Original Article

Specific IgE levels do not indicate persistence or transience of food allergy in children with atopic dermatitis

B. Niggemann, S. Celik-Bilgili, M. Ziegert, S. Reibel, C. Sommerfeld, and U. Wahn

Dept. of Pneumology and Immunology, University Children's Hospital Charité of Humboldt University, Berlin, Germany

Summary

Background: Food allergy in early childhood usually resolves with time; however, little is known about predictors for persistence or transience of food allergy in children with atopic dermatitis. The aim of the study was to evaluate whether specific IgE levels in serum could be a useful predictor of the outcome of oral re-challenges. Methods: In 74 children, 99 oral food challenges were performed (cow milk n = 48, hen egg n = 37, and wheat n = 14) and repeated after a median time interval of 16 months. In 15 of the 74 children, a third challenge (n = 22) could be performed, with a median time interval from second challenge to third challenge of 15 months. *Results:* There were 37 children with transient food allergy (positive first challenge and negative second challenge), while 62 children had persistent food allergy (positive first and positive second challenge). Comparison of the two groups showed that specific IgE as well as total IgE in serum was significantly higher in the latter group. However, looking at the time course, specific IgE did not decrease significantly during elimination diet. *Conclusion:* Our results indicate that specific IgE in serum - although very helpful at the time of the first diagnosis - cannot predict whether a child will become tolerant after a period of avoidance. Therefore, oral re-challenges remain mandatory.

Key words: allergy, atopy patch test, children, cow milk, DBPCFC, food challenge, hen egg, re-challenge, sensitization, specific IgE

Introduction

Clinically relevant food allergy is reported in around 40% of children with atopic dermatitis (AD) [1,2,3]. Both AD and food allergy are diseases with a predominance in early childhood [4,5]. Among the most common offending foods in children with AD are cow milk (CM), hen egg (HE), wheat and soy [3,6]. Adverse reactions to food range from mild skin symptoms to life threatening anaphylactic reactions [7,8,9]. The skin is the most frequently involved organ [3,10].

The diagnostic work-up of suspected food allergy includes skin prick tests (SPT) [11], the measurement of food specific IgE antibodies using serologic assays [12,13] and more recently, the atopy patch test (APT) [10,14,15]. However, double-blind, placebo-controlled food challenges (DBPCFC) still represent the 'gold standard' for diagnosing food allergy [3,16,17,18,19].

While there are many reports that food allergy of early childhood resolves with time [4,20,21,22,23], little is known about persistence or transience predictors. The aim of this study was to evaluate whether specific IgE levels could be a useful predictor for the outcome of oral food challenges. We therefore re-challenged children with AD and proven food allergy after at least one year of an adequate elimination diet by oral food challenges and performed specific IgE measurements in serum.

Methods

Patients

We investigated 74 children (46 boys, 28 girls) (Table 1) admitted consecutively to our ward for re-evaluation of food allergy who met the following inclusion criteria: (1) at least two oral food challenges with the same food, (2) at least the first challenge was positive, and (3) avoidance for at least 12 months. All children suffered from AD as defined by the criteria of Sampson [24] and Seymour [25], modified from Hanifin and Rajka [26].

Scoring of atopic dermatitis

Severity of eczema was assessed according to the SCORAD-score [27] with "topography" items (affected skin area), "intensity" criteria (extent of erythema, edema, crusts, excoriations, lichenification, xerosis) and subjective parameters (itchiness and loss of sleep). The maximum possible score was 103 points.

Food challenges

Inclusion criteria for performing follow-up oral challenges were re-evaluation of their proven food allergy at least one year after the initial positive challenge. Children on an antihistamine (solely cetirizine) were advised to avoid it 72 hours prior to provocation. Topical glucocorticosteroids were allowed twice daily (1% hydrocortisone or 0.01% betamethasone). Randomization and preparation of the challenges were performed by the clinical dietician. Briefly, successive doses (0.1, 0.3, 1.0, 3.0, 10.0, 30.0 and 100.0 ml) of fresh pasteurized cow milk and wheat powder (Kröner, Ibbenbüren, Germany - total of 10 g of wheat protein) or placebo (Amino acid formula: Neocate SHS, Liverpool, UK) were administered every 20 minutes. Raw hen egg was given in an analogous way except that the seventh dose was omitted. Full emergency equipment including epinephrine, antihistamines, glucocorticosteroids, and ß-agonists was at hand. The provocation was stopped if clinical symptoms were observed or when the highest dose was reached. A positive eczematous reaction was defined as an increase of at least ten SCORAD points during provocation. The children were observed as in-patients for 48 hours after each challenge (allergen and placebo).

Of the 99 first challenges, 64 were double-blind, placebo-controlled [18], 35 in an open manner. Thirty-nine of the second challenges were performed as DBPCFC, 60 openly. Of the 22 third challenges, 10 were double-blind, placebo-controlled, and 12 open. Open challenges were allowed if children were younger than one year and had a clear history of immediate type reactions; in other cases challenges were performed as DBPCFC. All oral challenges were performed on an inpatient basis. The food challenges were scored as positive by a paediatric allergy specialist (SR) if one or more of the following objective clinical reactions were noted: urticaria, angio-edema, wheezing, vomiting, diarrhoea, abdominal pain, shock or exacerbation of eczema. For presentation and calculation of data, combined reactions were classed as late phase reactions.

Determination of specific IgE antibodies

Blood was drawn prior to food challenge, and analyzed for concentrations of total IgE and specific IgE antibody titres to CM and HE, determined by FEIA using the Pharmacia CAP-system [28] (Pharmacia Diagnostics, Uppsala, Sweden). Children were regarded as sensitized if specific IgE was above the detection limit of 0.35 kU/l IgE.

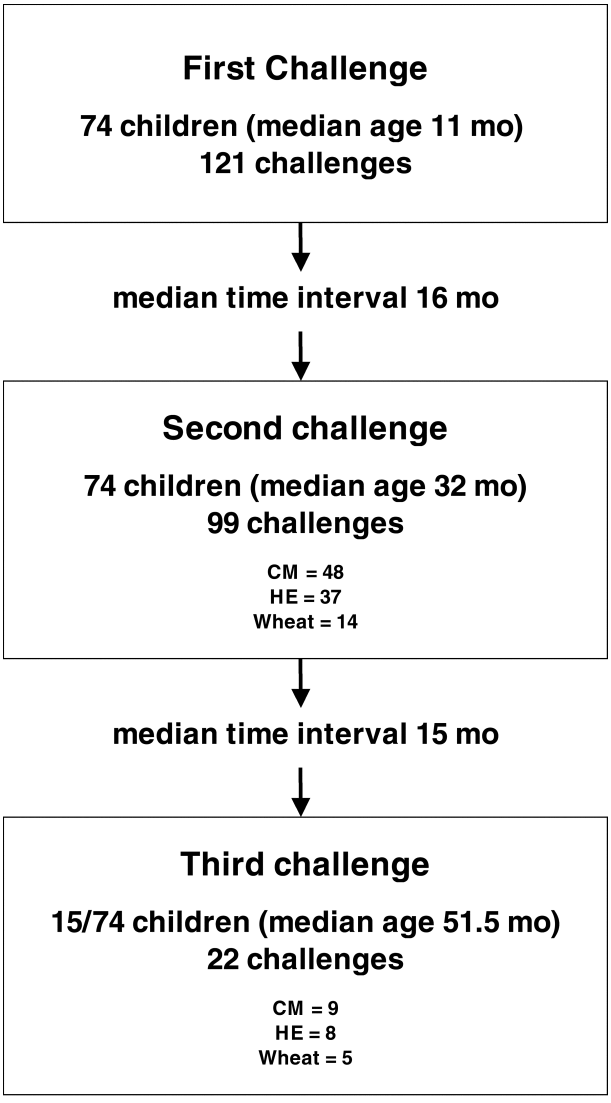

Figure 1. Number of children and oral food challenges, median ages and corresponding median time intervals.

Atopy patch test

Aluminium cups on adhesive tape (Finn Chambers on Scanpor, Hermal, Reinbek, Germany) with a diameter of 12 mm were used. 50 ml of fresh cow milk containing 3.5% fat, of whisked hen egg (white of egg and yolk), and of wheat powder (Kröner, Ibbenbüren, Germany) dissolved in water (1 g/10 ml) was put on filter paper and applied to the unaffected skin of the child's back. Application sites were checked after 20 minutes for immediate reactions. The occlusion time was 48 hours, and results were read 24 hours later for the final evaluation of the test. Final reactions (72 hours) were classified as positive if there was erythema together with infiltration [10,15].

Statistical analyses

We used SPSS for Windows (version 10.0, SPSS, Chicago, USA). To calculate differences between challenges (two paired samples) the Wilcoxon signed rank test was used for continuous variables (age, SCORAD, total IgE, specific IgE). Statistical significance was defined as a two-sided alpha level of $p < 0.05$.

Results

We analyzed 74 children who had undergone 99 positive first oral food challenges with at least one re-challenge (Figure 1). Forty-eight challenges (49%) were performed with cow milk, 37 (37%) with hen egg and 14 (14%) with wheat. The time interval between first challenge and second challenge ranged from 12 to 99 months (median 16 months). One placebo reaction was positive in this series (late eczematous reaction at second challenge).

Table 1. Patient characteristics at first oral food challenge and at second challenge (n=99)
Data presented as median values (in brackets: min; max).

Parameter	First challenge	Second challenge
Age (months)	11.0 (0; 173)	32.0 (9; 209)
SCORAD (points)*	18 (0; 80)	4 (0; 70)
Total IgE (kU/1)	110 (1; 13,368)	200 (1; 11,800)
Specific IgE (kU/1)		
CM	2.7 (<0.35; >100.0)	1.5 (<0.35; >100.0)
HE	3.8 (<0.35; >100.0)	2.0 (<0.35; >100.0)
Wheat	1.8 (<0.35; 78.2)	2.3 (<0.35; >100.0)

* = $p < 0.01$

Table 2. Comparison of transient and persistent food allergy
Data presented as median values (in brackets: min; max). n.s. = not significant

Parameter	Transient (n = 37) (first challenge positive, second challenge negative)	Persistent (n = 62) (first and second challenge positive)	p-value
Age (months) at first challenge	11.0 (4; 87)	13.5 (0; 173)	n.s
Age (months) at second challenge	32.0 (11; 117)	32.0 (9; 209)	n.s
SCORAD (points) at first challenge	15 (0; 80)	19 (0; 80)	n.s
SCORAD (points) at second challenge	5 (0; 50)	2 (0; 70)	n.s
Total IgE (kU/1) at first challenge	52.5 (1; 8360)	185.0 (6; 13,368)	0.005
Total IgE (kU/1) at second challenge	97.5 (1; 9845)	213 (11; 11,800)	0.034
Specific IgE (kU/1) at first challenge			
cow milk	1.3 (< 0.35; 67.8)	5.8 (<0.35; >100.0)	0.05
hen egg	0.5 (< 0.35; 34.6)	5.7 (<0.35; >100.0)	n.s
wheat	< 0.35; 1.8)	6.3 (< 0.35; 78.2)	0.02
Specific IgE (kU/1) at second challenge			
cow milk	< 0.35 (< 0.35; 69.7)	5.9 (< 0.35; > 100.0)	n.s
hen egg	< 0.35 (< 0.35; 13.3)	2.8 (< 0.35; > 100.0)	0.006
wheat	< 0.35 (< 0.35; < 0.35)	14.9 (< 0.35; > 100.0)	0.03

The clinical reactions observed in the first positive oral food challenge (n = 99) were: 34 children with acute urticaria, 23 with exacerbation of eczema, 14 with vomiting/diarrhea, and 4 with bronchial obstruction. In addition, 24 children developed combined symptoms: 7 urticaria plus eczema, 6 urticaria plus gastro-intestinal symptoms, 5 eczema plus gastro-intestinal symptoms, 4 urticaria plus respiratory symptoms, and 2 eczema plus respiratory symptoms.

Patient characteristics regarding ages, SCORAD-score, total IgE, and specific IgE to the three foods for the first challenges and the second challenges are shown in Table 1. Specific and total IgE in serum did not decrease significantly during the elimination diet.

Table 3. Atopy Patch Test results in transient and persistent food allergy (n = 20)

	Transient (n = 7)	Persistent (n = 13)
APT at first challenge	4 pos. / 3 neg.	6 pos. / 7 neg.
APT at second challenge	0 pos. / 7 neg.	4 pos. / 9 neg.

Table 4. Characteristics of children with three challenges (n = 22)
Data presented as median values (in brackets: min; max)

Parameter	First challenge		Second challenge		Third challenge
Age (months)	9.0 (0; 87)	- p < 0.001 -	30.0 (11; 105)	- p < 0.001 -	51.5 (23; 132)
SCORAD (points)	33 (8; 80)	- p < 0.002 -	10 (0; 50)	- n.s. -	0 (0; 55)
Total IgE (kU/l)	204.5 (15; 13,368)	- n.s. -	169.0 (12; 11,800)	- n.s. -	199 (10; 11,800)
Specific IgE (kU/1)	7.8 (< 0.35; > 100)	- n.s. -	16.3 (< 0.35; > 100)	- n.s. -	2.9 (< 0.35; > 100)

For further calculations, two groups were defined (Table 2): Transient food allergy (positive first challenge, but a negative second challenge, n = 37) and persistent food allergy (positive first challenge and positive second challenge, n = 62). Total IgE was significantly higher in the group of persistent food allergy at first and second challenge (p 0.005 and 0.034, respectively). Concerning specific IgE values, only wheat was significantly higher in the persistent group at both time points. CM and HE showed significantly higher specific IgE levels at the first or second challenge, respectively. Furthermore, there were no differences concerning the outcome of the APT (Table 3).

In 15 of the 74 children, three longitudinal challenges (n = 22: 9 CM, 8 HE, 5 wheat) could be performed, with a time interval from second challenge to third challenge ranging from 12 to 47 months (median 15 months) (Figure 1). The median severity of the eczema decreased significantly over the three time points (p <0.001) (Table 4). Total IgE and specific IgE values in serum showed no statistically significant differences.

Discussion

The clinical value of a predictive parameter can be twofold: (1) oral re-challenges may become superfluous if the predictor indicates oral tolerance; (2) to aid the counselling and reassurance of parents and patients on safety regarding inadvertent ingestion, if the probability of a severe clinical reaction on inadvertent ingestion after elimination [29] could be assessed more accurately. Specific IgE in serum - although very helpful at the time of the first diagnosis - seems not to predict whether an individual child will show a clinical reaction to cow milk or hen egg after a time of avoidance. Although statistically significant differences between the group of children with transient and persistent food allergy with higher total and specific IgE values in the latter group were observed, there was an inconsistent pattern looking at single allergens and there were no significant longitudinal changes.

In accordance with our results, other authors have reported that specific IgE in serum and the skin prick test (SPT) are not useful to predict loss of symptomatic food hypersensitivity [30,31]. There are conflicting reports on other serological parameters such as IgG or IgG subclass levels. Although IgG subclasses to ß-lactoglobulin increase over time during exposure to cow milk [32], IgG values do not seem to be a suitable parameter for predicting tolerance to the offending food [30]. One author reports that casein-specific and ß-lactoglobulin-specific IgE concentrations and the IgE/IgG ratio are helpful in predicting patients who would loose their clinical reactivity to cow milk [33]. A recent study proposed B-cell epitopes as a screening instrument

for persistent cow milk allergy [34]. However, all studies report results averaged over groups of children; so far no study has shown evidences that any individual parameter can predict clinical tolerance in children.

In 37/99 (37%) of the challenges we carried out, the patients lost their clinical reactivity to the offending food over time. Earlier studies report that of 40 children with severe AD re-evaluated after 1 to 2 years, 40% lost their hypersensitivity [35], as well as 25% of 75 children with AD studied after 1 year [31]. Other authors reported tolerance to cow milk of 56% by 4 years and 78% by 6 years after first diagnosis at 16 months [36]. Most infants with food allergy suffer from atopic dermatitis [33], but it remains unclear from the literature whether the coexistence of atopic dermatitis has any influence on the prognosis.

The fact that only 22 third challenges could be evaluated so far may represent a potential bias: children may have been transferred to our unit because parents or physician still suspect food allergy while other children – with an accidental intake of the corresponding food, which was then tolerated – may not come for reevaluation. However the medical histories of the parents at the time of the third challenge do not support this hypothesis.

The atopy patch test (APT) has become a promising new tool in the diagnostic work-up of food allergy in infants and children with atopic dermatitis [10,15]. Furthermore, at the time of the first diagnosis of a food allergy it could be shown that DBPCFC may be superfluous in some children with atopic dermatitis if specific IgE values and the atopy patch test are considered in combination [10]. Atopy patch tests could only be carried out on a small number of children in this study on at least two time points (n = 20). It remains unclear whether the atopy patch test could be a potentially promising predictor for indicating tolerance after a period of avoidance.

Our results indicate that children with higher total IgE levels and those with higher specific IgE levels to CM, HE, and wheat may have a higher risk of persistence of food allergy after 16 months of elimination diet. However, due to a large overlap, these parameters are not reliable in an individual patient. Therefore, re-challenges remain mandatory.

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Dr. Bodo Niggemann

MD, Dept. of Pediatric Pneumology and Immunology
Children's Hospital Charité
Humboldt University
Augustenburger Platz 1, 13353 Berlin, Germany
Tel.: +49 30 450 566643
Fax: +49 30 450 566931
E-mail: bodo.niggemann@charite.de