

NATURAL COURSE OF SENSITIZATION TO HEN'S EGG IN CHILDREN NOT PREVIOUSLY EXPOSED TO EGG INGESTION

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Background: Clinical adverse reactions to egg may occur in infants or children who have never eaten egg. They may be sensitized or even react at first egg ingestion. Few studies are available concerning the reality of egg white allergy in such sensitized children, the natural evolution of this condition and the appropriate decisions to make

Objectives: To analyze the actuality and natural course of egg allergy in children sensitized without previous of hen's egg ingestion.

Methods: We set up a clinical decision tree based on clinical history and specific egg white IgE to manage patients who had never ingested egg but were sensitized as demonstrated by a positive SPT and report a cohort of 30 such children

Results: The mean level of egg white specific IgE at first analysis, i.e. before 12 months, was high, 28.3 KU_A/L, with a large range, from 0.6 to > 100 KU_A/L, below 6 KU_A/L in only 8 patients.

In 6 children ("no challenge" group), IgE values remained > 8 KU_A/L by the end of the survey and the oral challenge with egg was always denied. Their mean + SD IgE level was at 51.7 + 38 KU_A/L at 1 year and 19.7 + 13 KU_A/L at a mean age of 34 + 5 months. All had an associated anaphylactic reaction with milk and 5 were still allergic to milk by the end of the survey.

In the remaining 24 infants, egg was given for the first time at a mean age of 30 + 9 months, by error in 4 cases, all exhibiting an immediate reaction, and in a hospital setting in 20, among whom 14 reacted. Among those 18, with a specific IgE level at 9.1 + 10 KU_A/L at 28 + 9 months, 4 became tolerant between 3 and 4 years, with specific IgE levels below 1.3 KU_A/L and a 5th one with specific IgE > 100 KU_A/L at 6 months tolerated scrambled eggs at age 7 year, with specific IgE at 2.6 KU_A/L.

In the 6 others, labeled "non allergic", egg white specific IgE levels were significantly lower, whatever the age, than in the "no challenge" group. The age at challenge was 35 + 8 months, with a mean specific IgE level at 1.0 + 0.9 KU_A/L.

Conclusion: In children sensitized to egg without previous ingestion of that food, egg tolerance appears probably in some by the age of 3 but may reveal much more prolonged in a limited number.

Egg allergy - Egg sensitization - Children - Egg white specific IgE.

Abbreviations : SPT: skin prick test.

Clinical adverse reactions to egg may occur in infants or children eating eggs for the first time (1, 2). Sensitization to hen's eggs manifested by a positive skin prick test (SPT) or raised specific IgE has also been described in infants with food allergy or at high risk of atopy, in the absence of any previous ingestion of egg (2, 3). Two potential fetal routes of exposure to allergens have been identified (4), the fetal gut by swallowing allergens in amniotic fluid (5, 6) and the direct transfer of allergens across the placenta (7, 8). A specific immune response in the child may also be elicited by allergens conveyed via the milk to a breast-fed infant (9, 10). The presence of a positive SPT or of raised specific IgE settles a difficult situation for the clinician, whose responsibility is to determine whether the child is allergic or only sensitized. Before a diagnosis can be made with a standardized oral challenge test, the gold standard in food allergy, those infants must be considered at risk,

especially since 1/ the oral challenge in itself places the patient at risk for a severe allergic reaction; 2/ the introduction of egg in food should be delayed in young infants with food allergy or at high risk of atopy (3). A previous study suggests that an oral challenge test might be superfluous in a significant number of patients after quantification of food-specific IgE: Sampson *et al.* (11) demonstrated that for egg white (CAP; Pharmacia, Uppsala, Sweden) a cut-off level at 6 KU_A/L predicts a clinical allergic reaction with more than 95% certainty. Sampson *et al.* (11) therefore suggest that "patients with food-specific IgE antibody levels greater than the 95% predicting value for egg [...] are extremely likely to experience an allergic reaction if they ingest the food and therefore do not need to be challenged to establish a diagnosis of symptomatic food hypersensitivity [...]". For the same authors (11), monitoring food-specific IgE antibody levels every 1 to 2 years may be useful in determining when to rechallenge patients, for example, when IgE antibody concentrations to egg fall to one

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third of the 95% predictive value. It is therefore now feasible to base, at least in part, the clinical survey of a child on its egg white specific IgE levels, thus both alleviating the clinical monitoring and facilitating the decision making relating to oral challenges.

Based on the suggestions of Sampson *et al.* (11), we set up a clinical decision tree to manage patients who had never ingested egg but were sensitized as demonstrated by a positive SPT and report a cohort of 30 such children to analyze the natural course of hen's egg sensitization. We show that egg tolerance appears probably in some of them by the age of 3 but may reveal much more prolonged in a limited fraction of them.

PATIENTS

Thirty children who had never eaten egg, 19M/11F, aged 6.5 months (mean), range 4 to 12 months, had a positive egg SPT. They were referred for suspected food allergy because of atopic dermatitis in 25, anaphylactic reaction or angio-edema with cow's milk in 15, digestive symptoms, such as vomiting, diarrhea or constipation in 8, failure to thrive in 2 and chronic bronchitis in 2. Allergy to cow's milk was present in 28. Allergy to extensively hydrolyzed formula in 10, and multiple food allergy in 2. Among the 2 children with no allergy to cow's milk, one, referred for investigation of Quincke edema triggered by kiwi at 7 months, was the only non breast-fed infant, and the other one was referred for eczema, digestive symptoms and bronchitis.

Following this first evaluation, the clinical care was carried out according to the decision tree (figure 1), designed to handle the potential egg allergy both on egg white specific IgE, as described by Sampson *et al.* (11), and on the clinical observation of the child. Egg white specific IgE were measured once a year (CAP System®, Pharmacia, Uppsala, Sweden) with results expressed as KU_A/L. Parents were carefully recommended not to introduce egg in their child's diet, and an outpatient clinic programmed every 6 months. At each consultation, a great care was taken to analyze whether, despite the recommendations, eggs and/or egg-containing food had been ingested between two consultations, in which case a careful analysis of symptoms was recorded. If the parents reported no reaction or a limited one, an oral challenge was carried out with raw egg. In case of immediate reaction such as angio-edema or anaphylaxis, the infant was labeled allergic. If no egg had been given to the child, an oral challenge was proposed every year if the egg specific IgE levels had fallen below 3 KU_A/L, half the cut-off of Sampson *et al.* (11). In addition, due to the beginning of school and of community feeding, a challenge was always programmed at age 3 years.

The mean duration of the survey was 4.5 + 1.2 years (range 2-7 years).

Statistics were calculated assuming the following values for extremes, 100 KU_A/L for a result > 100 KU_A/L, and 0.1 KU_A/L for undetectable IgE (< 0.35 KU_A/L).

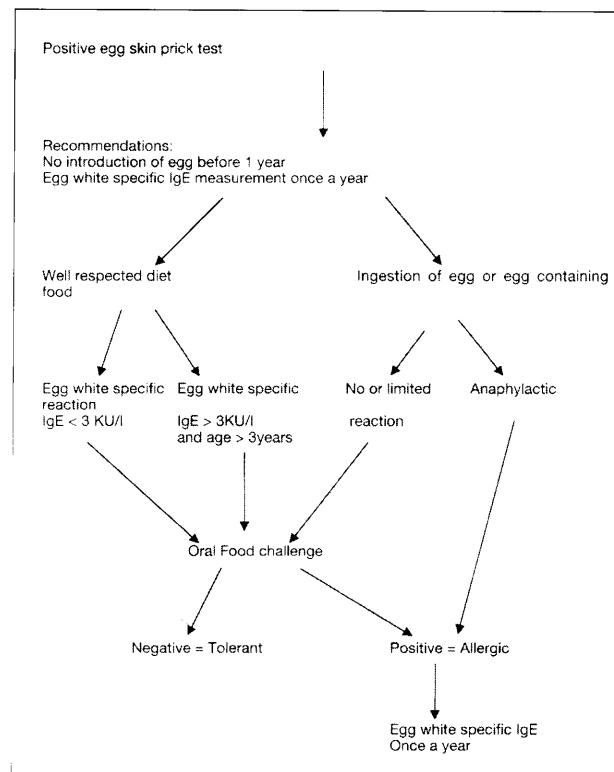


Figure 1: Decision tree: children were enrolled based only on a positive skin prick test to egg, before ingestion of any egg or egg derivative. They were followed up according to the following diagram.

RESULTS

Most infants had atopy in first degree relatives and had been breastfed (table 1). The mean level of egg white specific IgE at first analysis, i.e. before 12 months, was high, 28.3 KU_A/L, with a large range, from 0.6 to > 100 KU_A/L, below 6 KU_A/L in only 8 patients. Clinical data of groups are reported in Table 2 and individual evolution of egg white specific IgE in table 3. In 6 of these 30 children, IgE values remained > 8 KU_A/L by the end of the survey. They constitute the "no challenge" group since the oral challenge with egg was always denied and egg or egg-containing foods never given by error. They had a mean + SD IgE level at 51.7 + 38 KU_A/L (range 8.5 to > 100 KU_A/L) at 1 year and by the end of the study the IgE level was 19.7 + 13 KU_A/L (range 8.6 to 39 KU_A/L), at a mean age of 34 + 5 months. All of them had an anaphylactic reaction with milk and 5 were still allergic to milk by the end of the survey.

In the remaining 24 infants, egg was given for the first time at a mean age of 30 + 9 months. In 4 cases, egg was given at home by error, resulting in a Quincke edema, whereas all others were challenged in a hospital setting. In 14, the test triggered an immediate reaction witnessed by the medical staff. The latter, together with those having exhibited an immediate reaction at home were considered "allergic" to egg. In

6 cases, the test was negative and the child considered tolerant to egg, so-called "non allergic" group. In the 18 "allergic" patients, the challenge was done at 28 + 9 months (18 to 60 months), with a specific IgE level at 9.1 + 10 KU_A/L (< 0.35 to 35 KU_A/L). Among those 18, 4 patients became tolerant between 3 and 4 years, with specific IgE levels at 0.81 and 1.3 KU_A/L in 2 and < 0.35 in 2. A 5th allergic patient with specific IgE

Clinical data of patients (n=30)

Atopy in first degree relatives (n)	28
Breast feeding (n)	29
Duration of breast-feeding (months)	3.5 - 2.3 1-11
Clinical symptoms (n):	
Atopic dermatitis	25
Digestive symptoms	8
Failure to thrive	2
Chronic bronchitis	2
Anaphylactic reaction with milk	15
Cow's milk allergy (n)	28
Allergy to extensively hydrolysed formula (n)	10
Number of associated food allergies	2.3 + 1.6 (0-8)
Age at diagnosis (months)	6.5 + 2.3 (4-12)
Specific egg white IgE (KU _A /L)	
Before 12 months	28.3 + 33 (0.6- >100)
Between 12-24 months	15 + 19.8 (0.1-85)
Between 2-3 years	8.6 + 10.7 (0.1-41.6)
Duration of survey (years)	4.5 + 1.2 (2-7)

Table 1.

No challenge	Allergic	Non allergic	
N =	6	18	6
Sex (M/F)	3/3	12/6	4/2
Clinical symptoms:			
Eczema	4	16	5
Digestive symptoms	2	3	2
Cow's milk allergy	6	17	5
Anaphylactic reaction with milk	6	10	1
Specific egg white IgE (KU _A /L)			
Before 12 months	51.7 + 38	26.1 + 32	7.1 + 7*
Between 12-24 months	30.1 + 26	10.5 + 11	2.6 + 3.9*
Between 2-3 years	19.7 + 13	7.3 + 9	1 + 0.9*
Mean age at introduction (months)		28 + 9	35 + 8
IgE level at introduction (KU _A /L)		8.8 + 11	1.0 + 0.9

Table 2: Clinical data and results of specific IgE of patients in the different groups: patients never challenged with egg ("no challenge" group), clinically reactive ("allergic") or not ("non allergic").

* Difference was significant with p < 0.05 between non allergic and non challenge group.

Patients	< 1 year	1 year	2 years	3 years	4 years	> 5 years
No challenge patients						
1		>100	67	31		
2	2.1	8.5	14.6	9.8		
3	28.7	12.5	13.2	14		
4	25.9	35.7	39			
5	> 100	63	27	16		
6		18.4	7.9	8.6		
Allergic patients						
7	7.1	2.8	2.5	6.4	5.4	2.8
8	>100			24.3		10.7
9	2.6	0.5	<0.35	<0.35		
10		2.5	0.54		3.9	
11		1.6	3.9	0.8		
12	11	26	27	14	18	17
13	17.8	8.5	4.7	2.1	0.8	
14	19.6		3.1			
15	4.9	3.5		1.1		
16	8.4	4.6	1.6	2.2		
17	>100	49	14			2.6*
18	37	35	13			
19		30	23	18		2.9
20		8.4	2.9	1.3		
21	1.5	1.1		<0.35		
22	8.3	5.2	1.9			
23	23.5	49.2		17.8	16	
24	37.4	13.6	9.9	7.5	5.8	
Non allergic patients						
25	3.7		2.4	1.01		
26		17.8	8.75		2.41	
27	2.3		<0.35			
28	2.7	3.6	1.55			
29	0.6		<0.35			
30	10.3		0.6	0.6		

Table 3: Individual evolution of egg white specific IgE in children. Figure underlined indicates clinical reaction and bold characters tolerance.

* Patient tolerated scrambled eggs at age 7, but always presented an oral syndrome with raw egg.

>100 KU_A/L at age 6 months tolerated scrambled eggs at age 7 year, with specific IgE at 2.6 KU_A/L, but always presented an oral syndrome with raw egg. In the 6 "non allergic" children, egg white specific IgE levels were significantly lower, whatever the age, than in the "no challenge" group (Table II). In these "non allergic" children, the age at challenge was 35 + 8 months (range 24 to 48 months), with a mean specific IgE level at 1.0 + 0.9 KU_A/L (< 0.35 to 2.4 KU_A/L).

DISCUSSION

We describe a population of children with positive SPT to egg without previous ingestion of that food, document the actual allergy to egg in some of them and give a first indication of the natural evolution of this condition.

In infants at risk of food allergy, delaying introduction of highly allergenic foods such as egg, into the diet has been suggested to prevent sensitization (3). Such infants may nonetheless exhibit a positive SPT to egg and egg-specific IgE before ingestion (1-3, 12). According to Caffarelli *et al.* (1), a positive egg SPT in infants with food allergy predicts egg allergy before the introduction of that food in the diet and for Monti *et al* (12) patients with a wheal diameter SPT > 5mm exhibit a positive egg challenge in 100% of cases. We based this study on SPT positivity, as indicated in Patients, but the analysis of the wheal size may be misleading since SPTs were done on the back or the forearm, where, according to our experience, the wheal size may be smaller in the young child. All those patients were nonetheless at risk of allergic reaction during the first introduction of egg, even though having never ingested that food, as carefully checked during history taking. Even though sensitization may have occurred in utero, as discussed above (4), the high incidence of breast-feeding, 97%, notably higher than in the general population, deserves consideration (9, 10).

The major difficulty is to decide when to introduce egg in these atopic patients with egg sensitization. The standardized oral challenge test, gold standard in the diagnosis of food allergy, places the patient at risk for a severe allergic reaction, so that biology may reveal helpful: previous studies suggest that the oral challenge test might be superfluous in a significant number of patients after quantification of food-specific IgE. For Sampson *et al*, egg white specific IgE measured with the CAP-system exhibit at 6 KU_A/L a cut-off level above which a clinical allergic reaction is predicted with more than 95% certainty (11) and at 7 KU_A/L a 98% certainty (13). For Boyano *et al* (14) the oral challenge test is unnecessary in infants < 2 years of age with a positive case history of an immediate reaction to egg and egg white specific IgE > 0.35 KU_A/L. For Roehr *et al.* (15) egg

white specific IgE > 17.5 KU_A/L renders the oral challenge test unnecessary. Monti *et al* (12) studying patients with atopic dermatitis before egg introduction suggest that only the > 99 KU_A/L albumen cut-off offers a 100% certainty of egg clinical reactivity: oral egg challenges were negative in 2 patients with albumen specific IgE class 5 (50-99 KU_A/L), in 2 patients with class 4 (17.5-49 KU_A/L) and in 2 patients with class 3 (3.5-17.49 KU_A/L). In the present study, all egg challenges carried out with egg white specific IgE > 2.4 KU_A/L were positive. This difference may reflect differences in the clinical pattern, most of our patients having concomitant milk allergy and half of them reacting through anaphylaxis. For Osterballe *et al* (16), in a cohort of atopic dermatitis patients, the specific IgE level predicting clinical reactivity with > 95% certainty was 1.5 KU_A/L (CAP system). Even though occurring without previous egg ingestion, egg sensitization decreases with time, a common feature of food allergy, and the longitudinal survey of egg specific IgE shows a decrease with age in most cases, whatever the group. The effect of elimination diets on food-specific IgE in patients with atopic dermatitis has been described (17): specific IgE to hen's egg decreased gradually during elimination diets in 18 of the 22 patients with positive egg IgE while it did not decrease in 6 patients sensitive to egg but not adhering to an elimination diet. Such results strongly argue against any introduction of egg in very young atopic patients with high egg specific IgE levels. Following that mandatory elimination diet, children were challenged at a mean age of 30 + 8 months, an age which is in good agreement with the natural acquisition of tolerance in egg allergic children (14).

Based on this limited cohort, recommendations relating to the clinical handling of those children must remain careful. Among the points that can probably be made, the current study indicates that the specific IgE decrease is highly variable according to individuals and that an evaluation once or twice a year seems useful to check whether the level becomes compatible with an oral challenge. If this limited cohort does not allow proposing a cut-off value, it seems likely that egg introduction should be delayed until age 3 year, with egg white specific IgE <1.5 KU_A/L. The "no challenge" group, with a mean egg white specific IgE of 19.7 KU_A/L between 2 and 3 years indicates that some children remain at risk. A survey of these patients prolonged until egg challenge and tolerance acquisition will hopefully allow a better appraisal of this group.

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