

Natural course of sensitization to cow's milk and hen's egg in childhood atopic dermatitis: ETACTM Study Group

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Summary

Background Sensitization to food allergens has been implicated in the pathogenesis of atopic diseases, in particular atopic dermatitis (AD). The aim of the present paper is to investigate the natural course of sensitization to egg and to cow's milk and its relationship with the severity of AD.

Methods The placebo intention-to-treat population of the ETACTM (Early Treatment of the Atopic Child) study consisted of 397 children with AD aged 12–24 months (mean $\pm$ SD: 17.2 $\pm$ 4.1 months) who were followed for 18 months. All children were examined for objective SCORing Atopic Dermatitis (SCORAD) and specific IgE amongst other, to egg and to cow's milk at inclusion and after 3, 12 and 18 months. Fifteen patients were excluded from this analysis due to major protocol violations thus leaving 382 patients in the analysed population.

Results Sensitization to egg and to cow's milk was more common in atopic children with severe AD at all time-points. At inclusion, children sensitized to both egg and to cow's milk had the most severe AD (Kruskall-Wallis test $P = 0.007$). The degree of sensitization expressed in RAST classes was significantly related to the severity of AD. Furthermore, children sensitized to egg or to cow's milk at inclusion had a higher risk of persistence of AD (84% and 67%, respectively, vs. 57% in those not sensitized) and a higher objective SCORAD after 18 months follow-up.

Conclusion We found an association between severity of AD and sensitization to egg or to cow's milk. Moreover, sensitization to egg, and to a lesser extent cow's milk, indicates a worse outcome of AD in terms of persistence and severity of the disease.

Keywords egg sensitization, cow's milk sensitization, atopy, atopic dermatitis, children, predictor factor

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Introduction

Exposure to environmental allergens in early life results in sensitization and may trigger atopic disease [1]. Atopic disorders are often associated with the presence of immunoglobulin (Ig)E antibodies to common allergens. In atopic dermatitis (AD) increased levels of total IgE are found in 80% of the patients [2]. However, total IgE is only loosely associated with atopic diseases, and has no value in distinguishing between atopic and non-atopic children [3,4]. Specific IgE seems to be a more reliable parameter of atopy [5]. Egg and cow's milk are the most common allergens involved in atopic children during the first 24 months [6]. While transient low levels of specific IgE to food can commonly be present in non-atopics, higher levels of specific IgE are almost exclusively seen in atopic individuals [4,7].

As specific IgE to egg and to cow's milk are most common in infancy [8], food allergens are thought to be mainly involved in the young infant with AD, while inhalant allergens are thought to be involved in older children with AD and in the development of asthma. Although allergy to egg and to cow's milk disappears in most children at the age of 2–4 years, such sensitization is relevant as it may precede the appearance of inhalant allergy later in life [7]. Some studies suggested that sensitization to egg may predict the development of asthma [9–14]. Ingestion of food allergens in allergic individuals may induce AD to flare [15] and benefits of exclusion diets have been reported [15,16]. It is therefore reasonable to expect that sensitization may affect the severity and the outcome of AD.

However, only one earlier cross-sectional study reported a relation between sensitization to food allergens and severity of AD [17], while there is no longitudinal study to show this relation. In the present study we describe the pattern of sensitization to egg and to cow's milk in relation to the outcome of AD in children. We hypothesize that the presence of sensitization is associated with more severe AD and with a worse outcome of AD in the long-term.

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Materials and methods

A total of 397 children were randomised to the placebo group of the Early Treatment of the Atopic Child (ETACTM) study [18]. The ETACTM study is a prospective, randomised, double-blind, placebo-controlled, multi-centre trial on the prevention of asthma with cetirizine. The study population and study design has been extensively reported previously [18,19]. Briefly, the target population were infants aged 1–2 years with a positive family history of atopy (parent or sibling) and active symptoms of AD. Infants with a history of asthma or episodes of wheezing or nocturnal cough were excluded. Fifteen patients were excluded from this analysis due to major protocol violations (patients with an onset of symptoms of asthma at inclusion; patients without a mother, a father or at least one sibling with a history of atopy; patients suffering from a concomitant disease prohibiting inclusion; and patients who switched medication during the study), thus leaving 382 patients in the analysed population.

After written informed consent was obtained, a treatment period of 18 months (cetirizine or placebo) and a follow-up of 6 months were scheduled. Eight visits with five blood samples were performed in this period. At each visit the severity of AD was measured by the SCORAD index [20].

Amongst others, specific IgE to egg and to cow's milk were determined using the Pharmacia CAP[®] system (Pharmacia & Upjohn, Uppsala, Sweden). These analyses were made at baseline and after 3, 12, 18 and 24 months by a central laboratory (Institut Pasteur; Lille, France) according to the manufacturer's instructions and to routine clinical laboratory performances. A child was considered sensitized if IgE levels were ≥ 0.35 kUA/L (RAST class 1).

Scoring of severity of AD

The severity of disease was scored using the objective SCORAD [21] which includes the assessment of two items in a standardized manner: (a) extent (applying the rule of nine) and (b) intensity (erythema, oedema/papulation, oozing/crust, excoriation, lichenification and dryness on a scale from 0 to 3). This scoring system reflects the modified consensus of the European Task Force on Atopic Dermatitis. Unlike the initial version called SCORAD index [20], subjective symptoms are not included for the scoring of AD in the objective SCORAD [22].

Statistical analysis

The Spearman rank correlation was used to test monotonic relationships between the objective SCORAD and the levels of specific IgE to egg and to cow's milk. Non-parametric analysis of variance was used to analyse the objective SCORAD as a continuous variable for different categories of initial sensitization. The Chi square test was used to investigate the relationship between initial sensitization and the presence of AD after 18 months or the relationship between egg and cow's milk sensitization. All tests were carried out two-tailed at the level of significance of 5%.

Results

At the beginning of the study most of the atopic children had mild to moderate AD with a SCORAD index of 20.0 ± 11.3

(mean $\pm$ SD). At inclusion, sensitization to egg and to cow's milk was present in 50% and 36% of the children, respectively. While almost all the children sensitized to cow's milk were also sensitized to egg (88%), there was a considerable part of the sensitized children with sensitization to egg only (33%). During the follow-up, sensitization remained stable for cow's milk and decreased slightly for egg. Sensitization to cow's milk or to egg occurred before the age of 2 years in 75% of the children. In 10% of these children, sensitization disappeared after the age of 2 years.

At the beginning of the study, children sensitized to both egg and cow's milk had most severe AD (Kruskal-Wallis test, $P=0.007$). At inclusion the objective SCORAD (mean $\pm$ SD) was as follows: 17.9 ± 10 (children with normal specific IgE); 18 ± 10 (specific IgE to cow's milk only); 20.5 ± 12 (specific IgE to egg only); 23.1 ± 12 (specific IgE to both egg and cow's milk).

High levels of specific IgE (≥ 17.5 kUA/L) were obviously more common in children with moderate to severe AD (Fig. 1).

First, we investigated the evolution of sensitization in relation to the initial severity of AD. Sensitization to egg and to cow's milk was more common in children with more severe AD, which could be observed throughout this study at different follow-up visits (Fig. 2a and b). Furthermore, the degree of sensitization (RAST class) was related to the severity of AD (Table 1). For egg this relationship was present at all measurements and it was always stronger than for cow's milk. Thereafter, we investigated the natural course of AD in relation to initial sensitization. Sensitization at the beginning of the study was associated with a higher rate of persistence of AD (SCORAD >7) after a follow-up of 18 months (Chi Square test $P=0.006$). In children with initially no specific IgE to egg or to cow's milk, only 57% had active AD after 18 months. However, children with initially specific IgE to egg or to cow's milk had active AD in 84% and 67%, respectively, after 18 months ($P=0.006$). Moreover, initial sensitization was also reflected by a lesser decrease of objective SCORAD after 18 months (Kruskal Wallis test $P=0.027$).

Finally, we investigated whether there was a relationship between a change of the objective SCORAD and a change of sensitization to egg and to cow's milk in the course of the study.

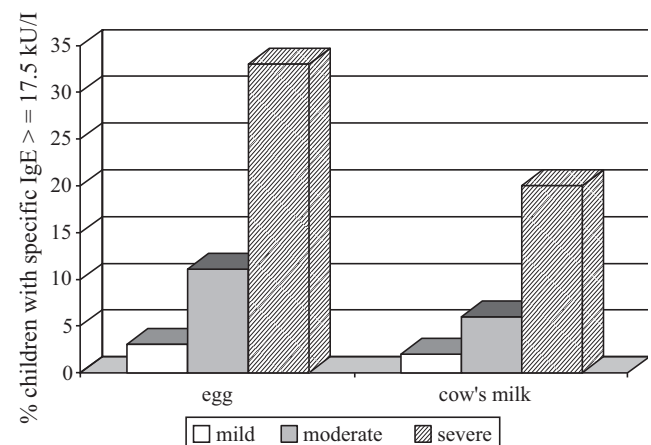


Fig. 1. Percentage of children with specific IgE levels $\geq$ RAST class IV (≥ 17.5 kUA/L) to egg and to cow's milk in mild, moderate and severe AD at the beginning of the study. An objective SCORAD below 15 indicates mild AD, between 15 and 40 indicates moderate AD, and above 40 indicates severe AD.

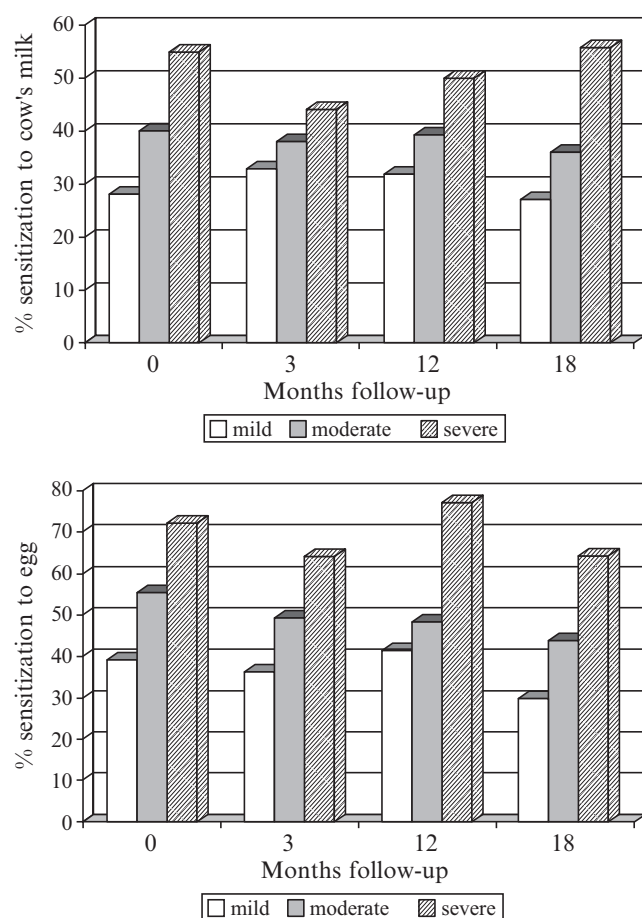


Fig. 2. Percentage of increased specific IgE levels (≥ 0.35 kUA/L) to cow's milk (a), and to egg (b), at the different follow-up visits in children with mild, moderate and severe AD. Severity of AD was scored by objective SCORAD at the beginning of the study. An objective SCORAD below 15 indicates mild AD, between 15 and 40 indicates moderate AD, and above 40 indicates severe AD.

Table 1. Correlation between the severity of AD at the beginning of the study and the degree of sensitization (RAST class) at different follow-up visits

	Cow's milk	Egg
Baseline	0.16**	0.22***
3 months	0.09 n.s.	0.15*
12 months	0.12*	0.16*
18 months	0.15*	0.21**

* $P < 0.05$, ** $P < 0.005$, *** $P < 0.0005$, n.s. not significant. Figures in the table represent correlation coefficients calculated by using the Rank Spearman test (correlation between two ranked data series).

As expected, AD improved on average. However, children in whom sensitization increased, were observed to have significantly less improvement (cow's milk) or even a deterioration (egg) of AD in the course of the study (Table 2).

Discussion

In a large number of infants we demonstrated an association between the severity of AD and the presence and degree of

Table 2. Summary statistics of the objective SCORAD percentage change over the period of 18 months

Sensitization	Cow's milk	Egg
Decreased	35.8 $\pm$ 58	38.1 $\pm$ 54
Unchanged	34.1 $\pm$ 75	33.2 $\pm$ 81
Increased	9.5 $\pm$ 75	-6.9 $\pm$ 71

Data (mean $\pm$ SD) represent the percentage improvement of AD in three groups of children. The three groups were defined on a change (increased, unchanged, decreased) in RAST by at least one class over the study period of 18 months. Non-parametric analysis of variance (Kruskal Wallis test: egg $P = 0.048$; cow's milk $P = 0.03$).

sensitization. Furthermore, we observed that the clinical outcome of AD after a follow-up of 18 months is worse if there is an early sensitization to cow's milk or to egg.

There is only one earlier cross-sectional study using a non-validated scoring system for AD in which an association between severity of AD and presence of sensitization to food was observed [17]. The same study reported that sensitization to food was a risk factor for asthma.

Allergic sensitization to food, particularly egg and cow's milk is the first allergens observed in the course of AD [1]. Their presence may be relevant as a first trigger of AD. It has been observed that food allergens can exacerbate AD, and elimination of the relevant food allergen may improve AD [15]. Further evidence for a role of food allergens in the pathogenesis of AD comes from the observation that epicutaneous patch testing (atopy patch test) with egg and cow's milk may induce eczematous lesions in some patients with AD [23]. A recent study in infants calculated that the attributable risk for IgE food sensitization as a cause of AD was 65% and 64% at 6 and 12 months, respectively [24]. Strictly speaking, from the present data we have no indication whether sensitization to food is a primary cause of more severe AD or just associated with more severe AD, although the first seems plausible from the above mentioned observations.

In the present study, severity of AD was clearly related to the presence and the degree of sensitization to egg and to cow's milk. Still, other factors influence the severity of AD. Apart from genetic factors, many environmental factors may influence the severity of AD; like other allergies (inhalant, other food, contact allergens), colonization with *Staphylococcus aureus*, general or local infections, contact with local irritants like soaps, water hardness or fatty acid composition of the food. However, specific IgE antibodies are the hallmark of atopy and high affinity (FcεRI) and low affinity (FcεRII) IgE receptors have been localized not only to mast cells and basophils, but also to eosinophils [25], Langerhans cells, monocytes and B cells [26]. This changed the traditional view of IgE as just a mediator of mast cell degranulation. Thereby IgE-FcεRI/FcεRII binding is involved in antigen presentation [26], and activation and degranulation of eosinophils [25]. In this light, sensitization may have an outstanding role in keeping the allergic reaction ongoing.

In agreement with earlier reports we demonstrated that sensitization to food commonly develops in the first 2 years of life. After the age of 2 years sensitization rates remained high; which is to some degree contradictory to the literature. However, a longer follow-up may be necessary to show clearance of sensitization to egg and to cow's milk.

As we did not control for food intake, we can not rule out the possibility of food intake being a confounding variable. However, in general, children with high IgE levels or severe AD were those with a higher chance of having a skin test for food allergy and therefore a higher chance of getting a diet. Therefore, food intake may be a confounder that rather weakened the associations we found than caused the associations found.

We defined sensitization at a low level (> 0.35 kUA/L) as this is widely used in the literature. While this is known to be a sensitive indicator of clinical reactivity to that food, it is a poor predictor of clinical reactivity [27]. However, previous retrospective studies suggested that higher concentrations of specific IgE to food are predictive of food-induced clinical symptoms [27,28]. Therefore a higher level of specific IgE may be more appropriate to define clinically relevant sensitization as was recently shown in a prospective study [28].

The reason why egg was found to be more closely related to AD is still unknown. However, other reports have underlined the importance of egg as a predictor for inhalant allergy [7,10] and respiratory allergic disease [9] later in life.

In conclusion we found an association between severity of AD and sensitization to egg or to milk. Moreover it is likely that sensitization to cow's milk and in particular to egg acts as a negative predictor for the outcome of AD in terms of persistence and severity of the disease.

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