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ORIGINAL ARTICLE

# Response of Specific Immunoglobulin E to Foods in Children with Atopic Dermatitis

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**Abstract** Food allergy is a common condition that plays an important role in the pathogenicity and maintenance of atopic dermatitis (AD), however, must be carefully investigated before imposing a restrictive diet. The aim of this study was to evaluate the sensitivity to foods in patients with AD, correlating it with the severity of the disease and other possible associated factors. One hundred and eleven children (6–180 months of age) with AD were evaluated and later followed up at the Allergy and Clinical Immunology Division, Department of Pediatrics at FMABC. The serum concentrations of specific IgE to cow's milk (CM), egg, soy, wheat, corn, peanut and fish were measured using an enzymatic fluorescence method (ImmunoCAP$^{TM}$). In order to identify the clinical reactivity, the open oral provocation test was performed when specific IgE was positive to CM, egg and wheat and in all those who related symptoms after the intake of such foods regardless of the presence or absence of sensitization. In total, 40.5 % of the studied population was sensitized to at least one food allergen, especially those between 73 and 180 months of age. There was a higher prevalence of sensitization in children with more severe AD, and foods like CM, egg and wheat were the most involved, but with low clinical reactivity. We observed increased severity of AD in cases that initiated symptoms earlier and who had shorter duration of exclusive breastfeeding as well as a linear increase in sensitization in the most serious cases. Serum-specific immunoglobulin E was the only factor associated with the relationship that showed sensitization. The occurrence of sensitization to foods was frequent, mainly in the age group of 6–9 years and in patients with severe AD; however, the validation of the clinical reactivity was negative in most of the provocations performed, which agrees with the need to prove the same before the imposition of restrictive diets, often unnecessary and complex.

**Keywords** Immunoglobulin E · Children · Atopic dermatitis

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## Introduction

Atopic dermatitis (AD) is a chronic inflammatory dermatosis characterized by the presence of relapsing eczema and associated frequently with intense itch (Leung and Bieber 2003). It usually manifests in childhood and adolescence with growing prevalence (Rhodees et al. 2001) which results from the close interaction between genetic, immunological, environmental, psychosomatic and pharmacological factors and the skin structure alteration (Castro et al. 2006).

Some researchers attribute an important role to food allergies in the pathogenicity and maintenance of the AD (Breuer et al. 2004; Niggemann et al. 1999; Sampson 1999; Sicherer and Sampson 1999), being a worsening factor in approximately 40 % in children under 5 years of age in severe AD (Eigenmann et al. 1998), which justifies its investigation in the absence of improvement in symptoms

with the usual therapeutic measures. Although there is evidence of hypersensitivity, particularly to egg, cow milk and peanuts (Guillet and Guillet 1992), the relationship between diet and induction or aggravation of AD remains controversial, since provocation tests do not reproduce the characteristic lesions of AD but erythematous reactions (Lever 2001).

It is important to point out that the detection of specific immunoglobulin E (sIgE) is not always associated with clinical alterations, and its presence may indicate sensitization or cross-allergenicity (Host et al. 2003).

The aim of the current study was to evaluate the sensitivity to foods most commonly considered responsible for allergic reactions in children with AD, correlating it with the severity of the disease and other possible associated factors (gender, age, disease onset, duration of breastfeeding, introduction of solids, co-morbidities, family allergy and serum concentration of IgE.

## Materials and Methods

This is a cross-sectional study with 111 children with AD diagnosis who were followed up at the Allergy and Clinical Immunology Division, Department of Pediatrics at Faculdade de Medicina do ABC for 2 years. For inclusion in the study, it was established to have a clinical diagnosis of AD based on the criteria of Hanifin and Rajka (1980) and submit the statement of consent signed by the person responsible. Failure to obtain the serum sIgE to one or more of the allergens studied was determined as exclusion criteria, resulting in a sample of 111 patients.

The severity of the AD was evaluated by means of the SCORAD (Sugarman et al. 1993) at the patient's admission. The researcher was responsible for all evaluations so that the uniformity of the study would be ensured.

After the clinical evaluations, blood samples were obtained by venipuncture. The samples were centrifuged at 3,500 rpm, and 1 mL of serum was stored at −20 °C for later determination of total IgE and sIgE. The presence of sIgE was detected using the fluorescent enzymatic system (ImmunoCAP$^{TM}$) according to the manufacturer's directions and the good clinical analysis practices. Antibody concentrations for cow's milk (CM), α-lactalbumin, β-lactoglobulin, casein, egg white and yolk, soy, wheat, corn, peanut and fish were obtained, and children with concentrations above 0.35 $KU_A/L$ were considered sensitized (Ballardini et al. 2006).

Additionally, the open oral provocation test (OPT) was performed in order to verify the clinical reactivity to the foods widely known as the cause of allergic reactions and those which are described as responsible for the worsening of AD (milk, egg and wheat). The OPT was carried out in all patients those were sensitized and in all those who related symptoms after the intake of such foods regardless of the presence or absence of sensitization. Firstly, all foods involved were excluded for at least 4 weeks, and during this period, intense cutaneous hydration and the use of topical corticoid (lowest possible strength) were kept whenever needed. Antihistamines were suspended 10 days before the test. In the event of sensitization to both foods, the challenge was performed on separate days with a 2-week gap (Werfel et al. 2007). All patients were followed up for 24 h after the end of provocation, and after 1 and 3 weeks, they were re-evaluated and the intensity of itch and eczema was measured by the SCORAD.

The statistical analyses were performed using software SAS 9.2, Minitab 15 and Microsoft Excel 2007. All tests $\chi^2$, Fisher's exact, Spearman's correlation, odds ratio and logistic regression) were bilateral, and the adopted significance level was of 5 %.

## Results

From the 111 evaluated patients, 61 (54.9 %) were male, age ranging between 6 and 180 months (mean 60 months); the onset of lesions was before 24 months of age in most patients (74.8 %) and in only five patients after 72 months of age (median 12 months); nutritional status with *Z*-score between −2 and +2 in 84.7 %. The onset of lesions was assessed with SCORAD, between 3.9 and 62.4 (median 12.5 months). In total, 71.2 % of the sample was composed of mild AD (SCORAD 12.7 ± 4.4), 22.5 % of moderate AD (SCORAD 36.5 ± 7.3) and 6.3 % of severe AD (SCORAD 56.1 ± 4.4). As to the total amount of time the child was breastfed, median of 5 and 3 months of exclusive breastfeeding was obtained. Among this amount, 17 were not breastfed. In total, 65.8 % of the babies were born by c-section, at term in 85.6 % of the cases, with a median weight of 3 kg. Allergic rhinitis was the most frequent comorbidity found (69.4 %), whereas 61.3 % of the patients had asthma. Rhinitis was also the mostly reported allergic manifestation among direct family members (mother 25.2 %, father 22.5 % and siblings 23.4 %) followed by asthma (mother 20.7 %, father 12.6 % and siblings 18 %) and AD (mother and father 3.6 % and siblings 6.3 %).

There was no significant correlation between the onset of lesions and introduction of solid foods (Spearman 0.166; $p = 0.097$), and the total amount of time the child was breastfed (Spearman 0.184; $p = 0.056$). A statistically weak correlation between the age at the onset of lesions and the amount of time of exclusive breastfeeding was observed (Spearman 0.235; $p = 0.013$), and an inverse correlation between the SCORAD values and the age at the

onset of lesions (Spearman −0.308; $p < 0.001$) and the amount of time of exclusive breastfeeding was observed (Spearman −0.236; $p = 0.012$).

In total, 40.5 % of the studied population was sensitized ($n = 45$): 22 to one allergen (median SCORAD 11.7), nine to two allergens (median SCORAD 22.1) and 14 to three or more allergens (median SCORAD 30.9).

There was a linear increase in sensitization in more severe cases ($p = 0.005$) as seen in Table 1.

Sensitization rate was higher in the age group 73–108 months (54.2 %) and lower in the age group 145–180 months (25.0 %) (Fig. 1).

Among the evaluated foods, there was a higher sensitization rate to CM ($n = 29$), followed by the α-lactalbumin fraction ($n = 22$), egg white and wheat ($n = 19$). However, the association between the severity of the AD and sensitization occurred only with the casein ($p = 0.02$).

In Table 2, the rate of sensitized patients to each allergen is presented according to the sIgE levels.

Among the patients who were sensitized to the CM, three of them had history of clinical worsening after its intake, a fact that was not confirmed by the OPT. As to the egg, only two patients had history of worsening after its intake, and after provocation, only one got worse with a ten-point increase in the evaluation score (SCORAD 33.7 before and 43.2 after). Two parents mentioned an occasional itch exacerbation with peanut intake and another with corn intake, none confirmed by the OPT. There were no reports of worsening after ingestion of wheat, and there was no change after OPT.

The odds ratio of patients with comorbidities and being sensitized by any of the allergens was 1.64 (95 % CI 0.67–4.03).

Total IgE serum concentration ranged 11–21.637 $KU_A/L$ (median 1,003) with significant correlation with age ($p = 0.00$) but not with the SCORAD, the only associated factor that presented a relationship with sensitization (OR 1.001, 95 % CI 1.001–1.002; $p = 0.00$).

**Table 1** Presence of sensitization according to AD severity

| Sensitization | Mild (%) | AD severity Moderate (%) | Severe (%) |
|---|---|---|---|
| No | 66.7 | 50.0 | 14.3 |
| Yes | 33.3 | 50.0 | 85.7 |
| Total | 100.0 | 100.0 | 100.0 |

## Discussion

According to the literature, there is a higher prevalence of AD in patients with a family history of atopic or those who already express another allergic manifestation (Illi et al. 2001), which was observed in the present study population. In patients with comorbidity, the chance to be touched was 1.64 times higher than in the absence of other allergic manifestation. Moreover, there are reports that individuals sensitized to foods have increased risk of developing asthma and subsequent rhinitis (Hahn and Bacharier 2005).

Eczema is in fact the atopic condition with higher serum concentrations of IgE (Wahn et al. 2008), and thus, it may increase the probability of sIgE detection. In this study, a 1.001-fold increase in the odds ratio of sensitization to foods in each added unit of IgE was observed. However, it was not possible to establish a correlation between the

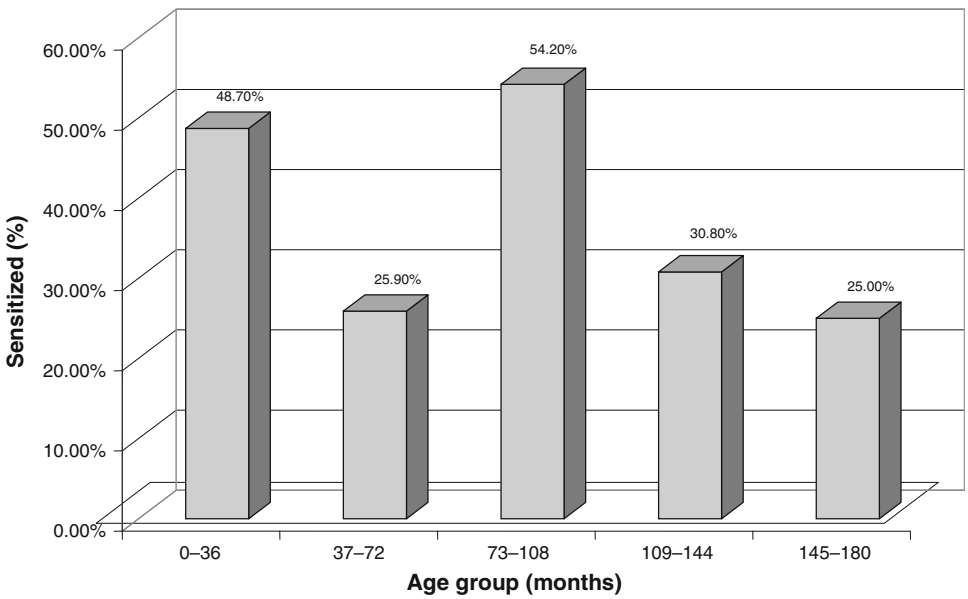


**Fig. 1** Sensitized patients (%) according to age group

**Table 2** Value range detection of sIgE by means of the ImmunoCAP® method in the patients included ($n = 111$)

| Allergens | 0.35–0.69 | 0.70–3.49 | 3.50–17.49 | 17.50–49.99 | ≥50.00 | Total (*n*/ %) |
|---|---|---|---|---|---|---|
| Cow's milk | 41.4 | 34.5 | 10.3 | 13.8 | – | 29/26.1 |
| α-lactalbumin | 41.0 | 31.8 | 18.2 | 9.0 | – | 22/19.8 |
| Egg white | 26.3 | 47.4 | 15.8 | 10.5 | – | 19/17.1 |
| Wheat | 68.4 | 31.6 | – | – | – | 19/17.1 |
| Casein | 38.9 | 33.3 | 5.6 | 22.2 | – | 18/16.2 |
| β-lactoglobulin | 52.9 | 17.6 | 17.6 | 11.8 | – | 17/15.3 |
| Soy | 46.2 | 53.8 | – | – | – | 13/11.7 |
| Corn | 63.6 | 27.3 | 9.1 | – | – | 11/9.9 |
| Peanut | 40.0 | 60.0 | – | – | – | 10/8.4 |
| Fish | 44.4 | 44.4 | 11.1 | – | – | 09/7.6 |
| Egg yolk | 42.9 | 57.1 | – | – | – | 07/5.9 |

serum level and the intensity of the disease as Somani et al. remarked (Laske and Niggemann 2004; Somani 2008).

The age group with 36 months of age or less showed the highest concentration of sIgE level, and over half of these infants presented this feature during their first year of life (52.6 %), indicating that sensitization really occurs in the beginning of life according to the data from the studies early treatment of the atopic child—ETAC (1998) and multicentre allergy study—MAS (Kulig et al. 1998). Differently from other cohort studies that point to egg white (Kulig et al. 1999; Nickel et al. 1997), CM was the main culprit in this study, and the reason for that may lie in the fact that low-aged children and mild cases prevailed in our sample. These peculiarities probably also corroborated to the lower sensitization rate found in this study when it is compared with results reported in the literature (Kulig et al. 1998; Nickel et al. 1997; Somani 2008; Wahn et al. 2008).

Among the main CM allergens, the casein was the only protein fraction that showed a significant association with the severity of the atopic eczema. Casein is considered a marker of persistence in CM allergy cases due to its conformational characteristics, resistance to thermal processes and its ability to keep part of its allergenicity, although being sensitive to proteolysis (Wal 2004).

The OPT, specially the double-blind and placebo-controlled trial, is still considered the gold standard for food allergy diagnosis. However, it is difficult to establish that symptoms are responsible for the test positivity in patients with AD. Some authors consider the worsening in the intensity of the eczema as a significant factor that must be evaluated by intensity scores. Therefore, the confirmation of the difference of at least ten points in the SCORAD is considered a positive reaction (Werfel et al. 2007), a value obtained in one patient after the process with egg white was triggered.

Due to difficulties and possible risks in the performance of OPTs, different studies have suggested the analysis of concentrations of food sIgE levels (cut-off points). Above these cutoff points, clinically significant allergies, with positive predictive value (PPV) 95–99 %, would be considered (Ballardini et al. 2006; Castro 2009; Garcia-Ara et al. 2001; Sampson 2001). However, it is important to point out that those values may vary according to region and studied food. Sampson (2001) indicated the value of 15 $KU_A/L$ for the CM, whereas a Spanish study suggested 5 $KU_A/L$ for patients below two years of age and 15 $KU_A/L$ for those over two (Garcia-Ara et al. 2001).

The cutoff points adopted in this study were suggested by other Brazilian study who evaluated the population from São Paulo city with the same environmental conditions and similar ethnic individuals evaluated. This study established the values of 3.06 $KU_A/L$ for the CM, 2.06 $KU_A/L$ for the α-lactalbumin, 1.85 $KU_A/L$ for the β-lactoglobulin and 1.47 $KU_A/L$ for the casein in children up to 13 years of age (PPV 95 % and specificity of 98 %) (Castro 2009). Concerning the egg, Sampson (2001) indicated the value of 2 $KU_A/L$ for the age group of up to 24 months of age and 7 $KU_A/L$ for those over 2 years. So far there is no data record for this allergen in Brazil.

Taking the Brazilian investigation results into consideration, we obtained superior values for the CM in 24.1 % of the cases and also for the protein fractions (α-lactalbumin 31.8 %; β-lactoglobulin 29.4 %; casein 44.5 %). However, no clinical reactivity was observed after the provocation, which suggests that new cutoff values must be established, considering the peculiarities inherent to the studied patients.

As to the egg white, in this study, only 42 % showed concentration of sIgE above the international cutoff values. After the triggering, a clinical correlation was observed in only one patient with an increase of 10.1 points in the SCORAD. However, the severity classification of the AD remained moderate.

Considering that sensitization occurs through the food intake or its passage through breast milk and that

symptoms may come up later after the intake, inhalation or even direct skin contact with allergens, patients with eczema present higher rates of sensitization and risk of symptoms due to the alteration in the dermal layer.

In the first months of life, it is known that breastfeeding plays an important role in the body defense system by antigenic similarity of the species and that breast milk contains immunological and non-immunological protection factors. Therefore, studies refer to its protective effect in breastfed infants with family history of atopy if these infants are exclusively breastfed until at least 4 months of age (Saarinen and Kajosaari 1995; van Odijk et al. 2003). Due to the immune system and gastrointestinal tract immaturity, the early introduction of food allergens might stimulate the production of sIgE and induce allergic manifestations in predisposed children (Brandtzaeg 2002). However, controversies on the oral tolerance induction with the early introduction of foods still remain (Greer et al. 2008). Despite these evidences, there was no significant correlation between the age lesions firstly appeared and breastfeeding total amount of time or even the time when solids were introduced in the diet. All the same, it was observed that the shorter the exclusive breastfeeding period, the higher was the AD severity, and thus suggesting that the earlier the exposition to food allergens, the higher is the risks of sensitization and that breast milk must be a protective factor in the beginning of the illness.

The current data show that the earlier the onset of lesions, the more severe the disease is. Yet, it is important to keep in mind that it is a multifactorial disease in which a longer evolution means a greater interference of environmental factors. Due to its peculiarities, AD demands attention on the attempt of determining or excluding probable aggravating factors, a fundamental aid for the disease control.

In this study, like in many others in the literature, a low clinical reactivity was observed, a fact that corroborates with the need of its confirmation before the imposition of restrictive diets, which are, most of the time, complex and unnecessary. Such diets expose children to a nutritional risk factor are harmful to their growth and development and deprive them and their families of a social life, which is a direct interference in their quality of life (Luccioli 2012).

In conclusion, the occurrence of sensitization to foods in children with AD was frequent and the main foods involved were the CM, the egg white and the wheat. However, there was no confirmation of the clinical reactivity in most of the performed provocation tests. The absence of significant correlation between OPT and the raised sIgE levels to cow's milk, egg and wheat in the study population may be a confounding factor. Is it because of some cross-sensitivity or past sensitization, which is responsible for the raised sIgE levels. The non-corroboration of history and OPTs suggests that the history provided by the patients may be biased and the trigger could be another food, consumed in the relevant time span.

In spite of all these, the fact still remains that food plays an important role in AD, and if sIgE levels along with other tests like OPT, prick tests or patch tests implicate specific foodstuffs, it would be worthwhile eliminating that from the diet, to favorably influence the course of the disease.

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