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The Natural History of Food Sensitization in Children With Atopic Dermatitis and the Prognostic Role of Specific Serum IgE

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Abstract: *Background*: The natural history and the prognostic factors for food tolerance in childhood atopic dermatitis (AD) are poorly understood.

Objective: We aimed at investigating the natural course of egg and milk allergy in children affected by AD and food allergy and identifying if the persistence of allergy is associated with high specific serum IgE (sIgE).

Methods: The retrospective study included 58 patients affected by AD, aged 9-16 months, with a first clinical examination between 1993 and 2002.

Results: Patients with AD and allergy to hen's egg (N=58) or cow's milk (N=44) were studied. In most patients milk and egg tolerance was reached before school age, but it was achieved later in children with severe AD and high egg sIgE.

Conclusions: The food tolerance is normally reached before school age and, at the time of diagnosis, levels of sIgE>5kU/L for hen's egg are risk factors for a later tolerance achievement.

Keywords: Atopic dermatitis, egg allergy, food allergy, milk allergy and specific serum IgE.

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease with specific immune and inflammatory mechanisms that affects between 15% to 30% of the pediatric population with an age dependency [1,2]. Food allergy is much more common in children with AD, with an association of 15-30% (even if some authors report it to be up to 80%) [3-6].

The main offending foods are cow's milk, hen's egg, peanuts and fish [7].

Sensitization to food occurs early, peaking at approximately 6 to 9 months of age [8] and generally does not increase later in childhood [9,10].

Three prospective studies showed that about two-thirds of children will outgrow their egg allergy by early school age [11-13]. However, a recent large, retrospective review by Savage *et al.* [14] of 881 egg-allergic individuals reported that a significant proportion of egg allergic patients was still allergic in their late childhood or adolescence.

The overall prognosis of cow's milk allergy is also good, with a total recovery of 56% at 1 year, 77% at 2 years, 87% at 3 years, 92% at 5 and 10 years and 97% at 15 years of age [15].

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In a previous study which included children with a diagnosis of AD and first examined at an age of 9 to 16 months, our group showed that the presence of allergic sensitization at one year of age might predict the development of respiratory allergy [16].

The aim of the present study is to investigate the natural course of and acquisition of tolerance in hen's egg and cow's milk allergy in children with AD and to identify if allergy persistence is associated with high sIgE.

MATERIALS AND METHODS

Study Population and Inclusion Criteria

Patients included in this study represent a part of the cohort already analyzed in a previous retrospective study [16], in which children were enrolled according to the following criteria:

a. diagnosis of AD at an age of 9 to 16 months made at our Pediatric Allergology Outpatients Clinic, with a first clinical examination between 1993 and 2002;

b. availability of a detailed family and personal history;

c. performance of allergometric tests (skin prick tests (SPTs) and sIgE serum level for food and inhalant allergens);

d. telephone availability;

e. informed consent by the parents.

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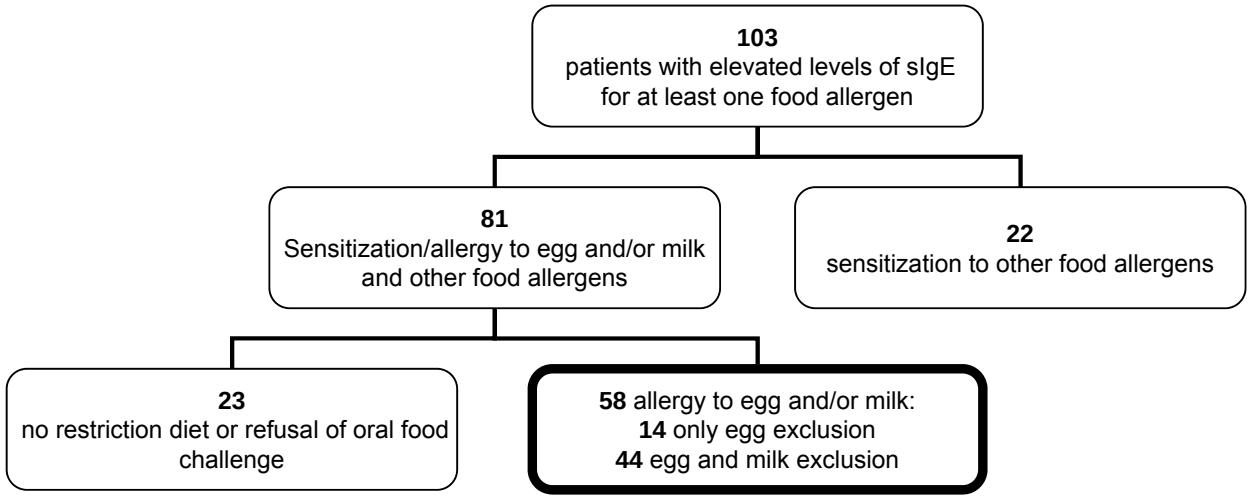


Fig. (1). Study population flow chart.

For the present analysis, we selected those patients with sIgE >0.35 kU/L for at least one food allergen at first observation (n=103), only 81 (78.6%) of whom with a sensitization and/or food allergy to cow's milk and hen's egg. Among them, 23 children were not on a restriction diet or refused to perform food challenge, whereas 58 were on hen's egg or cow's milk exclusion diet (Fig. **1**). Therefore, we performed our analysis on 58 children: 14 were allergic to hen's egg (with symptoms of urticaria in 11 patients and AD acute flares in 3) and on an egg-free diet; the others were allergic to milk and sensitized to egg, so that they followed a milk and egg restriction diet on the basis of milk-allergy symptoms, AD severity and elevated hen's egg sIgE. In the 44 children with cow's milk allergy the symptoms were: acute flares of AD (7 patients), urticaria (34 patients), respiratory (1 patient), gastrointestinal (2 patients) (Table **1**).

The patients were followed with periodic check-ups until AD was controlled and they had reached the tolerance for the food. Oral challenges were repeated every 6-9 months (mean: 8 months) for 24 months after a diagnostic challenge and on a yearly basis thereafter. Accidental ingestion of a considerable amount of the offending food without a clinical reaction was considered as a negative challenge: this happened in 5 children for cow's milk and in 6 children for hen's egg (Table **1**). If a reported accidental ingestion had produced clinical symptoms, the reported dose ingested was recorded. In this case, convincing symptoms were considered as positive oral food challenges and the scheduled follow-up was delayed of 6-12 months.

Milk/egg hypersensitivity was assumed to have resolved when a whole egg or an entire glass of milk (150 ml) could be eaten or drunk with no apparent symptoms.

Clinical Assessment

At the time of the first evaluation, the diagnosis of AD was made by the physicians on the basis of the criteria of Hanifin and Rajka [17] and the evaluation of the severity of AD was assessed by the SCORAD index [18]. SCORAD index < 25 shows a mild AD (8 patients, 14%), 25-50 a moderate form (39 patients, 67%), >50 a severe form (11 patients, 19%).

Allergometric Assessment

At the first evaluation (between 1993 and 2002) the determination of sIgE was performed by ImmunoCAP™ (Pharmacia, Sweden) in all patients for the following allergens: cow's milk, hen's egg, soybean, wheat, peanut, nut, codfish, apple. A patient was considered as sensitized to an allergen when having sIgE levels higher than 0.35 kU/L.

All the sera were tested for sIgE levels in the central laboratory of our hospital.

Statistical Methods

Standard statistical descriptions of parameters were used to characterize the data (mean, median and range).

The primary outcomes were tolerance onset to cow's milk and to hen's egg in children with AD and duration of intolerance to both food allergens.

Both outcomes were estimated using the method of Kaplan and Meier; comparison between probabilities in different patient groups was performed using the log-rank test [19].

Tolerance onset probabilities to cow's milk and to hen's egg were computed from the date of diagnosis to the date of tolerance onset to cow's milk and to hen's egg respectively, while duration of intolerance (or persistence of allergy) was calculated from the onset to the disappearing of the allergy or the last date of contact.

Results were expressed as probability (%). All P values are 2-sided and values less than 0.05 were considered as statistically significant.

The Statistical analysis was performed using the STATA package [20].

RESULTS

All the 58 patients (35 males, 23 females) were on an egg-free diet; 44 (76%) were also on a milk-free diet. The mean follow-up of these patients was 127.6 ± 24.7 months. The mean age of children at first observation was 11.2 months. At follow-up the mean age was 138.8 months.

Table 1. Characteristics of the Population

Patient Number	Food Allergy	Symtoms of Egg Allergy	Symtoms of Milk Allergy	sIgE Egg (kU/L)	sIgE Milk (kU/L)	OFC Egg	OFC Milk	OCF Egg Outcome	OCF Milk Outcome
1	Egg	U		100		Yes	Yes	T	T
2	Egg	U		64.1		Yes	Yes	T	T
3	Egg	U		44		Yes	Yes	T	T
4	Egg	U		25.4		Yes	Yes	T	T
5	Egg	U		30		Yes	Yes	T	T
6	Egg	U		26.8		Yes	Yes	T	T
7	Egg	U		21.8		Yes	Yes	T	T
8	Egg	U		39.3		Yes	Yes	T	T
9	Egg	U		21		Yes	Yes	T	T
10	Egg	U		15.9		Yes	Yes	T	T
11	Egg	U		19		Yes	Yes	T	T
12	Egg	ADaf		17		Yes	Yes	T	T
13	Egg	ADaf		15.1		Yes	Yes	T	T
14	Egg	ADaf		17.6		Yes	Yes	T	T
15	Egg+milk	N	U	15.3	23.6	A	Yes	T	T
16	Egg+milk	N	U	7.7	1	A	Yes	T	T
17	Egg+milk	N	U	6.6	7.3	A	Yes	T	T
18	Egg+milk	N	U	4.9	5.1	A	Yes	T	T
19	Egg+milk	N	U	3.7	5.7	A	Yes	T	T
20	Egg+milk	N	U	2.1	7.5	A	Yes	T	T
21	Egg+milk	N	U	13	4	Yes	A	T	T
22	Egg+milk	N	U	3.4	17.3	Yes	A	T	T
23	Egg+milk	N	U	1.9	2.7	Yes	A	T	T
24	Egg+milk	N	U	4.9	3	Yes	A	T	T
25	Egg+milk	N	U	10	2.2	Yes	A	T	T
26	Egg+milk	N	U	5.4	16	Yes	Yes	T	T
27	Egg+milk	N	U	1.7	2.7	Yes	Yes	T	T
28	Egg+milk	N	U	7.5	4.5	Yes	Yes	T	T
29	Egg+milk	N	U	5.5	3.6	Yes	Yes	T	T
30	Egg+milk	N	U	4.9	8	Yes	Yes	T	T
31	Egg+milk	N	U	3.5	5.1	Yes	Yes	T	T
32	Egg+milk	N	U	10	3.2	Yes	Yes	T	T
33	Egg+milk	N	U	7.7	44.8	Yes	Yes	T	T
34	Egg+milk	N	U	4.8	3.4	Yes	Yes	T	T
35	Egg+milk	N	U	2.4	7.1	Yes	Yes	T	T
36	Egg+milk	N	U	6.3	5.5	Yes	Yes	T	T
37	Egg+milk	N	U	2.2	2.1	Yes	Yes	T	T
38	Egg+milk	N	U	12	2	Yes	Yes	T	T
39	Egg+milk	N	U	4.1	44	Yes	Yes	T	T
40	Egg+milk	N	U	1.6	1.2	Yes	Yes	T	T
41	Egg+milk	N	U	2.8	0.9	Yes	Yes	T	T

(Table 1) contd…..

Patient Number	Food Allergy	Symtoms of Egg Allergy	Symtoms of Milk Allergy	sIgE Egg (kU/L)	sIgE Milk (kU/L)	OFC Egg	OFC Milk	OCF Egg Outcome	OCF Milk Outcome
42	Egg+milk	N	U	1.3	57.8	Yes	Yes	T	T
43	Egg+milk	N	U	11.6	9.8	Yes	Yes	T	T
44	Egg+milk	N	U	1.3	1.2	Yes	Yes	T	T
45	Egg+milk	N	U	1.1	10	Yes	Yes	T	T
46	Egg+milk	N	U	10.6	0.9	Yes	Yes	T	T
47	Egg+milk	N	U	0.6	12	Yes	Yes	T	NT
48	Egg+milk	N	U	12.3	1.6	Yes	Yes	NT	T
49	Egg+milk	N	R	13.7	88.3	Yes	Yes	NT	NT
50	Egg+milk	N	G	5.1	0.4	Yes	Yes	T	T
51	Egg+milk	N	G	1.3	0.5	Yes	Yes	T	T
52	Egg+milk	N	ADaf	0.6	0.7	Yes	Yes	T	T
53	Egg+milk	N	ADaf	0.4	1.5	Yes	Yes	T	T
54	Egg+milk	N	ADaf	0.5	0.4	Yes	Yes	T	T
55	Egg+milk	N	ADaf	0.5	0.4	Yes	Yes	T	T
56	Egg+milk	N	ADaf	0.4	0.4	Yes	Yes	T	T
57	Egg+milk	N	ADaf	0.5	1.5	Yes	Yes	T	T
58	Egg+milk	N	ADaf	0.5	0.5	Yes	Yes	T	T

OCF: Oral food challenge; A: accidental ingestion of the offending food; U: urticaria; R: respiratory, G: gastrointestinal; ADaf: AD acute flares; N: none; T: tolerance, NT: No Tolerance/

Out of all the patients, 56 children (97%) developed tolerance to egg at a mean age of 46 months (range 13-156) and 42 (96%) to milk at a mean age of 37 months (range 10-115) (Fig. **2A**, **B**).

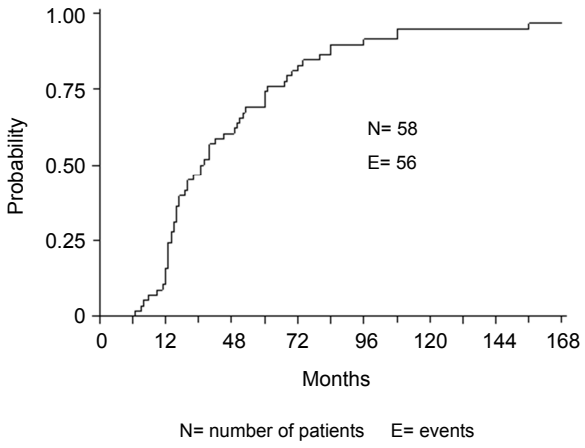


Fig. (2A). Tolerance onset to hen's egg in children with AD.

Furthermore, the patients with mild AD achieved the tolerance to milk and egg at a mean age respectively of 29 and 44 months, earlier than those with severe AD, who reached the tolerance respectively at a mean age of 53 and 57 months, although these differences were not statistically significant (Fig. **3A**, **B**).

Figs. (**4A**, **B**) show the Kaplan Meier curves for duration of the disease stratified according to the levels of sIgE.

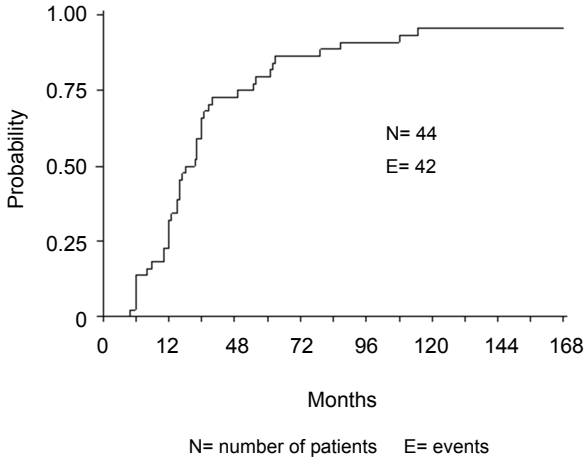


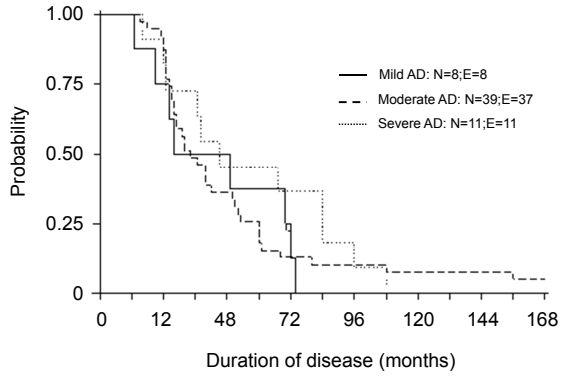
Fig. (2B). Tolerance onset to cow's milk in children with AD.

The patients were divided into two groups according to the median of sIgE (egg white: 5 kU/L, milk: 3 kU/L). Children with sIgE levels ≤5 kU/L for hen's egg white reached the tolerance significantly earlier than those with levels higher than 5 kU/L (*P=0.002*). Patients with cow's milk sIgE levels ≤3 kU/L apparently became tolerant earlier than those with sIgE >3 kU/L, but this difference was not statistically significant (Fig. **4A**, **B**).

DISCUSSION

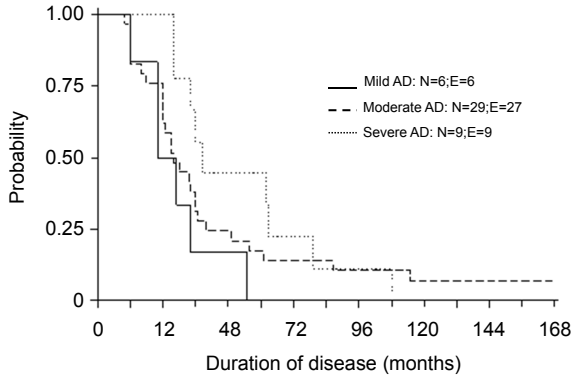
The natural course of food allergy is different for each allergen. Allergies to peanuts, nuts, and seafood are more likely to persist, with a small fraction of patients developing

tolerance, whereas allergies to milk, eggs, wheat, and soy generally resolve by childhood [21].



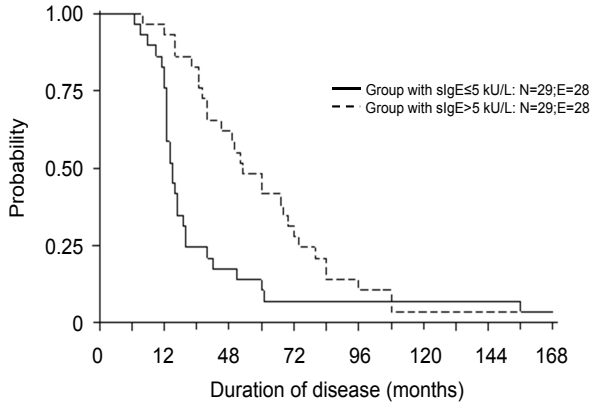
N= number of patients, E= events; Overall Log-rank p = 0.68

Fig. (3A). Curve for duration of hen's egg white intolerance stratified according to the severity of AD.



N= number of patients, E= events; Overall Log-rank p = 0.23

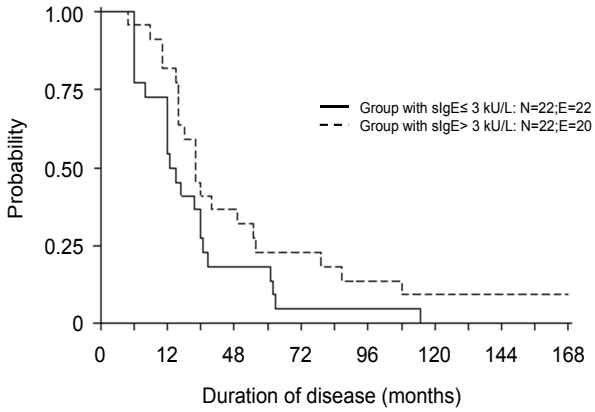
Fig. (3B). Curve for duration of cow's milk intolerance stratified according to the severity of AD.



N= number of patients, E= events; Log-rank p = 0.0023

Fig. (4A). Curve for duration of the disease stratified according to the **hen's egg white** IgE levels. The patients were divided into two groups according to the median of sIgE (5 kU/L).

In the paper, we found that the tolerance for egg and milk was reached early: at 46 months to egg and at 37 months of age to milk (Fig. **2A**, **B**). Several studies report that most children with egg allergy outgrow their allergy by the early school-age years, whereas children affected by cow's milk allergy will probably tolerate the food by the age of 3[15, 10, 22-24].



N= number of patients, E= events; Log-rank p = 0.095

Fig. (4B). Curve for duration of the disease stratified according to the **cow's milk** IgE levels. The patients were divided into two groups according to the median of sIgE (3kU/L).

Other studies report that between 31% and 51% of children allergic to egg usually overcome the problem [11,25-27]. According to Boyano-Martinez *et al*. [13], who studied 58 patients younger than 2 years of age with egg allergy, half of the children will tolerate the food at 35 months of follow-up and 66% after 5 years. In a prospective, birth cohort study on 1749 Danish children who were followed up to the age of 3, Høst and Halken [15] found that the prevalence of milk allergy was 2.2% and that, by the age of 3, most of the allergic children were able to tolerate milk.

However, other studies suggest a modification of the natural history of cow's milk and hen's egg allergy, with increasing persistence until a later age [14, 28]. In the large, retrospective review of 881 egg allergic individuals by Savage *et al.* [14], the rate of tolerance development, depending on the definition of egg allergy, was 36-66% by 10 years, 61-86% by 14 years and 80-95% by age 16 years. Skripak *et al.* [28] retrospectively analyzed 807 patients with IgE-mediated milk allergy and, despite the use of 3 sets of increasingly broad criteria to define tolerance, incidence rates of resolution at 4 years ranged from <1% to 26%, substantially lower than previously reported.

Unfortunately, it is difficult to compare results between studies because of different ages at study entry, different follow-up times and unlike populations; it is also possible that ethnic and genetic variations play a role in the development of oral tolerance. The main limitation of our study is that 44 patients were diagnosed with egg allergy on the basis of sIgE alone and did not have a history of reaction to food. This occurred because these children were being evaluated for AD before egg had been introduced into their diet, and then strict egg avoidance was instituted on the basis of a milk-free diet, the elevated sIgE and/or the severity of AD. An oral provocation test had not been proposed to the parents until the levels of sIgE were below the threshold of 7 kU/L, which predicts a high risk of reaction to food ingestion.

Although the natural history of egg and milk allergy has been thoroughly evaluated, previous results have been somewhat contradictory and an exact determination of when tolerance is acquired in each individual case is still not possible. Moreover, the prognostic factors for the development of tolerance in food allergy are poorly understood. Another aim of our study was to analyze the relationship between tolerance acquirement and the values of sIgE and AD severity as assessed at the time of the first examination. The predictive factors identified may help to define the prognosis of food allergy in each particular case and to answer parents' common questions about when their child will tolerate the ingestion of the offending food and when he or she will be able to reintroduce food in his or her diet.

Similarly to what has been reported by others [13, 29, 30], we found a very important role of high sIgE in predicting the persistence of allergy and, in particular, that patients with levels of sIgE for hen's egg white higher than 5 kU/L at diagnosis reach the tolerance later than those with lower levels (Fig. **4A**).

In a study which included children between 3 months and 14 years of age, 61% with AD and 90% with a family history of atopy [29], Sampson and Ho reported that in the presence of egg sIgE ≥7 kU/L, provocation testing would not be indicated, given the high probability that the test would prove positive. In the work by Boyano-Martínez *et al*. [13], the sIgE level is an important prognostic marker in children who only had cutaneous symptoms. Savage *et al*. [14], examining the relationship between the peak of egg sIgE level and the development of tolerance, have identified an egg sIgE level ≥50 kU/L as a marker of persistent egg allergy.

Montesinos *et al*. [30] performed a retrospective study of patients with egg allergy and found that the initial levels of sIgE for egg white were significantly lower in those patients who reached tolerance: sIgE levels of 1.52, 1.35 and 2.59 kU/L predicted clinical reactivity at the different follow-up timepoints analyzed (25-36, 37-48 and 49-60 months respectively).

Our study shows that high levels of sIgE for milk are not a risk factor for a later tolerance achievement.

However, in a recent study [31] on a population of 139 Portuguese children with milk allergy, higher sIgE levels to cow's milk (>17.5 kU/L) during the follow-up period were associated with a reduced likelihood of acquiring oral tolerance.

Also in the work of Vanto *et al*. [32] the milk sIgE levels >2 kU/L are useful prognostic indicators of the development of tolerance to milk in infants with milk allergy.

Levy *et al*. [33] compared patient with transient milk allergy with those with persistent milk allergy: no differences were found between the groups in mean age and symptoms and signs at the first allergic reaction and family history of atopy.

Food-sensitized children have been shown to have more severe and persistent AD [5,34,35]. The patients that develop AD before 3 months of age are at significantly greater risk of acquiring food allergies compared with those who develop AD after 12 months of age [5,36]. These data suggest that the presence of food sensitization and allergy earlier in life predicts a prognosis of severe AD, but conclusions about its role in the pathogenesis of AD cannot be drawn. In our study the patients with mild AD achieved the tolerance to milk and egg (with a mean respectively of 29 and 44 months) earlier than those with severe AD (with a mean respectively of 53 and 57 months) although not statistically significant (Fig. **3A**, **B**).

In conclusion, our study seems to highlight that, in the case of milk and egg allergy, food tolerance is normally reached before school age and that initial sIgE levels >5 kU/L for hen's egg white are risk factors for a later tolerance achievement.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

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