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Evaluation of baked egg oral immunotherapy in French children with hen's egg allergy.

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Hen's egg allergy and immunotherapy

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Background: Introduction and gradual incremental escalation of a low dose of baked egg may accelerate the resolution of severe hen's egg (HE) allergy for some children. The purpose of our study is to evaluate the efficacy and safety of baked egg oral immunotherapy (OIT) in children with HE allergy after a low-dose baked egg oral food challenge (OFC). **Methods:** In a retrospective analysis of OFC performed between 2013 and 2018 at the Children's Hospital of Toulouse (France), we identified 71 children with HE allergy and high egg-white (EW) and ovomucoid specific IgE levels, who underwent a total of 164 OFC (71 baked egg then 93 unbaked egg). Mean age at 1st low dose baked egg OFC was 6 years. Median EW specific IgE was 14.0 kUAI, and median ovomucoid specific IgE was 11.7 kUAI. **Results:** Most children were treated with baked egg OIT. Our study shows that 78.9% of the children did not react to 1st low dose baked egg OFC (702 mg of HE protein). 8.7% of children discontinued OIT at home. Finally, desensitization to unbaked HE was achieved in 47 children (66.2% of children allergic to HE). Children with lower EW specific IgE levels had a significantly higher probability of becoming desensitized to HE. We did not report any anaphylactic reactions to baked egg OIT. **Conclusion:** Most children with HE allergy and high egg-white (EW) and ovomucoid specific IgE levels tolerate the introduction of baked egg. Baked egg OIT is safe and anaphylaxis to baked egg OIT has not been observed.

Keywords: Food Allergy, Hen's egg Allergy, Oral Immunotherapy, Baked Food, Anaphylaxis, Pediatric, Oral Food Challenge, Efficacy, Safety

Key message: It is already known that frequency of hen's egg allergy is increasing in children, including more severe and persistent forms. Most of children can tolerate baked egg after oral food challenge, even if the allergy is severe. Introduction and gradual incremental escalation of a low dose of baked egg may accelerate the resolution of severe hen's egg allergy for these children. Our study included hen's egg allergic French children, with high specific IgE levels. Most of them could start baked egg oral immunotherapy. Less than nine percent of children stopped OIT at home, mainly because of mild reactions. Desensitization to unbaked hen's egg was achieved in 66.2% of hen's egg allergic children. Children with lower egg-white-specific IgE levels have a significantly higher probability of becoming desensitized to unbaked egg.

Introduction

Food allergies (FA) in children have been increasing in prevalence over the past few years^{1, 2}. Cow's milk and hen's egg (HE) allergies are the most frequent and the most disabling, due to the ubiquitous presence of these foods in our diets. It is estimated that HE allergy affects 0.4 to 2% of children^{3, 4}. The prognosis has historically been considered good overall, with a reported resolution rate of 80% by the time children reach school age. However, in more recent studies, the allergy was outgrown in only 50% of children who were school-aged⁵ or sometimes-even older⁶. Persistent HE allergy is associated with higher egg white (EW) and ovomucoid specific IgE levels^{7, 8}. Oral immunotherapy (OIT) is the only treatment currently available in FA. It is widely used in French hospitals; however, its side effects are frequent⁹. Using baked egg for OIT may reduce side effects and it may be tolerated better: 70% of children allergic to HE could tolerate baked HE¹⁰. If it has not yet been introduced at home, baked egg is usually introduced after an initial hospital baked egg oral food challenge (OFC). Thereafter, the regular ingestion of baked food helps accelerate resolution of the FA and improves the quality of life for a HE allergic child and his family^{11,12}. The purpose of our study is to evaluate the implementation, efficacy and safety of baked egg OIT after a low-dose baked egg OFC in children with HE allergy.

Materials and Methods:

a) Study overview

We carried out a retrospective chart review of all OFC to HE and baked egg performed at the Children's University Hospital of Toulouse, during the period July 2013 to December 2018. We included children with HE allergy, which is defined by the onset of a type I allergic hypersensitivity reaction after consumption of HE, associated with high specific IgE: EW specific IgE >7 kUA/l after 2 years old, or >2 kUA/l before 2 years old¹³. The exclusion criteria included: age ≥18 years, refusal to take part in the study, reaction to traces of HE or baked egg in the previous 6 months, tolerated consumption of baked egg (according to clinical history), negative skin prick tests (SPT) and negative specific IgE. We did not include cases in which there was not at least a 2nd OFC (unbaked HE) after implementation of the baked egg OIT (completed after December 2018), and those without a 1st low dose baked egg OFC. A history of anaphylaxis was not an exclusion criterion. Before starting OIT, the patients underwent a low-dose OFC with Madeleine (small cookie). At least one additional OFC with HE at a higher dose was then performed, after OIT, to reassess the patients' unbaked HE tolerance. This process is part of our standard clinical care for these children.

b) Data collection on inclusion

For each patient, we collected clinical characteristics including age, sex, initial allergy symptomatology, presence of respiratory allergies, asthma, and associated FA. The diagnosis of allergy to other foods was made when these foods caused a type I allergic hypersensitivity reaction, associated with SPT and/or positive specific IgE. We collected the SPT results for raw EW, as well as specific IgE tests: EW specific IgE, and ovomucoid specific IgE (*Phadia Thermo Scientific Assay*). Allergic reactions were graded according to the Ring & Messmer classification¹⁴:

I: Generalized cutaneous signs: erythema, urticaria, with or without angioedema

II: Moderate multi-organ involvement with cutaneous signs, hypotension and tachycardia, bronchial hyperreactivity: cough, difficulty to ventilate.

III: Severe life threatening multiorgan involvement: collapse, tachycardia or bradycardia, arrhythmias, bronchospasm. Cutaneous signs may be present or may occur only after arterial blood pressure is restored.

IV: Cardiac and/or respiratory arrest

c) Oral food challenge

OFC were performed under the supervision of a senior physician from the Pediatric Pneumo-allergology team of the Children's Hospital of Toulouse. The first baked egg OFC included a total dose of 5.4 grams (g) of baked HE (702 mg of HE protein) in the form of madeleines. For reference, the madeleine we used (industrial manufacturing madeleine "Saint Michel® aux œufs frais") weighs about 15 g, and contains 16% HE, *i.e.* 2,4 g of HE and 312 mg of HE protein. It was administered sequentially according to the following scheme: 0.2 g of madeleine, then 0.5 g of madeleine, 1 g of madeleine, 2 g of madeleine, 5 g of madeleine, 10 g of madeleine, and 15 g of madeleine. The 2nd OFC, about one year later, consisted of the sequential administration of a total dose of 38.7 grams of unbaked HE (5 grams of HE protein, about two-thirds of an egg), in the form of hard-boiled egg. The administration scheme was: 5 mg of HE, then 10 mg, 50 mg, 200 mg, 500 mg, 1 g, 2 g, 5 g, 10 g, and 20 g. Children who passed this test successfully were considered desensitized and this 2nd OFC was the last challenge for them. For the children who failed this 2nd OFC because of clinical reactions, the baked egg OIT was continued, and a new unbaked HE OFC was performed one year later, with the same scheme as the 2nd one. Generally, doses were administered at 20 minutes intervals, and children were monitored at least 2 hours after the last dose of the OFC. The reactogenic dose and the type of clinical reaction were detailed for the positive OFC, according to the Ring & Messmer classification previously described¹⁴.

d) Oral immunotherapy

After the first OFC, we initiated baked egg OIT. The family's commitment to follow the proposed OIT protocol was assessed. A dietician and a senior physician met with every family for an education session about allergic co-factors, the emergency kit, the use of adrenaline, and the conditions that would lead to its use. OIT was started in the days following the OFC and involved the daily intake with progressive increase at home of the food to be reintroduced. As per the baked egg OIT protocol, patients generally started with 1 g of baked egg. They started at a lower dose if they had shown a reaction before the last dose of the first OFC. Patients then increased their daily baked egg dose by one g every month, until reaching 5 g per day, except for those who reacted during the first OFC, and who did not exceed the reactogenic dose.

At this point, patients were seen in medical consultation and generally continued this same dose until the 2nd OFC (38.7 grams of unbaked HE), which was performed one year after the first OFC. OIT was not discontinued before the 2nd OFC. When the 2nd OFC was still positive, we adjusted the OIT dosing by increasing it if possible until half the reactogenic dose, and a new OFC (same

scheme as the 2nd one) was scheduled one year later. The dietitian and the senior physician could be contacted (telephone number and mail address were given to the family) if an allergic reaction occurred or in case of any other difficulty, and a medical consultation was carried out if necessary. The family was recommended to reduce the dosage during illness, to avoid non-steroidal anti-inflammatory drug and to avoid exercise before and after taking daily doses.

Data collected included the occurrence of reaction to the baked egg OIT, the severity (or grade) of reactions, the presence of any allergic co-factors, and any treatment needed for OIT-related reactions, including whether adrenaline was administered. We also reviewed whether OIT was terminated for any reason.

e) Ethics

The study complies with the requirements of the French National Commission for Data Protection and Freedom and the General Data Protection Regulation. Informed consent and assent were obtained.

f) Statistical analysis

The statistical analysis was performed by a Chi-square test (or Fisher exact test according to the theoretical numbers) for the qualitative variables, and by a Student's t-test (or a Mann Whitney U test if the normality or the homoscedasticity of distributions were not verified) for quantitative variables. The statistical tests were performed with the STATA v13.1 software and were conducted with a bilateral approach and a risk of error of the alpha risk set at 5%. We considered a $p < 0.05$ statistically significant.

Results

a) Characteristics

We included 71 children, for a total of 164 OFC. The clinical characteristics of children and their evolution are detailed in Table 1. Forty eight of 71 (67.6%) children were boys, with an average age of 6 years (range [2-17 years]) at the 1st OFC. Most children had at least one additional FA: tree nuts (59.3%), peanuts (46.3%), CM (38.9%), mustard (27.8%), legumes other than peanuts (18.5%), fish and/or shellfish (16.7%), wheat (13%), kiwifruit (11%), sesame (2.8%), banana, beef, mussels, grapefruit, and rice (1.4%). The mean diameter of the SPT wheal for raw EW was 11 mm (measured in 23 children (32.4%)).

b) First OFC and OIT

The initial baked egg OFC was positive 21.1% of the time, with mostly grade II allergic reactions (80%). On average, it was positive at a cumulative reactogenic dose of 3.9 g of baked egg, *i.e.* 0.5 g of HE protein. No reaction required adrenaline. Baked egg OIT could be implemented in 69 children of our entire cohort (97.2%). The two children who did not start OIT had grade II reactions at a cumulative dose of 1.4 g of baked egg, and families declined OIT. Of the 69 children doing baked egg OIT at home, 10 (14.1%) had some reaction to home dosing, including oral itching (n=2, 2.8%), skin reactions (n=1, 1.4%), asthma exacerbation (n=2, 2.8%), and digestive reactions (n=5, 7.0%). None of these reactions required adrenaline. OIT was discontinued (*i.e.* complete stop without resumption) in six children (8.7% of children following the OIT). These reactions and discontinuations are detailed in Table 2.

c) Last OFC

The average age of the children at last OFC was 7.3 years. The mean diameter of the SPT wheal for raw EW was 10 mm (measured in nine children (12.7%)). The unbaked egg OFC was positive for 24 children (33.8%), with an average cumulative reactive dose of 16.7 g of HE, *i.e.* 2.2 g of HE protein. Sixteen children needed more than 2 OFC to follow OIT program towards desensitization (tolerance of 5 g of unbaked HE protein), because of reactions during the 2nd OFC. Overall, desensitization was achieved in 47 children (rate of 66.2% for our entire population), after an average of 2.26 OFC, and an average duration of 452 days (1 year, 2 months, and 26 days) following the 1st OFC.

d) Initial characteristics of children achieving desensitization

Forty-seven children achieved desensitization, as demonstrated by their passing unbaked HE OFC following baked egg OIT. Baseline mean EW specific IgE levels were significantly lower among the 47 children who achieved desensitization as compared to the 24 who did not: 18 kUA/L versus 30 kUA/L ($p=0.048$). We found no significant difference in baseline ovomucoid specific IgE between these two groups: 14.4 kUA/L in desensitized children versus 23.6 kUA/L ($p=0.12$) in those who were not desensitized after baked egg OIT. We found no significant difference between the two groups about the age of the children at the time of the 1st OFC, or the presence of atopy (asthma, respiratory allergy, associated FA, and number of associated FA). These data are shown in Figure 1.

Discussion

In our study, the average age of HE allergic children at 1st baked egg OFC was 6 years, comparable to previous studies^{13, 15}. Most of the children were atopic, with asthma and at least one associated FA. For most of our cohort, presumptive diagnosis of HE allergy was already known by allergy testing, which is consistent with data from the literature pointing out an increase in FA discoveries through eczema and sensitizations¹⁶⁻¹⁸. In France, HE is generally introduced after other foods, like CM, wheat, fruits, vegetables, and sensitizations can be found on severe atopic dermatitis or any other atopy. Thereafter, in our study, all these children subsequently developed allergic reactions during exposure accidents, confirming HE allergy. Moreover, the mean specific IgE levels at the 1st OFC (EW: 22.1 kUA/L; ovomucoid: 17.1 kUA/L), were predictive of true clinical reactivity to HE.

In our cohort, the initial baked egg OFC was negative 78.9% (56/71) and indicated tolerance of baked egg. In the Turner study, of 236 egg-allergic children (median age 3.8 years), 64% tolerated baked egg¹⁵. The IgE levels of these children were not reported. In the Bartnikas cohort, of 169 children with IgE-mediated HE allergy, 84% tolerated baked egg¹⁹. It should be noted however that this study mixes hospital OFC and reintroduction at home and is not strictly superimposable to ours. In the Lemon-Mule study, of 117 children (mean age 6.9 years) with an IgE-mediated HE allergy, 70% tolerated baked egg but reacted to raw HE¹⁰. This study was continued in 79 egg-allergic individuals (mean age 5.8 years), followed for 37.8 months¹³. At the end of OIT, 53% were able to reintroduce regular HE after OFC. The median time required to

tolerate regular HE was 42 months (58 months if there was an initial reaction to baked egg). In our study, the success rate following the 1st OFC is slightly higher, but with a smaller ingested dose (5.4 g of HE, *i.e.* 0.7 g of HE protein, versus 13 g of HE, *i.e.* 1.7 g of HE protein¹⁰). The desensitization rate in our cohort of 66.2% was slightly higher, and the average duration of 15 months to achieve desensitization was shorter. Thus, larger concentrations of HE protein may not be essential for a desensitization protocol.

Regarding SPT and IgE, in Leonard et al's study of factors that accelerate resolution of egg allergy, egg allergic children who tolerated baked egg had significantly lower EW specific IgE (1.9 kUa/l versus 13.5 kUa/l) and smaller EW-SPT (6 mm versus 8 mm) than subjects who did not tolerate baked egg¹³. The thresholds recommended in this study for offering a baked egg OFC are EW>7 kUa/l if >2 years old, and EW>2 kUa/l if <2 years old. If the levels are lower, some authors propose OFC with unbaked HE. If EW>50 kUa/l, some authors recommend continued avoidance of all forms of HE and re-evaluation of the child's HE allergy 6 to 12 months later¹⁰. In the Bartnikas study, lower EW specific IgE (1.31 kUa/l versus 6.00 kUa/l) and lower ovomucoid specific IgE (<0.35 kUa/l versus 0.76 kUa/l) predicted success of the baked egg OFC¹⁹. It was proposed in this study to avoid baked egg OFC if EW>9.65 kUa/l, ovomucoid>3.38 kUa/l, or EW-SPT>25 mm. The results vary depending on the studies because it depends on how the food is cooked and the populations tested. Specific IgE seems interesting, but SPT shows a less discriminatory response. We found this trend in our study, with a significantly lower EW specific IgE rate among children who did not achieved desensitization.

Regarding OIT procedure, daily ingestion of baked egg is usually well tolerated with few serious allergic reactions^{13, 20-23}. However, moderate reactions are common, which may make it difficult to track the progress of OIT²⁴. Some studies report anaphylactic reactions during the introduction of baked egg and advise caution^{13, 22}. In our study, 14.1% of the children had reactions during OIT, with 8.7% discontinuing OIT at home. Adrenaline was never used. Nevertheless, families should be informed about the possibility of reactions, including anaphylaxis, to home OIT dosing, and should be prepared to treat with adrenalin if needed. For this reason, we emphasize the availability of an emergency kit with auto-injectable adrenaline for all patients with FA on OIT²⁵⁻²⁷. Its use must be reviewed in detail and parents/caregivers and patients must demonstrate proficiency with a training device (or demo pen). Patients need to be educated about cofactors that may promote a reaction to OIT dosing²⁸.

Finally, we would like to highlight that even for children who did not achieve desensitization (*i.e.* the 24 children who did not pass the HE exit OFC), we found an increase in the reactogenic dose between the 1st and last OFC. Indeed, the average reactogenic dose increased from 3.9 g of baked egg to 16.7 g of unbaked HE.

One limit of our study is the absence of a control group. However, in France, the practice of OIT after OFC for HE allergy is widespread, and it would not be ethical to exempt some children while they are eligible. This is also a monocentric retrospective study and some data, such as adverse events, could potentially be underestimated. Quality of life was not assessed in our study; however, prior studies have shown that OIT contributes to a better quality of life for FA children and their families compared to those not realizing it¹².

Conclusion

In our study, 66.2% of children allergic to HE were desensitized to unbaked HE after completing a course of baked egg OIT. At baseline, most children could introduce baked egg, even children who reacted during the 1st OFC to baked egg. This introduction seems to be safe and well tolerated in most cases. A few patients on OIT stop at home (8.7% in our retrospective study) for various reasons. Children with a lower EW specific IgE level have a significantly higher probability of achieving desensitization. As with all OIT protocols in which individuals are exposed to their food allergens, it is necessary to keep in mind that allergic reactions, including anaphylaxis, can occur at any time during a desensitization protocol. Patients and their families must be informed about this potential and must be provided with an adrenalin auto-injector.

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Table No. 1: Detailed clinical characteristics and patient evolution. The results are expressed in number (percentage) and average (standard deviation) / median [range].

	HE allergy
Number of patients	71
Number of OFC carried out	164
Gender (Male)	48 (67.6%)
Atopic comorbidities:	
Asthma (Doctor diagnosed)	46 (64.8%)
Respiratory allergy	43 (60.6%)
Other FA	54 (76.1%)
1–2	29 (40.8%)
3–4	21 (29.6%)
≥ 5	4 (5.6%)
Initial diagnosis made on:	
Sensitization†	39 (54.9%)
Grade I Allergy	13 (18.3%)
Grade II Allergy	17 (23.9%)
Grade III Allergy	2 (2.8%)
Age (years) at 1 st OFC	6 (3.67)
Specific IgE (kUA/l) at 1 st OFC	
EW	22.1 (24.6) / 14.0 [97.6]
Ovomucoid	17.1 (21.7) / 11.7 [96.4]
1 st positive OFC (n=)	15 (21.1%)
Grade I Allergy	3 (4.2%)
Grade II Allergy	12 (16.9%)
Grade III Allergy	0
Age (years) at last OFC	7.3 (3.73)
Specific IgE (kUA/l) at last OFC	
EW	17.2 (23.2) / 7.9 [98.8]
Ovomucoid	10.6 (17.0) / 7.8 [99.2]
Last positive OFC (n=)	24 (33.8%)
Grade I allergy	7 (9.9%)
Grade II allergy	17 (23.9%)

Grade III allergy

0

Average time until the last OFC (months)

14.9 (4.7)

† For these children, HE allergy was initially discovered by allergy testing, but they all subsequently developed allergic reaction, confirming HE allergy.

Table No. 2: Detailed characteristics of the 10 children reacting during OIT, including the 6 OIT discontinuations.

Patient N°	Age (years)	Reaction	Dose (g)	Cofactors	Medication used	Time since starting OIT	Decision of discontinuation
1	5	Vomiting, abdominal pain	2	No	Metiquazine	3 months	By doctor
2	9	Abdominal pain / Disgust	1	No	No	1 month	By family
3	3	Asthma	1	No	Salbutamol, prednisolone	3 months	By doctor
4	7	Asthma	2	Grass pollen allergy	Salbutamol, prednisolone	2 months	By doctor
5	9	Abdominal pain	1	No	Desloratadine, prednisolone	1 month	By family
6	15	Oral itching	3	No	No	3 months	By family
7	10	Oral itching	2	Exercise	Desloratadine	2 months	No
8	7	Abdominal pain	4	No	Desloratadine, prednisolone	4 months	No
9	5	Abdominal pain, diarrhoea	4	No	Prednisolone	4 months	No
10	3	Erythema of the face	5	No	No	6 months	No

Figure 1: Evolution of children with HE allergy.

