 35 (40%) to <250 mg (equivalent to 1/4 muffin). 71% of children with prior anaphylaxis to egg passed OFC to baked egg. The size of the SPT to egg white in children with positive reaction was not significantly different from those with negative challenges (*p* > 0.05, Fig. 2 and Table 2). Skin prick test to egg white was therefore not predictive of challenge outcome (*p* > 0.05). There was no relationship between SPT size and dose of baked egg to which the child reacted. Children with food allergy to three or more food groups were more likely to have a positive challenge outcome (*p* = 0.02). A history of prior anaphylaxis, asthma (on preventer therapy), or other atopic condition was not predictive of challenge outcome (Table 2; *p* > 0.05). A history of anaphylaxis to foods other than egg foods was not found to be a risk factor for anaphylaxis to baked egg.

Symptoms elicited during positive challenges

Of those children who reacted, 12 (14%) experienced anaphylaxis to baked egg, according to WAO criteria (5% of total cohort). Four of these children reacted to <100 mg protein. Intramuscular adrenaline was administered to five children, one of whom required a second dose due to persistent hypotension. The remaining children received treatment with inhaled salbutamol and/or antihistamine. Only 3 of these 12 children had a history of prior anaphylaxis to egg; six had previously experienced mild symptoms only, while three were avoiding egg on the basis of IgE sensitization alone.

The remaining children had mild reactions with skin and/or gut symptoms only. The most common reported reactions were as follows: urticaria (37%), itchy mouth and/or throat (31%), abdominal pain (28%), and vomiting (20%). Ninety four percent of reactions occurred within 1 h; the remainder were gastrointestinal symptoms. Two children passed OFC but developed abdominal symptoms at home with ongoing exposure 1 wk later.

Table 1 Patient characteristics

Characteristic	Prior allergic reaction to egg	Sensitized only with >95% PPV on testing
Total no. of patients	143	93
Age at challenge to baked egg, median (interquartile range)	4.5 yr (2.1–6.8 yr)	2.8 yr (1.7–5.8 yr)
SPT to egg white at OFC, median (interquartile range)	8 mm (7–10 mm)	8.5 mm (7.5–11 mm)
Gender, no. (%)		
Male	83 (58%)	56 (60%)
Female	60 (42%)	39 (42%)
Other atopy, no. (%)		
Asthma, on preventer therapy	26 (18%)	17 (18%)
Allergic rhinitis	49 (34%)	20 (22%)
Eczema	93 (65%)	67 (72%)
Food allergy to ≥ 3 allergen groups	49 (34%)	36 (39%)
Prior anaphylaxis to food other than egg	23 (16%)	13 (14%)
Previous reaction to egg, no. (%)		
Anaphylaxis	31 (22%)	N/A
Prior reaction to baked egg	4 (3%)	N/A
Outcome of OFC to baked egg, no. (%)		
Passed challenge	94 (66%)	56 (60%)
Failed challenge – mild-mod reaction	40 (28%)	34 (37%)
Failed challenge – anaphylaxis	9 (6%)	3 (3%)

Data not shown for sIgE values as these were only performed in a minority of patients enrolled.

SPT, skin prick test; OFC, oral food challenge; PPV, positive predictive value.

Challenge outcome in 'mild' egg-allergic children

Subgroup analysis was conducted on those children in whom there was no history of prior severe allergic reaction to egg or asthma requiring preventer therapy. A total of 114 children (age 1.9, IQR 1.5–3.0 yr) met the criteria for 'mild egg allergy'. Of these, 34 (30%) reacted to baked egg within 2 h of allergen exposure, four of whom had anaphylaxis. Intramuscular adrenaline was administered in two children. Nine children reacted to 100 mg egg protein or less, including two children with anaphylaxis. The size of the SPT to egg white in children with positive reaction on muffin challenge (median 9 mm) was not significantly different from those with negative challenges (median 8 mm).

Discussion

Previous studies have demonstrated a significant adverse impact on the quality of life and anxiety of both the affected child and their parents, in children with egg allergy (13). Successful introduction of baked egg permits the liberalization of the diet, allowing the lifting of social restrictions (such as eating baked foods at children's parties) with consequential benefits to the child and their family. It may also hasten resolution of the allergy to the native antigen (14). Up to 70% of egg-allergic children tolerate baked egg (1, 3–5, 14, 15), a finding confirmed in this study. However, to date, no test has been identified as being reliably predictive of tolerance to baked egg for the majority of egg-allergic children (15); thus, tolerance can only be confirmed through dietary exposure. In this study, we found no good predictors of clinical reactivity to baked egg, although the presence of IgE-mediated food allergy to at least two other food groups was associated with a high likelihood of reactivity to baked egg. Given the high prevalence of nut allergy in Australian children (1), we chose to use a criteria of clinical allergy to at least two other food groups (as opposed to nut allergy and egg allergy alone). We did not identify a particular food allergen was associated with a higher rate of tolerance or allergy to baked egg. We therefore consider

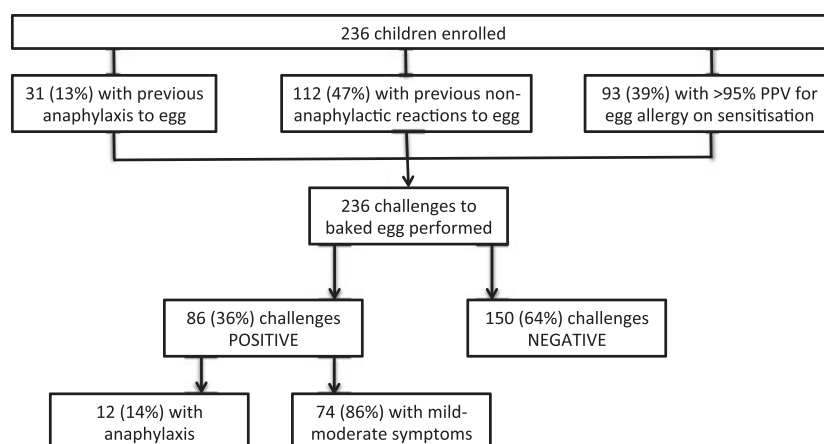
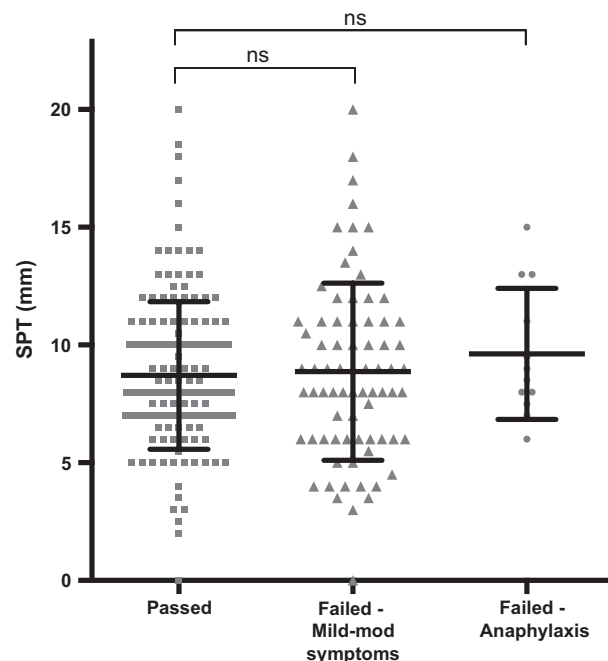
**Figure 1** Study recruitment and outcome.

Table 2 Challenge outcome

Characteristic	Negative OFC: Tolerates baked egg	Positive OFC: Mild-moderate symptoms	Positive OFC: Anaphylaxis
Total no. of patients	150	74	12
Age at challenge, median (interquartile range)	3.2 yr (1.8–5.8 yr)	4.7 yr (1.9–6.8 yr)	4.8 yr (3.0–5.9 yr)
SPT to egg white at OFC, median (interquartile range)	8 mm (7–10 mm)	9 mm (6.0–11.0 mm)	9 mm (8–11.5 mm)
Gender, no. (%)			
Male	91 (61%)	40 (53%)	7 (58%)
Female	59 (39%)	35 (47%)	5 (42%)
Other atopy, no. (%)			
Asthma, on preventer therapy	24 (16%)	15 (20%)	4 (33%)
Allergic rhinitis	39 (26%)	23 (31%)	7 (58%)
Eczema	100 (66%)	49 (66%)	11 (92%)
Food allergy to $\geq$ allergen groups	46 (31%)*	31 (42%)*	8 (67%)*
Prior anaphylaxis to food other than egg	18 (12%)	16 (22%)	2 (9%)
Previous reaction to egg, no. (%)			
Anaphylaxis	22 (15%)	6 (8%)	3 (25%)
Non-anaphylactic reaction	72 (48%)	34 (46%)	6 (50%)
Prior reaction to baked egg	3 (2%)	1 (1%)	0
No previous reaction to egg	56 (37%)	34 (46%)	3 (25%)

SPT, skin prick test; OFC, oral food challenge.

* $p = 0.02$.**Figure 2** Skin prick test (SPT) weal size to egg white at OFC, by challenge outcome. Data are shown as median with interquartile ranges. ns – not significant.

children with multiple food allergies to be more at risk due to an increased level of atopy, rather than an allergy to a particular food.

This series is the largest published cohort of egg-allergic children undergoing prospective OFC to baked egg. We have demonstrated that while the majority will pass their challenge, up to 30% in our population experienced a food allergic reaction, including anaphylaxis. OFC are time-consuming, and access to a challenge service is subject to local health provision and waitlist availability. To address this, some guidelines propose initial introduction of baked egg within the home environment without prior supervised OFC. For example, recent guidance from the British Society for Allergy and Clinical Immunology (BSACI) suggests that non-asthmatic children with a history of mild symptoms (i.e., cutaneous symptoms only) on significant exposure (e.g., a mouthful of scrambled eggs) could have baked egg introduced at home, with a staged introduction over 1–2 wk (6). In our study cohort, 114 children would have met these criteria for ‘mild egg allergy’, of whom 30% reacted including four who had anaphylaxis. Nine children reacted to 100 mg egg protein or less (including two with anaphylaxis), a dose consistent with that advocated in the BSACI guideline during initial phase of home introduction. While the BSACI protocol recommends introduction over a period of days (in contrast to a single day OFC over 4 h in our study), it is unlikely that the immunologic mechanisms underlying the IgE-mediated reaction would be sufficiently varied by the slower introduction, as to render this comparison invalid. Other authors have cautioned against the use of asthma and prior reaction to egg only as the basis on which to decide where to undertake OFC (16). Lieberman et al. also reported children with prior mild symptoms to egg who experienced anaphylaxis on exposure to baked egg (5). In contrast to our findings and those of other cohorts (1, 3, 5, 15),

Clark et al. reported no severe allergic reactions in 58 children undergoing OFC to baked egg (4). This may be due to the much smaller study population (58 vs. 236) and/or these children having a milder phenotype compared with our own and other cohorts. We therefore suggest that guidelines which recommend home introduction of baked egg in egg-allergic children by screening out children with asthma or previous severe reactions may not be appropriate in our own (and potentially other) populations of children with egg allergy.

Children with a past history of anaphylaxis to whole egg had a high probability of successfully passing the baked muffin OFC in our population. This suggests that anaphylaxis to non-extensively heated egg is not a contraindication to introduction of baked egg. The benefits of introduction, in terms of reducing anxiety relating to accidental exposure, may be increased in these children. Our cohort also included four children with a prior reaction to baked egg, three of whom subsequently passed their challenge to baked egg.

The mechanism by which egg-allergic children may tolerate baked egg (but not other forms of egg) is likely to be related to several factors, including the protein denaturation resulting in conformational changes in the major allergenic epitopes (17). Another factor is the interaction of heated egg within a complex food matrix; a recent study demonstrated that the presence of wheat in a baked egg matrix is important in explaining the tolerance of egg-allergic children to baked egg, in addition to the effect of heat on protein denaturation (18). Foods with higher fat content are more prone to the action of gastric enzymes due to an effect on gastric emptying (19); an additional possibility therefore is that the higher fat content of the muffin might slow gastric emptying, thus exposing the egg protein to increased degradation by gastric enzymes *in vivo*. However, this would not explain the reduced IgE-binding to egg proteins modified through a baking process observed *in vitro* in previous studies (18). Tolerance to baked egg is not simply a function of exposure to a reduced dose of allergen.

Lemon-Mule et al. reported 30 subjects who were able to tolerate 2.2 g of extensively heated egg protein in a muffin but reacted to a lower dose of protein when using lightly cooked scrambled egg during OFC (3). Within our own service, we have identified a number of children who react to under 300 mg of egg protein at OFC but tolerate over 1 g of heated egg protein in a muffin.

A potential limitation of this study is that children were not all formally challenged to conclusively establish egg allergy at entry, prior to OFC to baked egg. Although this would have strengthened the study, it was considered unethical to challenge children with a very high probability of clinical reaction (PPV > 95% SPT/ssIgE), including 16% with a past history of anaphylaxis to egg. The proportion of children who passed OFC to baked egg and who were avoiding egg on the basis of sensitization alone was not different from those with a recent convincing history of egg allergy, suggesting that the underlying rate of true egg allergy in each group was similar. Our inclusion criteria are typical of children presenting to health professionals for management of food allergies in daily practice. We believe ours is a pragmatic approach aimed at assisting the clinician in the appropriate management of a child with a high likelihood of egg allergy on the basis of history and/or sensitization. We have demonstrated the relative safety of OFC to baked egg in egg-allergic children including those with previous reaction to baked egg or anaphylaxis to whole egg. Based upon our population, we recommend that initial introduction of baked egg should occur under direct medical supervision in an environment where severe reactions can be managed appropriately, until better predictors for severe allergic reactions can be identified.

Acknowledgment

We thank the parents and children who participated in this study.

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Appendix 1

Parents were provided with the recipe below and instructed to prepare the muffins at home. Adherence to these instructions (ingredients and baking process) was confirmed through direct questioning to the parent(s) immediately prior to challenge.

Rather than provide muffins produced in hospital, we chose to ask parents to prepare muffins at home as we considered it more important to demonstrate the ability and enthusiasm to follow the recipe as an indicator of ensuring ongoing exposure to baked egg after challenge. This also had the advantage of catering for those children with multiple food allergies in whom some modification of the recipe was required (see below).

Preparation of baked egg in muffin

Ingredients

- ½ cup (125 g) butter or margarine
- ⅔ cup (160 g) sugar
- 1¾ cup (220 g) plain flour (or gluten free flour in wheat allergic children)

- ½ cup (125 ml) cow's milk (or milk substitute in milk-allergic children)
- Two level teaspoons baking powder
- Two large eggs (egg size approximately 50 g).

Preparation instructions

- Pre-heat conventional oven to 180°C
- Mix flour, baking powder, and sugar together
- Add softened butter/margarine and mix until a crumbly mixture is formed
- Whisk or beat the eggs and milk together and stir into the flour mix.
- Stir ingredients until just combined.
- Place muffin paper cases into a muffin tray
- Distribute batter evenly into each muffin cup
- Bake for 20 min, until golden brown and slightly firm to touch.